CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 74-726/S-009, S-011, S-015, S-016, and S-017

Name: Klor-Con® M (Potassium Chloride Extended-release Tablets USP, 10 mEq and 20 mEq)

Sponsor: Upsher-Smith Laboratories, Inc.

Approval Date: June 6, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-009, S-011, S-015, S-016 and S-017

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-009, S-011, S-015, S-016 and S-017

APPROVAL LETTER

ANDA: 74-726/S-009, S-011, S-015, S-016 and S-017 JUN 6 2003

Upsher-Smith Laboratories, Inc.
Attn: Mark S. Robbins, Ph.D., J.D.
14905 23rd Avenue North
Minneapolis, MN 55447

Dear Sir:

This is in reference to your supplemental new drug applications dated February 14, 2001 (S-009 and S-011) and May 6, 2002 (S-015, S-016 and S-017) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), regarding your abbreviated new drug application for Klor-Con® M, (Potassium Chloride Extended-Release Tablets), USP 10 mEq and 20 mEq.

Reference is also made to your amendments dated April 11, 2003 and May 22, 2003.

The supplemental applications, submitted as "Prior Approval Supplements" provide for the following changes:

S-009: Reformulation of the 10 mEq and 20 mEq tablets.
S-011: Labeling for the 10 mEq & 20 mEq tablets.
S-015: Manufacturing Revision (Scale-up of (b) (4)).
S-016: New Strength (15 mEq extended-release tablet).
S-017: Labeling for 15 mEq extended-release tablet.

With regard to S-016 providing for an additional strength (15 mEq) of the drug product, we note that the listed drug product (RLD) referenced in your application, K-Dur Extended-release Tablets of Key Pharmaceuticals, Inc., is subject to a period of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", U.S. patent 4,863,743 (the '743 patent) is scheduled to expire on September 5, 2006. Your application contains a paragraph IV patent certification to the '743 patent under Section 505(j)(2)(A)(vii)(IV) of the act stating that the '743 patent will not be infringed by your manufacture, use, or

sale of Klor-Con M Extended-release Tablets, 15 mEq. Section 505(j)(5)(B)(iii) of the act provides that approval of an ANDA shall be made effective immediately unless an action is brought against Upsher-Smith Laboratories, Inc. (Upsher-Smith) for infringement of the '743 patent. This action must be brought against Upsher-Smith prior to the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) was received by the patent/NDA holder. You have notified FDA that Upsher-Smith complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for patent infringement was brought against Upsher-Smith within the statutory forty-five day period. You have also informed the agency that the marketing of the 15 mEq strength of the drug product falls within the license to the '743 patent granted to Upsher-Smith by Schering-Plough under a settlement agreement signed in June 1997.

Furthermore, with regard to S-016 providing for Klor-Con M15 Extended-release Tablets, reference is made to the suitability petition submitted under Section 505(j)(2)(C) of the Act and approved on July 9, 2001, permitting you to submit this supplemental ANDA for a drug product that differs in strength from that of the reference listed drug product (RLD).

We have completed the review of these supplemental applications and have concluded that all three strengths of the drug product are safe and effective for use as recommended in the submitted labeling. Accordingly, the supplemental applications are approved. The additional strength of the drug product, Klor-Con M15 Extended-release Tablets can be expected to have the same therapeutic effect as that of an equivalent dose of the listed drug product upon which the agency relied as the basis of safety and effectiveness. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your supplemental application.

We note that Upsher-Smith was the first applicant to submit a substantially complete ANDA containing a paragraph IV certification to the '743 patent. Therefore, with this approval and as provided for under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) in Section 505(j)(5)(B)(iv) of the act, Upsher-Smith is eligible for 180-day generic drug exclusivity for Klor-Con M15 Extended-release Tablets with respect to the '743 patent. This exclusivity will begin to run on the date Upsher-Smith begins first commercial marketing of Klor-Con M15 Extended-release Tablets.

With respect to the "first commercial marketing" trigger for the commencement of this exclusivity, please refer to 21 CFR 314.107 (c)(4). The agency expects that Upsher-Smith will begin commercial marketing of the additional strength of this drug product in a prompt manner. Please submit correspondence to your ANDA stating the date that commercial marketing of the additional strength commenced.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described 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.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns for the additional strength. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

The material submitted is being retained in our files.

Sincerely yours,

/S/ for 6/6/2003

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

cc: ANDA 74-726 S-009, S-011, S-015, S-016 and S-017
Division File
Field Copy

Endorsements:

HFD-625/APendse/5/6/03 5/27/-3
HFD-625/MSmela/5/6/03 M Smela 5/28/03
HFD-617/PChen/5/6/03 5/28/03
HFD-613/APayne/5/6/03 5/27/03
HFD-613/JGrace/5/6/03 5/27/2003

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F/T by:

CHEMISTRY REVIEW: ~~APPROVABLE~~ 6/6/2003

APPROVAL

PS Tbg/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-009, S-011, S-015, S-016 and S-017

LABELING

KLOR-CON® M
(Potassium Chloride
Extended-release
Tablets, USP)
MICRO-DISPERSIBLE
TECHNOLOGY®

00150301

KLOR-CON® M
10 mEq, 15 mEq and 20 mEq

DESCRIPTION

Klor-Con® M20 is an immediately dispersing extended-release oral dosage form of potassium chloride containing 1500 mg of microencapsulated potassium chloride, USP equivalent to 20 mEq of potassium in a tablet.

Klor-Con® M15 is an immediately dispersing extended-release oral dosage form of potassium chloride containing 1125 mg of microencapsulated potassium chloride, USP equivalent to 15 mEq of potassium in a tablet.

Klor-Con® M10 is an immediately dispersing extended-release oral dosage form of potassium chloride containing 750 mg of microencapsulated potassium chloride, USP equivalent to 10 mEq of potassium in a tablet.

These formulations are intended to slow the release of potassium so that the likelihood of a high localized concentration of potassium chloride within the gastrointestinal tract is reduced.

Klor-Con® M is an electrolyte replenisher. The chemical name of the active ingredient is potassium chloride, and the structural formula is KCl (molecular weight: 74.55). 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.

Klor-Con® M is a tablet formulation (not enteric coated or wax matrix) containing individually microencapsulated potassium chloride crystals which disperse upon tablet disintegration. In simulated gastric fluid at 37°C and in the absence of outside agitation, Klor-Con® M begins disintegrating into microencapsulated crystals within seconds and completely disintegrates within one minute. The microencapsulated crystals are formulated to provide an extended release of potassium chloride.

Inactive Ingredients: croscarmellose sodium, ethylcellulose and microcrystalline cellulose.

CLINICAL PHARMACOLOGY

The 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 as a consequence of therapy with diuretics, primary or secondary hyperaldosteronism, 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 EXTENDED-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 intoxication 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.

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 or amiloride) (see **OVERDOSAGE**).

Extended-release formulations of potassium chloride have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be given as a liquid preparation or as an aqueous (water) suspension of Klor-Con® M (see **PRECAUTIONS;** *Information for Patients* and **DOSAGE AND ADMINISTRATION** sections).

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 doses to exert anticholinergic effects) cause for arrest or delay in tablet 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 adjustment.

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 extended-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

4. Swirl the suspension and consume the entire contents of the glass immediately by drinking or by the use of a straw.
5. Add another one fluid ounce of water, swirl and consume immediately.
6. Then, add an additional one fluid ounce of water, swirl and consume immediately.

Aqueous suspension of Klor-Con® M extended-release tablet that is not taken immediately should be discarded. The use of other liquids for suspending Klor-Con® M tablets is not recommended.

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 at once if tarry stools or other evidence of gastrointestinal bleeding is noticed.

Laboratory Tests: 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: Pregnancy Category C: Animal reproduction studies have not been conducted with Klor-Con® M. 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.

ADVERSE REACTIONS

One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS** and **OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see **CONTRAINDICATIONS** and **WARNINGS**).

The most common adverse reactions to oral potassium salts are nausea, vomiting, flatulence, abdominal pain/discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals or reducing the amount taken at one time.

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 S-T 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 injection containing 10-20 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 patient. The dose for the prevention of hypokalemia is typically in the range of 20 mEq per day. Doses of 40-100 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.

Each Klor-Con® M20 tablet provides 1500 mg of potassium chloride equivalent to 20 mEq of potassium.

Each Klor-Con® M15 tablet provides 1125 mg of potassium chloride equivalent to 15 mEq of potassium.

Each Klor-Con® M10 tablet provides 750 mg of potassium chloride equivalent to 10 mEq of potassium.

Klor-Con® M tablets should be taken with meals and with a glass of water or other liquid. This product should not be taken on an empty stomach because of its potential for gastric irritation (see **WARNINGS**).

Patients having difficulty swallowing whole tablets may try one of the following alternate methods of administration:

a. Break the tablet in half and take each half separately with a glass of water.
b. Prepare an aqueous (water) suspension as follows:
1. Place the whole tablet(s) in approximately one-half glass of water (4 fluid ounces).
2. Allow approximately 2 minutes for the tablet(s) to disintegrate.
3. Stir for about half a minute after the tablet(s) has disintegrated.
4. Swirl the suspension and consume the entire contents of the glass immediately by drinking or by the use of a straw.
5. Add another one fluid ounce of water, swirl and consume immediately.
6. Then, add an additional one fluid ounce of water, swirl and consume immediately.

Aqueous suspension of Klor-Con® M extended-release tablet that is not taken immediately should be discarded. The use of other liquids for suspending Klor-Con® M tablets is not recommended.

HOW SUPPLIED

Klor-Con® M20 Extended-release Tablets, 1500 mg of potassium chloride (20 mEq of potassium) are available in bottles of 90 (NDC 0245-0058-90); bottles of 100 (NDC 0245-0058-11); bottles of 500 (NDC 0245-0058-15); bottles of 1000 (NDC 0245-0058-10); and cartons of 100 for unit dose dispensing (NDC 0245-0058-01). Klor-Con® M20 tablets are white, oblong, imprinted KC M20 and scored for flexibility of dosing.

Klor-Con® M15 Extended-release Tablets, 1125 mg of potassium chloride (15 mEq of potassium) are available in bottles of 100 (NDC 0245-0150-11); bottles of 1000 (NDC 0245-0150-10); and cartons of 100 for unit dose dispensing (NDC 0245-0150-01). Klor-Con® M15 tablets are white, oblong, imprinted M 15 and scored for flexibility of dosing.

Klor-Con® M10 Extended-release Tablets, 750 mg of potassium chloride (10 mEq of potassium) are available in bottles of 90 (NDC 0245-0057-90); bottles of 100 (NDC 0245-0057-11); bottles of 1000 (NDC 0245-0057-10); and cartons of 100 for unit dose dispensing (NDC 0245-0057-01). Klor-Con® M10 tablets are white, oblong and imprinted KC M10.

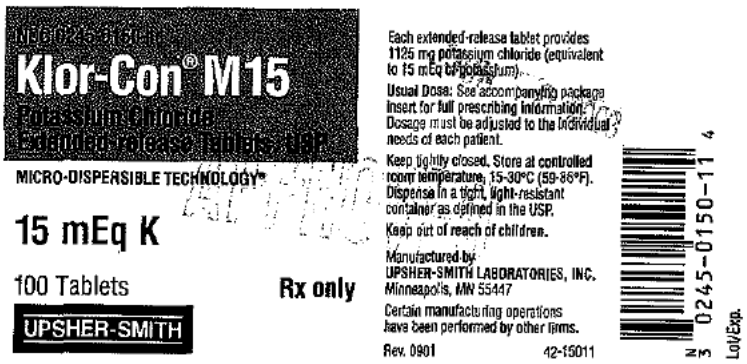
Storage Conditions: Keep tightly closed. Store at controlled room temperature, 15-30°C (59-86°F).

Manufactured by
UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447
Certain manufacturing operations have been performed by other firms.

Rev. 0301
40-00150

Original

Upsher-Smith Laboratories, Inc.
Klor-Con® M (Potassium Chloride Extended-release Tablets, USP)
ANDA 74-726: Major Amendment to Supplements (b) (4)



032

Klor-Con® M15

Potassium Chloride
Extended-release Tablets, USP

MICRO-DISPERSIBLE TECHNOLOGY®

15 mEq K

1000 Tablets

Rx only

UPSHER-SMITH

Each extended-release tablet provides 1125 mg potassium chloride (equivalent to 15 mEq of potassium).

Usual Dose: See accompanying package insert for full prescribing information. Dosage must be adjusted to the individual needs of each patient.

Keep tightly closed. Store at controlled room temperature, 15-30°C (59-86°F). Dispense in a tight, light-resistant container as defined in the USP.

Keep out of reach of children.

Manufactured by
UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447

Certain manufacturing operations have been performed by other firms.

Rev. 1101 42-15010

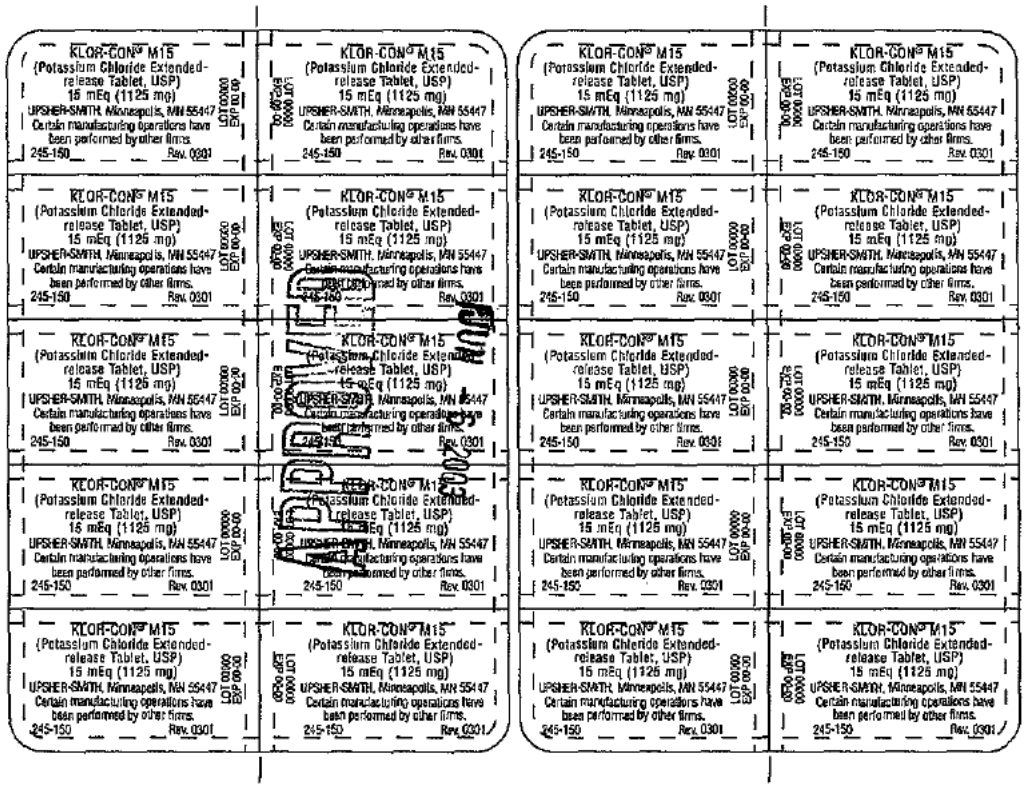
0245-0150-10

LabExp

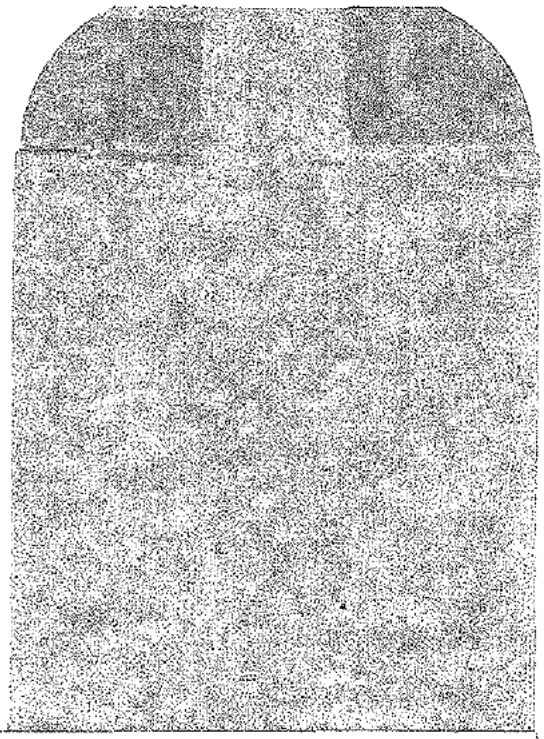
Upsher-Smith Laboratories, Inc.
Klor-Con® M (Potassium Chloride Extended-release Tablets, USP)
ANDA 74-726: Major Amendment to Supplements (5) (4)

Original

NEW MASTER 03/16/01



034



NDC 0245-0160-01

Klor-Con® M15

Potassium Chloride Extended-Release Tablets, USP

MICRO-DISPERSIBLE TECHNOLOGY®

15 mEq K

Unit Dose, 100 Tablets **Rx only**

UPSHER-SMITH

Each extended-release tablet provides 1125 mg potassium chloride (equivalent to 15 mEq of potassium).

Usual Dose: See accompanying package insert for full prescribing information. Dosage must be adjusted to the individual needs of each patient.

Store at controlled room temperature, 15-30°C (59-86°F).

This unit dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

Keep out of reach of children.

UPSHER-SMITH

Unit Dose, 100 Tablets

15 mEq K

MICRO-DISPERSIBLE TECHNOLOGY®

Klor-Con® M15

Potassium Chloride
Extended-Release Tablets, USP

N 3 0245-0150-01 5

Klor-Con M15

Manufactured by
UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447

Certain manufacturing operations have been performed by other firms.

Rev. 0901 49-15001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-009, S-011, S-015, S-016 and S-017

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING #1
SUPPLEMENT
FPL

DATE OF REVIEW: November 4, 2002
ANDA #: 74-726/SL-017 combined with SC-015 and 016
NAME OF FIRM: UPSher Smith
NAME OF DRUG: Potassium Chloride Extended Release Tablets USP, 15 meq
PROPERITARY NAME: Klor-Con M
DATE OF SUBMISSION: May 6, 2002

COMMENTS:

1. CONTAINER - 100s unit-dose blister and (b) (4) 1000s bottles - 15 meq. Satisfactory in FPL vol. 10.1

2. CARTON - 10 X 10 unit dose blisters - Satisfactory in FPL vol 10.1.

3. INSERT: #40-00150 rev.03/01 is satisfactory for approval in FPL (vol.10.1).

RECOMMENDATIONS: Approve only after Supplements 005-008 and (b) (4) are approved. The insert labeling for S-017 will superceded (b) (4) for approval.

Done HFS will be concurrent HFS

NOTE TO CHEMIST: The insert Labeling submitted in supplement S-017 will supercede the insert labeling SL-008 and S-011.

FOR THE RECORD:

1. Review based on the labeling of K-Dur® (Potassium Chloride Extended-release Tablets) Schering-Plough Research; NDA N19-439/S-015; Approved December 20, 1990.

2. Supplement –017 provide for a new strength product 15 meq.

3. Chemistry supplements 005, 006, 007 and Labeling S-008 must be approved before S-011 must be approved before or simultaneously with S-017. Provisions for S-005-8 and S-011 are contained in S-017. Therefore the insert found in S-017 will superceded the previous insert labeling submitted (b) (4)

cc: ANDA 74-726/S-017
Dup/Division File
HFD-613/APayne/ JGrace (no cc:)
V:/firmsnz/upsher/lets&rev/74726s017.apL
Review

John D. Grace 11/7/2002
Jane 11/04/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-009, S-011, S-015, S-016 and S-017

CHEMISTRY REVIEWS

ANDA: 74-726/S-009, S-011, S-015, S-016 and S-017 CR5

NAME AND ADDRESS OF APPLICANT:
Upsher-Smith Laboratories, Inc.
Attn: Mark S. Robbins, Ph.D., J.D.
14905 23rd Avenue North
Minneapolis, MN 55447

Telephone: (763) 473-4412

PURPOSE OF SUPPLEMENT:
S-009: Reformulation of 10 mEq and 20 mEq Tablets
S-011: Labeling for 10 mEq & 20 mEq tablets
S-015: Manufacturing Revision (Scale-up of (b) (4).)
S-016: New Strength Addition (15 mEq via Suitability Petition)
S-017: Labeling for 15 mEq Tablet

DATE(S) OF SUBMISSION(S) and OTHERS(AMENDMENTS,TELECON OR OTHERS):
2/14/01 OS of S-009, S-011
5/6/02 OS of S-015, S-016, S-017
12/6/02 Minor Amendment for all above
2/7/03 Minor amendment
*4/11/03 Minor amendment (Response to NA dated 4/4/03).

NONPROPRIETARY NAME:
Potassium Chloride Extended-Release Tablets USP

PHARMACOLOGICAL CATEGORY	TRADE NAME
Potassium Supplementation	Klor-Con® M

DOSAGE FORM	POTENCY	RX OR OTC
Tablets	10 mEq, 15 mEq & 20 mEq	R_x

REMARKS AND CONCLUSION: Approvable

Labeling Review: Acceptable per Payne/Grace on 1/7/03
Bio Review: Acceptable per Tran/Nerurkar on 3/11/03

Reviewer: Anil D. Pendse **Date Completed:** 5/06/03

20. COMPONENTS AND COMPOSITION: N/C

21. FACILITIES: N/C

22. SYNTHESIS: N/C

DMF [redacted] (b)(4) became adequate on 5/06/03..

23. RAW MATERIAL CONTROLS: N/C

24. OTHER FIRM(s): N/C

25. MANUFACTURING AND PROCESSING: N/C

26. CONTAINER: N/C

27. PACKAGING AND LABELING: N/C

28. LABORATORY CONTROLS (IN-PROCESS AND FINISHED DOSAGE FORM): N/C

29. STABILITY: N/C

30. MICROBIOLOGY: N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS: N/A

32. LABELING: OK per Payne/Grace on 1/03

33. ESTABLISHMENT INSPECTION: N/A

34. BIOEQUIVALENCE: Acceptable as of 3/11/03. The dissolution test and limits used for release and stability are identical to those recommended by DBE. (See CR2)

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: N/A

36. DMF CHECKLIST FOR ANDA # 74726/S009,S011,S015;S016,S017 CR5

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW
[redacted] (b) (4)		1	Adequate	5/06/03
		4		
		4		
		4		
		4		
		4		
		4		
		4		
		4		
		4		
		4		
		4		

ACTION CODES: (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").

Anil D. Pendse
Reviewer

Signature

5/27/03
Date

REMARKS AND CONCLUSION: Approvable

ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes_____ No ___x____
Minor amendment

Spot? Yes_____, No____X___

Endorsements:

HFD-625/APendse/Review chemist/5/06/03 5/27/03
HFD-625/MSmela/Team leader/5/06/03 M Smela 5/28/03

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Chemistry Review: Approvable

Patent amendment requested by Paras Patel dated 5/22/03 to be acknowledged in approval letter. M Smela

ANDA: 74-726/S-009, S-011, S-015, S-016 and S-017 CR#4

NAME AND ADDRESS OF APPLICANT:
Upsher-Smith Laboratories, Inc.
Attn: Mark S. Robbins, Ph.D., J.D.
14905 23rd Avenue North
Minneapolis, MN 55447

Telephone: (763) 473-4412

PURPOSE OF SUPPLEMENT:
S-009: Reformulation of 10 mEq and 20 mEq Tablets
S-011: Labeling for 10 mEq & 20 mEq tablets
S-015: Manufacturing Revision (Scale-up of (b) (4))
S-016: New Strength Addition (15 mEq via Suitability Petition)
S-017: Labeling for 15 mEq Tablet

DATE(S) OF SUBMISSION(S) and OTHERS(AMENDMENTS,TELECON OR OTHERS):
2/14/01 OS of S-009, S-011
5/6/02 OS of S-015, S-016, S-017
12/6/02 Minor Amendment for all above
*2/7/03 Minor amendment (Response to NA dated 2/6/03).

NONPROPRIETARY NAME:
Potassium Chloride Extended-Release Tablets USP

PHARMACOLOGICAL CATEGORY	**TRADE NAME**
Potassium Supplementation	Klor-Con® M

DOSAGE FORM	**POTENCY**	**RX OR OTC**
Tablets	10 mEq, 15 mEq & 20 mEq	R_x

REMARKS AND CONCLUSION: Not approvable-Minor

Labeling Review: Acceptable per Payne/Grace on 1/7/03
Bio Review: Acceptable per Tran/Nerurkar on 3/11/03

Reviewer: Anil D. Pendse **Date Completed:** 3/27/03

20. **COMPONENTS AND COMPOSITION:** N/C

21. **FACILITIES:** N/C

22. **SYNTHESIS:** N/C

DMF (b)(4) has become deficient for failure to report Annual Updates.

23. **RAW MATERIAL CONTROLS:** N/C

24. **OTHER FIRM(s):** N/C

25. **MANUFACTURING AND PROCESSING:** N/C

26. **CONTAINER:** N/C

27. **PACKAGING AND LABELING:** N/C

28. **LABORATORY CONTROLS (IN-PROCESS AND FINISHED DOSAGE FORM):** N/C

29. **STABILITY:** N/C

30. **MICROBIOLOGY:** N/A

31. **SAMPLES AND RESULTS/METHODS VALIDATION STATUS:** N/A

32. **LABELING:** OK per Payne/Grace on 1/03

33. **ESTABLISHMENT INSPECTION:** N/A

34. **BIOEQUIVALENCE:** Acceptable as of 3/11/03. The dissolution test and limits used for release and stability are identical to those recommended by DBE. (See CR2)

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:** N/A

36. DMF CHECKLIST FOR ANDA # 74726/S009,S011,S015,S016,S017 CR4

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW
[redacted] (b) (4)		1	Inadequate	3/27/03
		4		
		4		
		4		
		4		
		4		
		4		
		4		
		4		
		4		
		4		
		4		

ACTION CODES: (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").

Anil D. Pendse
Reviewer

Signature 4/31/03
Date

REMARKS AND CONCLUSION: Not approvable

ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes_____ No ___x____
Minor amendment

Spot? Yes_____, No____X___

Endorsements:

HFD-625/APendse/Review chemist/3/27/03 4/3/03

HFD-625/MSmela/Team leader/3/28/03

M Smela 4/4/03

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Chemistry Review: Not Approvable Minor

ANDA: 74-726/ S-009, S-011, S-015, S-016 and S-017 CR#3

NAME AND ADDRESS OF APPLICANT:
Upsher-Smith Laboratories, Inc.
Attn: Mark S. Robbins, Ph.D., J.D.
14905 23rd Avenue North
Minneapolis, MN 55447

Telephone: (763) 473-4412

PURPOSE OF SUPPLEMENT:
S-009: Reformulation of 10 mEQ and 20 mEQ tablets
S-011: Labeling for 10 mEQ & 20 mEQ tablets
S-015: Manufacturing Revision (Scale-up of (b) (4))
S-016: New Strength addition (15 mEQ via Suitability Petition)
S-017: Labeling for 15 mEQ tablet

DATE(S) OF SUBMISSION(S) and OTHERS(AMENDMENTS,TELECON OR OTHERS):
2/14/01 OS of S-009, S-011
5/6/02 OS of S-015, S-016, S-017
*12/6/02 Minor Amendment for all above (subject of this review)

NONPROPRIETARY NAME:
Potassium Chloride Extended-Release Tablets USP

PHARMACOLOGICAL CATEGORY	TRADE NAME
Potassium Supplementation	Klor-Con® M

DOSAGE FORM	POTENCY	RX OR OTC
Tablets	10 mEq & 20 mEq	R_x

REMARKS AND CONCLUSION:
Labeling Review: Satisfactory per Payne/Grace on 1/7/03
Bio Review: Pending for S-009 and S-016
Chemistry: Completed

Reviewer: Anil D. Pendse, Ph.D. **Date Completed:** 1/10/03

Following this page, 2 Pages Withheld in Full as (b)(4)

(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").

Anil D. Pendse, Ph.D. — Reviewer
Signature — Date: 1/15/03

REMARKS AND CONCLUSION: Chemistry completed pending bio review.

ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes_____ No ____X___
Minor amendment

Spot? Yes_____ No____X___

cc: ANDA 74-726/S-009,S-011,S-015,S-016,S-017 CR3
Division File
Field Copy

Endorsements:
HFD-625/APendse/Review Chemist/1/10/03 1/15/03
HFD-625/MSmela/Team Leader/1/10/03 1/15/03

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F/t by:
Chemistry Review: Closed

Bio unacceptable. Deficiencies faxed on 2/4/03. NA (minor) to issue. 2/4/03

There was no 'Chemistry Review No. 2' located in the files.

ANDA: 74-726/ S-009, S-011, S-015, S-016 and S-017

NAME AND ADDRESS OF APPLICANT:
Upsher-Smith Laboratories, Inc.
Attn: Mark S. Robbins, Ph.D., J.D.
14905 23rd Avenue North
Minneapolis, MN 55447

Telephone: (763) 473-4412

PURPOSE OF SUPPLEMENT:

(b) (4)

S-015: Manufacturing Revision (Scale-up of Coated Granules)
S-016: New Strength addition (15 mEQ via Suitability Petition)
S-017: Labeling for 15 mEQ tablet

DATE(S) OF SUBMISSION(S) and OTHERS(AMENDMENTS,TELECON OR OTHERS):

(b) (4): 2/14/01 Original submission (PAS) Vol. 6.1
S-015, S-016, S-017: 5/6/02 Original Submission (PAS) Vol. 10.1 includes amendment to S-009, S-011 and withdrawal request for S-010
S-015, S-016, S-017: 7/12/02 Amendment (Filing Issues)

NONPROPRIETARY NAME:
Potassium Chloride Extended-Release Tablets USP

PHARMACOLOGICAL CATEGORY	**TRADE NAME**
Potassium Supplementation	Klor-Con® M

DOSAGE FORM	**POTENCY**	**RX OR OTC**
Tablets	10 mEq, 15 mEq & 20 mEq	R_x

REMARKS AND CONCLUSION:
Labeling Review: Pending for S-017, Acceptable for S-011 by A. Pyane on 7/01.
Bio Review: Pending for S-009 and S-016
Chemistry: Not Acceptable. (b) (4) needs to be acknowledged

Reviewer: Anil D. Pendse, Ph.D. **Date Completed:** 9/19/02

Following this page, 11 Pages Withheld in Full as (b)(4)

adequate stability data will be generated according to the protocol and subsequently reported in the annual report or in a supplement.
Satisfactory

LABELING: Acceptable for S-011 per A. Pyane on 7/01. Pending for S-017

BIOEQUIVALENCY: Pending review for 5/6/02 amendment which includes response to deficiencies for S-009 and new strength (S-016).

37. **DMF CHECKLIST FOR ANDA # 74-726/S015, S016, S017 CR1**

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETE
[redacted] (b) (4)		3	Reviewed by M Shaikh on 7/9/01 and found adequate.	
		4		
		4		
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		4		
		4		
		4		
		4		
		4		

ACTION CODES: (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").

Anil D. Pendse, Ph.D.
Reviewer

Signature

10/22/02
Date

REMARKS AND CONCLUSION:

ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes____X_____ No _____
Spot? Yes_____, No____X___

cc: ANDA 74-726
Division File
Field Copy

Endorsements:

HFD-625/APendse/10/11/02 10/22/02
HFD-625/MSmela/10/11/02 M Smela 10/22/02

\\CDS008\WP51F99\FIRMSNZ\UPSHER\LTRS&REV\74726 S015,S016,S017Cr1

F/t by: gp/10/22/02

Chemistry Review: **Not Approved Minor**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-009, S-011, S-015, S-016 and S-017

BIOEQUIVALENCE REVIEWS

JUN 3 . 2003

Potassium Chloride Extended Release Tablets
Klor-Con^{R}, 10, 15 and 20 mEq
ANDA #74-726/SCR-011,009
ANDA #74-726/SCQ 016
Reviewer: Nhan L. Tran

Upsher-Smith
Minneapolis, MN
Submission Date:
February 7, 2003

REVIEW OF AMENDMENTS TO SUPPLEMENT

HISTORICAL BACKGROUND:

This submission is a response from firm to the deficiencies cited in the review of the supplements on January 24, 2003 (see review attached).

REVIEW OF THE AMENDMENT

REVIEW OF THE FIRM'S RESPONSES.

Deficiency 1.

For lot # 67454 (submission date March 2001) and lot # 66221 (submission date May 6, 2002) of 10 mEq ER tablet, it is not clear whether these lots are manufactured with approved formulation or with the proposed formulation. Please clarify.

Firm's response:
Lot # 67454: Approved formulation
Lot # 66221: Proposed formulation

FDA Comment: Acceptable

Deficiency 2.

For 20 mEq tablets, please provide half tablet dissolution data on lot # 18981 (test biolot—proposed formula) and lot # 9JNR808 (RLD biolot) using USP Apparatus 2 (paddle) at 50 RPM and 900 ml of water as the dissolution medium. Samples should be taken at 1, 2, 6, and 12 hours.

Firm's response:
Firm indicated that lot # 18981 was just a packaging lot number of the test biolot # 66210 (reformulated). Biolot # 66210 was packaged into packaging lot # 18981 (90 count bottles), packaging lot # 18982 (1000 count bottles) and packaging lot # 18996 (unit dose cartons of 100 tablets). Data on comparative dissolution of the half tablets of the biolots (test and RLD) are provided below:

Dissolution Method: USP Apparatus II (Paddle) at 50 RPM
Volume: 900 ml of water.

Products:

Test: Lot # 66210 (biolot)
Reference; Lot # 9JNR808 (RLD biolot)

Parameter	1 hour		2 hours		6 hours		12 hours	
	Test	Ref	Test	Ref	Test	Ref	Test	Ref
Av. (N=12)	25	24	43	44	86	93	105	106
Max.	(b) (4)							
Min.								
%CV	2.9	3.5	4.4	3.2	3.7	1.4	1.6	1.6

F2: 71

FDA Comment: Dissolution data of the half tablets of the test and reference tablets (biolots) are comparable. The response is acceptable.

Deficiency 3.

Please provide the lot size of the test biolot for 20 mEq ER tablet # 18981. Please also provide the date of manufacture of the lot # 18981 (biolot).

Firm's response:
As indicated in the response to the Deficiency #2, lot # 18981 was a packaging lot of the biolot # 66210 (reformulated). Biolot # 66210 was packaged into packaging lot # 18981 (90 count bottles), packaging lot # 18982 (1000 count bottles) and packaging lot # 18996 (unit dose cartons of 100 tablets). Lot # 66210 was manufactured in June 2000 and lot size was (b) (4) tablets.

FDA Comment: Acceptable

Deficiency 4.

For the approval of 15 mEq strength, firm is requested to provide the half tablet dissolution data on RLD lot # 9JNR808 using USP Apparatus 2 (paddle) at 50 RPM and 900 ml of water as the dissolution medium. Samples should be taken at 1, 2, 6, and 12 hours.

Firm's response:
Firm submitted the following data for its half tablet of 15 mEq tablet:

Dissolution Method: USP Apparatus II (Paddle) at 50 RPM
Volume: 900 ml of water.

Products:
Test: Lot 67135
Reference: Lot # 9JNR808 (RLD biolot)

Parameter	1 hour		2 hours		6 hours		12 hours	
	Test	Ref	Test	Ref	Test	Ref	Test	Ref
Av. (N=12)	25	24	41	44	83	93	101	106
Max.	[redacted] (b) (4)							
Min.								
%CV	5.1	3.5	5.4	3.2	6.4	1.4	2.8	1.6

F2: 61.5

FDA Comment: Acceptable

Waiver Request:

This supplement for a new strength is submitted via a suitability petition (Docket No. 01P-0108/CP1, approved on July 9, 2001). The reference products listed in the Citizen petition were K-Dur (potassium chloride) extended release tablets USP, 10 mEq AND 20 mEq, manufactured by Key Pharmaceuticals. The firm has requested a waiver of the in vivo bioequivalence study requirements for its potassium chloride extended release 15 mEq tablets.
To support the waiver request, the following information was submitted:

- Comparative formulation information
- Comparative dissolution in 4 different media.
- Comparative dissolution of the half tablet since the 15 mEq tablet is scored.

Reviewer's Comments:

1. The *in vivo* fasting bioequivalence study conducted by the firm on its 20 mEq tablet is acceptable.

2. The formulation of the firm's 15 mEq tablet is proportionally identical to that of the 20 mEq tablet with respect to active and inactive ingredients.

3. The dissolution data submitted by the firm are acceptable.

4. The waiver request for the firm's 10 and 15 mEq tablets can be granted.

Recommendations:

1. The *in-vivo* bioequivalence study conducted under fasting conditions by Upsher-Smith on its potassium chloride 20 mEq extended release tablet, lot #66210, comparing it to the reference product K-Dur® 20 mEq tablet, lot #9JNR808, manufactured by Key Pharmaceuticals, has been found to be acceptable to the Division of Bioequivalence. The results of that study demonstrate that under fasting conditions, the potassium chloride 20 mEq tablet manufactured by Upsher-Smith is bioequivalent to the reference product, K-Dur® 20 mEq tablet, manufactured by Key Pharmaceuticals.

2. The *in vitro* dissolution tests conducted by Upsher-Smith on its potassium chloride 20 mEq, 15 mEq and 10 mEq extended release tablets have been found acceptable by the Division of Bioequivalence. The dissolution testing should be conducted in 900 mL of water, using USP Apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

Tolerances:	1 hr	NLT (b)(4)% and NMT (b)(4)%
	2 hrs	NLT % and NMT %
	6 hrs	NLT % and NMT %
	12 hrs	NLT %

3. The waiver of bioequivalence requirement for the 10 and 15 mEq strengths of the test product is granted.

Nhan L. Tran, Ph. D.
Review Branch II

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR 6/3/2003

Concur: Date: 6/3/03
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 74-726 (original), HFD-655 (Nerurkar, Tran), Drug File, Division File

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-726/S-009,011,016 APPLICANT: Upsher-Smith

DRUG PRODUCT: Potassium Chloride Extended Release tablets

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

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water, using USP Apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

Tolerances:	1 hr	NLT (b) (4)% and NMT (b) (4)%	
	2 hrs	NLT % and NMT %	
	6 hrs	NLT % and NMT %	
	12 hrs	NLT %	

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,

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

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
HFD-651/Bio Drug File
HFD-655/Reviewer
HFD-655/TL

6/3/03

Endorsements: (Final with Dates)
HFD-655/ Reviewer
HFD-655/ Bio team Leader
HFD-650/ D. Conner 6/3/03

BIOEQUIVALENCY - ACCEPTABLE

Submission date: February 7,2003

1. **STUDY AMENDMENT (STA)**
(ANDA 74-726/S-011)
All Strengths
Outcome: **AC**

2. **DISSOLUTION DATA (DIS)**
(ANDA 74-726/S-015)
15 mEq Strength
Outcome: **AC**

Outcome Decisions: **AC** - Acceptable

WinBio Comments:

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

GENERIC NAME: **Potassium Chloride Extended Release** ANDA #: 74-726/S-011,016
SPONSOR: **Upsher-Smith Pharmaceutical**
DOSAGE FORM: Tablet
STRENGTH(S): 10 , 15 and 20 mEq
TYPES OF STUDIES: Fasting BE
CLINICAL STUDY SITE(S): MDS Pharma Services, Montreal, Canada
ANALYTICAL SITE(S): [redacted] (b) (4)

In-vivo and in-vitro studies are acceptable.
Waiver for 10 and 15 mEq strengths is granted.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic No New facility NA For cause NA Other	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: Nhan L. Tran, Ph.D. BRANCH: II
INITIAL : DATE : 6/3/03

TEAM LEADER : Shriniwas Nerurkar, Ph.D. BRANCH: II
INITIAL : DATE : 6/3/2003

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.
INITIAL : DATE : 6/3/03

MAR 11 2003

10-1

Potassium Chloride Extended Release Tablets
Klor-Con[R], 10, 15 and 20 mEq
ANDA #74-726/SCR-011,009
ANDA #74-726/SCQ 016
Reviewer: Nhan L. Tran

Upsher-Smith
Minneapolis, MN
Submission Date:
February 7, 2003

REVIEW OF AMENDMENTS TO SUPPLEMENT

HISTORICAL BACKGROUND:

This submission is a response from firm to the deficiencies cited in the review of the supplements on January 24, 2003 (see review attached).

REVIEW OF THE AMENDMENT

REVIEW OF THE FIRM'S RESPONSES.

Deficiency 1.

For lot # 67454 (submission date March 2001) and lot # 66221 (submission date May 6, 2002) of 10 mEq ER tablet, it is not clear whether these lots are manufactured with approved formulation or with the proposed formulation. Please clarify.

Firm's response:
Lot # 67454: Approved formulation
Lot # 66221: Proposed formulation

FDA Comment: Acceptable

Deficiency 2.

For 20 mEq tablets, please provide half tablet dissolution data on lot # 18981 (test biolot—proposed formula) and lot # 9JNR808 (RLD biolot) using USP Apparatus 2 (paddle) at 50 RPM and 900 ml of water as the dissolution medium. Samples should be taken at 1, 2, 6, and 12 hours.

Firm's response:
Firm indicated that lot # 18981 was just a packaging lot number of the test biolot # 66210 (reformulated). Biolot # 66210 was packaged into packaging lot # 18981 (90 count bottles), packaging lot # 18982 (1000 count bottles) and packaging lot # 18996 (unit dose cartons of 100 tablets). Data on comparative dissolution of the half tablets of the biolots (test and RLD) are provided below:

Revise A

Dissolution Method: USP Apparatus II (Paddle) at 50 RPM
Volume: 900 ml of water.

Products:

Test: Lot # 66210 (biolot)
Reference; Lot # 9JNR808 (RLD biolot)

Parameter	1 hour		2 hours		6 hours		12 hours	
	Test	Ref	Test	Ref	Test	Ref	Test	Ref
Av. (N=12)	25	24	43	44	86	93	105	106
Max.	[redacted] (b) (4)							
Min.								
%CV	2.9	3.5	4.4	3.2	3.7	1.4	1.6	1.6

F2: 71

FDA Comment: Dissolution data of the half tablets of the test and reference tablets (biolots) are comparable. The response is acceptable.

Deficiency 3.

Please provide the lot size of the test biolot for 20 mEq ER tablet # 18981. Please also provide the date of manufacture of the lot # 18981 (biolot).

Firm's response:
As indicated in the response to the Deficiency #2, lot # 18981 was a packaging lot of the biolot # 66210 (reformulated). Biolot # 66210 was packaged into packaging lot # 18981 (90 count bottles), packaging lot # 18982 (1000 count bottles) and packaging lot # 18996 (unit dose cartons of 100 tablets). Lot # 66210 was manufactured in June 2000 and lot size was [redacted] (b) (4) tablets.

FDA Comment: Acceptable

Deficiency 4.

For the approval of 15 mEq strength, firm is requested to provide the half tablet dissolution data on RLD lot # 9JNR808 using USP Apparatus 2 (paddle) at 50 RPM and 900 ml of water as the dissolution medium. Samples should be taken at 1, 2, 6, and 12 hours.

Firm's response:
Firm submitted the following data for its half tablet of 15 mEq tablet:

Dissolution Method: USP Apparatus II (Paddle) at 50 RPM
Volume: 900 ml of water.

Products:
Test: Lot 67135
Reference: Lot # 9JNR808 (RLD biolot)

Parameter	1 hour		2 hours		6 hours		12 hours	
	Test	Ref	Test	Ref	Test	Ref	Test	Ref
Av. (N=12)	25	24	41	44	83	93	101	106
Max.	[redacted] (b) (4)							
Min.								
%CV	5.1	3.5	5.4	3.2	6.4	1.4	2.8	1.6

F2: 61.5

FDA Comment: Acceptable

Waiver Request:

This supplement for a new strength is submitted via a suitability petition (Docket No. 01P-0108/CP1, approved on July 9, 2001). The reference products listed in the Citizen petition were K-Dur (potassium chloride) extended release tablets USP, 10 mEq AND 20 mEq, manufactured by Key Pharmaceuticals. The firm has requested a waiver of the in vivo bioequivalence study requirements for its potassium chloride extended release 15 mEq tablets.
To support the waiver request, the following information was submitted:

- Comparative formulation information
- Comparative dissolution in 4 different media.
- Comparative dissolution of the half tablet since the 15 mEq tablet is scored.

Reviewer's Comments:

1. The *in vivo* fasting bioequivalence study conducted by the firm on its 20 mEq tablet is acceptable.

2. The formulation of the firm's 15 mEq tablet is proportionally identical to that of the 20 mEq tablet with respect to active and inactive ingredients.

3. The dissolution data submitted by the firm are acceptable.

4. The waiver request for the firm's 15 mEq tablet can be granted.

Recommendations:

1. The *in-vivo* bioequivalence study conducted under fasting conditions by Upsher-Smith on its potassium chloride 20 mEq extended release tablet, lot #66210, comparing it to the reference product K-Dur® 20 mEq tablet, lot #9JNR808, manufactured by Key Pharmaceuticals, has been found to be acceptable to the Division of Bioequivalence. The results of that study demonstrate that under fasting conditions, the potassium chloride 20 mEq tablet manufactured by Upsher-Smith is bioequivalent to the reference product, K-Dur® 20 mEq tablet, manufactured by Key Pharmaceuticals.

2. The *in vitro* dissolution tests conducted by Upsher-Smith on its potassium chloride 20 mEq, 15 mEq and 10 mEq extended release tablets have been found acceptable by the Division of Bioequivalence. The dissolution testing should be conducted in 900 mL of water, using USP Apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

Tolerances:	1 hr	NLT (b)(4)% and NMT (b)(4)%
	2 hrs	NLT % and NMT %
	6 hrs	NLT % and NMT %
	12 hrs	NLT %

3. The waiver of bioequivalence requirement for the 15 mEq strength of the test product is granted.

Nhan L. Tran, Ph. D.
Review Branch II

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR 3/6/2003

Concur: Date: 3/11/03
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 74-726 (original), HFD-655 (Nerurkar, Tran), Drug File, Division File

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-726/S-009,011,016 APPLICANT: Upsher-Smith

DRUG PRODUCT: Potassium Chloride Extended Release tablets

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

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water, using USP Apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

Tolerances:	1 hr	NLT (b) (4)% and NMT	(b) (4)%
	2 hrs	NLT % and NMT	%
	6 hrs	NLT % and NMT	%
	12 hrs	NLT %	

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,

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

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
HFD-651/Bio Drug File
HFD-655/Reviewer
HFD-655/TL

8/6/03

Endorsements: (Final with Dates)
HFD-655/ Reviewer
HFD-655/ Bio team Leader
HFD-650/ D. Conner 3/11/03

BIOEQUIVALENCY - ACCEPTABLE

Submission date: February 7, 2003

1. **STUDY AMENDMENT (STA)**
(ANDA 74-726/~~S-011~~ 9)
All Strengths
Outcome: **AC**

2. **DISSOLUTION DATA (DIS)**
(ANDA 74-726/S-~~015~~ 16)
15 mEq Strength
Outcome: **AC**

Outcome Decisions: **AC** - Acceptable

WinBio Comments:

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

GENERIC NAME: **Potassium Chloride Extended Release** ANDA #: 74-726/S-011,016
SPONSOR: **Upsher-Smith Pharmaceutical**
DOSAGE FORM: Tablet
STRENGTH(S): 10 , 15 and 20 mEq
TYPES OF STUDIES: Fasting BE
CLINICAL STUDY SITE(S): MDS Pharma Services, Montreal, Canada
ANALYTICAL SITE(S): [redacted] (b) (4)

In-vivo and in-vitro studies are acceptable.
Waiver for 15 mEq strength is granted.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic No New facility NA For cause NA Other	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Nhan L. Tran, Ph.D. BRANCH: II
INITIAL : _____ DATE : 3/6/03

TEAM LEADER : Shriniwas Nerurkar, Ph.D. BRANCH: II
INITIAL : _____ DATE : 3/6/2003

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.
INITIAL : _____ DATE : 3/11/03

JAN 24 2003

Potassium Chloride Extended Release Tablets
Klor-Con^{R}, 15 mEq
ANDA #74-726/SCR-015
ANDA #74-726/SCQ 016
Reviewer: Nhan L. Tran

Upsher-Smith
Minneapolis, MN
Submission Dates:
May 6, 2002
July 12, 2002

REVIEW OF AMENDMENTS TO SUPPLEMENT (SCR-015 and SCQ-016)

HISTORICAL BACKGROUND:

The firm previously conducted an acceptable in-vivo bioequivalence study on its test product, Potassium Chloride Extended Release 20 mEq Tablets and received Agency approval on November 20, 1998. The firm submitted a waiver request (Supplements 001 and 002) for its Potassium Chloride Extended Release 10 mEq Tablets based on acceptable dissolution testing on the test and reference products of 10 mEq tablets, and proportional compositions of 10 mEq and 20 mEq tablets of the test product. The waiver request for Potassium Chloride Extended Release 10 mEq Tablets was approved on August 9, 2000. Subsequently, the firm submitted a series of supplements and a summary of those supplements is given below:

Suppl. #	Date	Nature of submission	Approval date	Note
S-001/002	8/5/1999	Request waiver for 10 mEq strength	8/9/2000	No biostudy was required
S-003	4/21/2000	In-process accountability specification changes associated with the manufacture of (b) (4).	10/10/2000	Submitted to Chem. Division (SUPAC)
S-004	8/25/2000	Adding (b) (4) as an alternate analytical testing	Annual Report- CBE-30	Submitted to Chem. Division
S-005/006 /007/008	9/14/2000	Submitted as a CBE-30 for scale up, equipment and process changes, tablet deboss change for Klor-Con M20, and addition of a 90- count bottle for Klor-Con M10 and M20.	Approved	Submitted to Chem. Division (SUPAC) and DBE
(b) (4)	2/14/2001	Firm wants to remove sorbitan monooleate from the formulation	A BE study is needed. Review is underway. Approval pending.	BE study submitted on 20meq strength
S-012/013 /014	10/05/2001	Submitted as a CBE-30 for scale up, equipment and process changes	3/26/02	Chemistry OK
S-015	5/6/02	Responses to Bioequivalence deficiencies (b) (4)	This review	
S-016	7/12/2002	Addition of new strength (15 mEq)	This review	

REVIEW OF SUPPLEMENTS S-015 and S-016

This submission has two main components.

1. The first component contains the firm's response to the deficiencies that were communicated to the firm.
2. The second component has a request for the approval of a new strength viz. 15 mEq ER tablet.

A. Review of Supplement S-015: Submission date: 5/6/02.

Firm's responses to DBE Deficiencies of 11/26/01.

Summary: Upsher-Smith wanted to remove a non-release controlling excipient, sorbitan monooleate from its currently approved formulation. A BE study was submitted on 02/14/2001 to compare the bioavailability of reformulated Upsher-Smith's potassium chloride 20 mEq ER tablet (lot # 18981) to the RLD (lot # 9JNR808, expiration date 10/2001), Key's K-Dur® 20 mEq, in healthy volunteers under fasting conditions (Protocol # P00-002 and Project #00327).
The clinical portion of the study was conducted by MDS Pharma Services, Montreal, Canada from 7/15 - 7/31/2000. The analytical portion was conducted by (b) (4) (b) (4) from 8/8 - 8/23/2000.
(Note the 20 mEq ER tablet is scored while the 10 mEq ER tablet is not scored).
This study was reviewed by the DBE and found it deficient. Deficiencies were communicated to the firm and the firm's responses are provided below:

REVIEW OF THE FIRM'S RESPONSES.

I. Analytical Methodology deficiencies:

Deficiency 1. The firm has not submitted any selectivity data to show that the presence other ions such as NaCl, Na_2SO4, and CsCl do not interfere with the determination of urinary potassium. The firm is requested to submit a complete documentation of assay selectivity.

Firm's response: Firm indicated that specificity and selectivity were demonstrated during the validation. Validation report is attached in this submission.
FDA Comment: Acceptable

Deficiency 2. The firm has used a solution of CsCl instead of blank urine with known level of potassium (as stated in its SOP) for the sample dilution. The firm should justify the use of CsCl solution and provide appropriate validation that links CsCl dilution to dilution by blank urine.

Firm's response: Due to the fact that the endogenous level of potassium in urine is high and variable, the use of blank urine for sample dilution is not possible. The use of a CsCl solution to dilute samples has been used by the firm and was evaluated in the validation process and the validation demonstrated acceptable results. The use of CsCl for sample dilution was described in the firm's SOP (b) (4), which superceded general SOP (b) (4). Hence, there was no deviation from any SOP.
FDA Comment: Acceptable.

Deficiency 3. The firm is requested to submit all pertinent analytical SOPs including the SOPs for sample repeat and sample dilution (SOP (b) (4)).

Firm's response: All requested SOPs were provided.
FDA Comment: No deviation was found, and the response is acceptable.

II. In vivo Bioequivalence Study deficiencies:

Deficiency 1. Please provide the baseline urinary potassium excretion (mEq) at 0-1, 1-2, 2-4,4-6, 6-8, 8-12, 12-16, 16-24, 24-36, and 36-48 hours; cumulative excretions Ae 0-24, and Ae 0-48 as individual and mean (with %CV) values for all 35 subjects, in both periods.

Firm's response: Requested data was provided.
FDA Comment: From the data provided, the reviewer re-ran SAS and 90 %C.I. of parameters. The firm results and the reviewer's results are in agreement. The response is acceptable.

Deficiency 2. Please provide an explanation of the method of baseline adjustment used for all pharmacokinetic parameters.

Firm's response: Predose amount excreted (Ae) and predose rate of excretion (Re) of the 2 baseline days were averaged (mean baseline). The adjustment was performed by subtracting the mean baseline from post dose Ae and Re.
FDA Comment: The response is adequate and acceptable.

Deficiency 3. Please provide an explanation for deleting potassium excretion values based on inadequate creatinine clearance and documentation of the statistical test used to determine outlier.

Firm's response: MNR (maximum normed residual) test was used for outlier detection. This is the firm's routine method for outlier testing (SOP (b) (4)). The firm stated that the FDA Division of Scientific Investigation (DSI) has audited the procedure (Dr. Michael Skelly) and found it acceptable.
FDA Comment: The response is acceptable.

Deficiency 4. Please provide the ANOVA and 90% C.I on data without deleting any potassium excretion value.

Firm's response: Data was submitted as requested in the diskette.
FDA Comment: The response is satisfactory.

III. In-vitro Dissolution Study deficiencies:

Deficiency 1. The firm requests a waiver for the reformulated 10 mEq strength. Per SUPAC-MR Guidance, Components and Composition--Nonrelease controlling excipient --Level 3 change, the firm is requested to submit comparative dissolution data for the potassium extended release tablet 10 mEq in various dissolution media (0.1N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8) for evaluation.

Firm's response: The firm indicated that the requested data was provided in March 2001. Also in this submission, the following data was provided:

Test Product: KlorCon, 10 mEq tablets, **Lot # 66211**, Upsher-Smith (proposed formulation)
Reference Product: K-Dur 10 mEq, **Lot # 9XBJ666**, Key Pharmaceuticals (same lot as used in the submission dated 2-14-2001).

Dissolution Method: USP Apparatus II (Paddle) at 50 RPM
Volume: 900 ml of various media: 0.1 N HCl, pH 4.5 and 6.8 buffer and water.

a. 0.1N HCl

Parameter	1 hour		2 hours		4 hours		6 hours		8 hours	
	Test	Ref	Test	Ref	Test	Ref	Test	Ref	Test	Ref
Av. (N=12)	25.1	21.6	40.5	37.1	67.6	66.5	84.5	83.1	95	93.4
Max.										(b) (4)
Min.										
%CV	4.6	5.5	3.5	3.8	3.2	2.3	2.2	2.9	1.4	2.3

F2: 79

b. 0.05M acetate buffer, pH 4.5

Parameter	1 hour		2 hours		4 hours		6 hours		8 hours	
	Test	Ref	Test	Ref	Test	Ref	Test	Ref	Test	Ref
Av. (N=12)	24.5	22.8	41	41.4	70.3	71.5	89.7	91.9	102	93.6
Max.										(b) (4)
Min.										
%CV	1.9	2.7	2.5	2	1.3	1.7	2.4	1.8	2.4	2

F2:69

c. 0.5M Phosphate buffer, pH 6.8

Parameter	1 hour		2 hours		4 hours		6 hours		8 hours	
	Test	Ref	Test	Ref	Test	Ref	Test	Ref	Test	Ref
Av. (N=12)	26.2	21.3	43.2	37.8	70.4	66.9	88	87	98.2	99
Max.										(b) (4)
Min.										
%CV	4.4	3.5	2.4	2.2	1.5	1.4	1.5	1.9	1.6	1.6

F2: 71

d. Water

Parameter	1 hour		2 hours		4 hours		6 hours		8 hours	
	Test	Ref	Test	Ref	Test	Ref	Test	Ref	Test	Ref
Av. (N=12)	25.9	19.4	41.7	37.5	69	66.3	88	82.2	97.3	93.7
Max.										(b) (4)
Min.										
%CV	2.5	10.3	3.4	6.8	1.4	3.9	1.6	3.4	1.1	2.5

F2: 66

FDA Comment: Data submitted in March 2001 was from a different lot (lot # 67454), not from lot # 66211 as reported in this submission. The firm is requested to clarify the difference between lot # 67454 (approved formulation?) and lot # 66211 (proposed formulation?).

Deficiency 2. Since potassium chloride extended release tablets 20 mEq are scored, the firm is requested to submit dissolution data on the half tablet, using water as dissolution medium and paddle at 50 RPM. Samples should be taken at 1, 2, 6 and 12 hours.

Firm's response: Firm submitted the following data for its half tablet of 20 mEq tablet:
Test: **Lot # 66210** (proposed) not the biolot (#18981)
Ref: **Lot # 68580** (approved)

Method: Paddle at 50 RPM, 900 ml of water as a dissolution medium.

Parameter	1 hour		2 hours		6 hours		12 hours	
	Test	Ref	Test	Ref	Test	Ref	Test	Ref
Av. (N=12)	25	20	43	33	86	73	105	102
Max.	(b) (4)							
Min.								
%CV	2.9	4.3	4.4	5.4	3.7	3.9	1.6	3.5

F2: 53

FDA Comment: The firm did not use test and RLD biolots for this comparative dissolution testing. The should provide the comparative dissolution of the half tablet of 20 mEq strength of the biolots (test and RLD) or explain why these lots (# 18981 and 9JNR808) were not used.

Deficiency 3. Information on the size of the biobatch of the test product is missing.

Firm's response: Firm reported the following information:
For 20 mEq tablets: Lot # 66210, lot size: (b) (4) tablets.
For 10 mEq tablet: Lot # 66211, lot size (b) (4) tablets.
For 15 mEq tablet: Lot # 67135, lot size (b) (4) tablets.
FDA Comment: The firm is requested to provide the size of Lot # 18981 (biolot).

B. Review of Supplement S-016:
Review A Request to add a new strength (15 mEq)

(Submission date: July 12, 2002).

The firm has requested a waiver of the in vivo bioequivalence study requirements for its new strength: Potassium chloride extended release 15 mEq tablets. This supplement for a new strength is submitted via a suitability petition (Docket No. 01P-0108/CP1, approved on July 9, 2001). The reference products listed in the Citizen petition were K-Dur (potassium chloride) extended release tablets USP, 10 mEq AND 20 mEq, manufactured by Key Pharmaceuticals. Per OGD Regulatory Support Branch's request, the DBE has examined the waiver request and has determined that the waiver meets statutory requirements (6/25/2002).

To support the waiver request, the following information was submitted:

- Comparative formulation information
- Comparative dissolution in 4 different media.

Review of the waiver request:

Comparative formulations:

The firm provides the following:

Component Description	Proposed Formulation		
(mg/tablet)	**10 mEq**	**15 mEq**	**20 mEq**
Potassium Chloride, USP	750 mg	1125 mg	1500 mg
Ethyl Cellulose, NF			(b) (4)
Microcrystalline Cellulose, NF			
Croscarmellose Sodium, NF			
TOTAL TABLET WEIGHT			

Comments:

a. Formulations of 10 mEq, 15 mEq and 20 mEq are proportional with respect to active and inactive ingredients.

b. The firm's 10 mEq tablet strength was approved by the OGD based on dissolution data and formulation information.

Comparative dissolution:

To support the new strength, the firm has provided the comparative dissolution data in multiple pH dissolution media between the new strength and the RLD. Also, since the new strength is scored, dissolution of the half tablet is provided.

Review of dissolution data:

Test Product: KlorCon, 15 mEq tablets, Lot 67135, Upsher-Smith (proposed formulation)

Reference Product: K-Dur 20 mEq, lot 9JNR808, Key Pharmaceuticals. (biolot)

Note : Dissolution data on RLD are different from the data submitted on 2-14-2001. This lot had the expiration date of 10/2001. The dissolution data was probably obtained on the expired biolot of RLD.

Dissolution Method: USP Apparatus II (Paddle) at 50 RPM
Volume: 900 ml of various media: 0.1 N HCl, pH 4.5 and 6.8 buffer and water.

a. 0.1N HCl

Parameter	1 hour		2 hours		4 hours		6 hours		8 hours	
	Test	Ref	Test	Ref	Test	Ref	Test	Ref	Test	Ref
Av. (N=12)	21	19	35	35	57	64	72	81	87	91
Max.	[redacted] (b) (4)									
Min.										
%CV	3.9	3	1.6	2.2	2.1	9.5	1.1	2.4	1.2	1.9

F2: 63

b. 0.05M acetate buffer, pH 4.5

Parameter	1 hour		2 hours		4 hours		6 hours		8 hours	
	Test	Ref	Test	Ref	Test	Ref	Test	Ref	Test	Ref
Av. (N=12)	22	24	37	43	61	72	79	86	91	94
Max.	[redacted] (b) (4)									
Min.										
%CV	4.5	3.6	2.6	2.8	2.2	2	2	1.1	1.4	0.9

F2: 59

c. 0.5M Phosphate buffer, pH 6.8

Parameter	1 hour		2 hours		4 hours		6 hours		8 hours	
	Test	Ref	Test	Ref	Test	Ref	Test	Ref	Test	Ref
Av. (N=12)	20	21	36	39	62	65	72	81	86	93
Max.	[redacted] (b) (4)									
Min.										
%CV	3.9	4.9	6	2.4	2.3	1.8	2	1.2	1.3	1.1

F2: 63

d. Water

Parameter	1 hour		2 hours		4 hours		6 hours		8 hours	
	Test	Ref	Test	Ref	Test	Ref	Test	Ref	Test	Ref
Av. (N=12)	23	22	41	41	66	70	86	88	96	97
Max.	[redacted] (b) (4)									
Min.										
%CV	3.6	3.2	1.5	3.4	4.6	1.7	3.4	1.5	4.3	1.4

F2: 82

Dissolution for the half tablet:

Firm's response: Firm submitted the following data for its half tablet of 15 mEq tablet:

Test: Lot 67135
Ref: Not reported

Dissolution Method: USP Apparatus II (Paddle) at 50 RPM
Volume: 900 ml of various media: 0.1 N HCl, pH 4.5 and 6.8 buffer and water.

Parameter	1 hour		2 hours		6 hours		12 hours	
	Test	Ref	Test	Ref	Test	Ref	Test	Ref
Av. (N=12)	25		41		83		101	
Max.	[redacted] (b) (4)							
Min.								
%CV	5.1		5.4		6.4		2.8	

Comment:

Dissolution data is incomplete. Comparative dissolution data of the half tablet of the test product, Klor-Con, 15 mEq tablets, Lot #67135, and the half tablet of the innovator product, K-Dur 20 mEq, lot #9JNR808, Key Pharmaceuticals, is requested.

SUMMARY OF COMMENTS:

The review of the first component viz. the firm's response to the deficiencies.

1. There were three deficiencies pertaining to the analytical methodological sections. The firm has provided acceptable response to the deficiencies.

2. There were four deficiencies in the *in vivo* bioequivalence study section. The firm has provided acceptable responses to the deficiencies.

3. There were three deficiencies in the *in vitro* dissolution study section. The firm has not provided satisfactory responses to these deficiencies.

The review of the second component viz. the firm's request for the approval of a new strength (15 mEq)

4. The firm has requested an approval of its new strength viz. 15 mEq ER tablet. The comparative dissolution testing data submitted for the approval of this new strength were deficient.

RECOMMENDATIONS:

1. The firm's response to the three deficiencies pertaining to the analytical methodology section and the four deficiencies pertaining to the in vivo bioequivalence study section is acceptable.

2. The firm's response to three deficiencies in the in vitro dissolution study section is incomplete. The deficiencies in the firm's response are shown below.

a) In the response to the deficiency 1, the firm has provided dissolution data on lot # 67454 (submission date March 2001) and lot # 66221 (submission date May 6, 2002) of 10 mEq ER tablet. It is not clear whether these lots are manufactured with approved formulation or with the proposed formulation. The firm should provide that information with dates of manufacture of the lots and the date(s) on which the dissolution testing was conducted.

b) In response to the deficiency 2, the firm has provided the half tablet dissolution data on 20 mEq ER tablet lot #s 66210 (proposed) and 68580 (approved). The firm should provide the half tablet dissolution data on lot # 18981 (test biolot) and # 9JNR808 (RLD biolot) using USP Apparatus 2 (paddle) at 50 RPM and 900 ml of water as the dissolution medium. Samples should be taken at 1, 2, 6, and 12 hours.

c) In response to the deficiency 3, the firm has provided lot sizes of lot # 66210 (20 mEq), #66211 (10 mEq) and # 67135(15 mEq). The firm should to provide the lot size of the test biolot for 20 mEq ER tablet # 18981. Please also provide the date of manufacture of 20 mEq ER tablet lot # 18981 (biolot).

3. The firm's request for the approval of the 15 mEq ER tablet is denied at this time. For the approval of this strength the firm has correctly provided the multimedia comparative dissolution testing on full tablets of test (lot # 67135) and RLD (20 mEq K-Dur biolot #9JNR808). However, the firm has provided the dissolution testing data only on the half test tablet (lot # 67135). The firm did not provide the half tablet dissolution data on RLD (20 mEq ER tablet lot # 9JNR808). Please, provide the half tablet dissolution data on RLD lot # 9JNR808 (**see recommendation 2b**) using USP Apparatus 2 (paddle) at 50 RPM and 900 ml of water as the dissolution medium. Samples should be taken at 1, 2, 6, and 12 hours.

1/21

Nhan L. Tran, Ph. D.
Review Branch II

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR

1/22/2003

Concur: _____ Date: 1/24/03
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 74-726 (original), HFD-655 (Nerurkar, Tran), Drug File, Division File

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
HFD-651/Bio Drug File
HFD-655/Reviewer
HFD-655/Team Leader

1/22/03

Endorsements: (Final with Dates)
HFD-655/Reviewer
HFD-655/Bio team Leader
HFD-650/D. Conner 1/24/03

BIOEQUIVALENCY - INCOMPLETE

Submission dates:
May 6, 2002 (ANDA 74-726/S-015)
July 12, 2002 (ANDA 74-726/S-016)

1. **STUDY AMENDMENT (STA)**
(ANDA 74-726/**S-015**)

20 mEq Strength
Outcome: **IC**

2. **DISSOLUTION DATA (DIS)**
(ANDA 74-726/**S-016**)

15 mEq Strength
Outcome: **IC**

Outcome Decisions: **IC** - Incomplete

WinBio Comments:

BIOEQUIVALENCY DEFICIENCIES

ANDA: 74-726/S015 (reformulated) and S016 (new strength) APPLICANT: Upsher-Smith

DRUG PRODUCT: Potassium Chloride Extended Release Tablets, USP Klor-Con^{R}) 10, 15 and 20 mEq

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet and has the following comments:

1. Your response to the three deficiencies pertaining to the analytical methodology section and the four deficiencies pertaining to the in vivo bioequivalence study section is acceptable.

2. Your response to three deficiencies in the in vitro dissolution study section is incomplete. The deficiencies in your response are shown below.

   a) In the response to the deficiency 1, you have provided dissolution data on lot # 67454 (submission date March 2001) and lot # 66221 (submission date May 6, 2002) of 10 mEq ER tablet. It is not clear whether these lots are manufactured with approved formulation or with the proposed formulation. Please provide that information with dates of manufacture of the lots and the date(s) on which the dissolution testing was conducted.

   b) In response to the deficiency 2, you have the half tablet dissolution data on 20 mEq ER tablet lot # 66210 (proposed) and # 68580 (approved). You should provide the half tablet dissolution data on lot # 18981 (test biolot) and # 9JNR808 (RLD biolot) using USP Apparatus 2 (paddle) at 50 RPM and 900 ml of water as the dissolution medium. Samples should be taken at 1, 2, 6, and 12 hours.

   c) In response to the deficiency 3, you have provided lot sizes of lot # 66210 (20 mEq), #66211 (10 mEq) and # 67135(15 mEq). You should provide the lot size of the test biolot for 20 mEq ER tablet # 18981. Please also provide the date of manufacture of 20 mEq ER tablet lot # 18981 (biolot).

4. Your request for the approval of the 15 mEq ER tablet is denied at this time. For the approval of this strength you have correctly provided the multimedia comparative dissolution testing on full tablets of test (lot#67135) and RLD (20 mEq K-Dur biolot #9JNR808).

However, you have provided the dissolution testing data only on the half test tablet (lot # 67135). You did not provide the half tablet dissolution data on RLD (20 mEq ER tablet lot # 9JNR808). Please, provide the half tablet dissolution data on RLD lot # 9JNR808 (see recommendation 2b) using USP Apparatus 2 (paddle) at 50 RPM and 900 ml of water as the dissolution medium. Samples should be taken at 1, 2, 6, and 12 hours.

Sincerely yours,

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

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
HFD-651/Bio Drug File
HFD-655/Reviewer
HFD-655/Team Leader

Endorsements: (Final with Dates)
HFD-655/Reviewer 1/23/03
HFD-655/Bio team Leader
HFD-650/D. Conner 1/24/03

BIOEQUIVALENCY - INCOMPLETE

Submission dates:
May 6, 2002 (ANDA 74-726/S-015)
July 12, 2002 (ANDA 74-726/S-016)

1. **STUDY AMENDMENT (STA)**
(ANDA 74-726/**S-015**)
20 mEq Strength
✓ Outcome: **IC**

2. **DISSOLUTION DATA (DIS)**
(ANDA 74-726/**S-016**)
✓ 15 mEq Strength
✓ Outcome: **IC**

Outcome Decisions: **IC** - Incomplete

WinBio Comments:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-009, S-011, S-015, S-016 and S-017

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 74-726/S-016 Applicant Upsher-Smith Laboratories, Inc.
Drug Potassium Chloride Strength 15 mEq
Extended-Release Tablets

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

REVIEWER:	DRAFT Package	FINAL Package
1. Project Manager, PETER CHEN	Date 5/9/03	Date
Review Support Br/ Team 2	Initials CC	Initials

Application Summary:

Original Rec'd date 5/7/02
Date Acceptable for Filing
Patent Certification (type) IV
Date Patent/Exclus.expires 9/5/06
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
(If YES, Pediatric Exclusivity Tracking System (PETS)
RLD =
Date checked _____ NDA# _____
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☐ OAI ☐
Date of EER Status N.A.
Date of Office Bio Review 3/11/03
Date of Labeling Approv. Sum 11/4/02
Date of Sterility Assur. App. NA.
Methods Val. Samples Pending Yes ☐ No ☒
Commitment Rcd., from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐
* INTERIM DISSOL. SPECS NOT INCLUDED IN AP LETTER.

Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def./N/A Minor issued ☐ Date
Comments:

(b) (4)

2. Gregg Davis (PIV ANDAs Only) Date 5/23/03 Date
Deputy Director, DLPS Initials P.M.P Initials

Contains GDEA certification: Yes ☒ No ☐
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☒
Has case been settled: Yes ☐ No ☐
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Comments:

Determ. of Involvement? Yes ☒ No ☐
Pediatric Exclusivity System
Date Checked 5/23/03
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐

Entered into licensing agreement for '943 patent

15 mEq ready for full approval. Received copies of return receipts on 5/22/03. RR dated 7/20/02. Also copy of licensing agreement to market 15 meq.

3. Div. Dir./Deputy Dir. Date Date
Chemistry Div. I Initials Initials
Comments:

OGD APPROVAL ROUTING SUMMARY

ANDA # 74-726/S-016 **Applicant** Upsher-Smith Laboratories, Inc.
Drug Potassium Chloride Extended-Release Tablets **Strength** 15 mEq

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

REVIEWER:

1. Project Manager, PETER CHEN
   Review Support Br/ Team 2

DRAFT Package
Date 5/9/03
Initials PC

FINAL Package
Date 5/27/03
Initials PC

Application Summary:

Original Rec'd date 5/7/02
Date Acceptable for Filing
Patent Certification (type) IV
Date Patent/Exclus.expires 9/5/06
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
(If YES, Pediatric Exclusivity Tracking System (PETS)
RLD =
Date checked _____ NDA# _____
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☐ OAI ☐
Date of EER Status N.A.
Date of Office Bio Review 3/11/03
Date of Labeling Approv. Sum 11/4/02
Date of Sterility Assur. App. NA
Methods Val. Samples Pending Yes ☐ No ☒
Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐
* INTERIM DISSOL. SPECS NOT INCLUDED IN AP LETTER

Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____
Comments:

(b) (4)

2. Gregg Davis **PRIV ANDAs Only**
   Deputy Director, DLPS

Date 6/5/03
Initials RLL

Date _____
Initials _____

Contains GDEA certification: Yes ☒ No ☐
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☐ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐
Date settled:
Is applicant eligible for 180 day Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Comments:

Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
Date Checked N/A
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

PIV (15 mEq strength) RLD = Klor-Con Extended-release Tablets Key Pharmaceuticals, Inc. (500, 5011) 20 mEq NDA #19-435 (001)

PIV for -743 received 5/7/02 in Key 7/20/02
letter from Schering stating that 15mEq strength can be considered in the 1997 licensing agreement - not sued w/in 45 days - OK for full approval

3. Div. Dir./Deputy Dir.
   Chemistry Div. I
   Comments:

Date 5/28
Initials RS

Date 5/29
Initials

OK for new strength specs are in CR 2
DMF now OK

REVIEWER:	DRAFT Package	FINAL Package
4. Frank Holcombe Assoc. Dir. For Chemistry Comments: (First generic drug review) N/A	Date_____ Initials_____	Date_____ Initials_____
5. Peter Rickman Director, DLPS	Date 6/5/03 Initials [illegible]	Date 6/5/03 for Initials [illegible]

Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐

Comments: Bio study of reformulated 20mg product v. 12LD (S009, S011) found acceptable 6/3/03. Dissolution data found acceptable. Waiver granted to lower strength. Bio study conducted by HDS Pharma Services (closing [redacted] (b) (4)). This facility has an acceptable OSI systemic history. Office Level bio endorsed 6/3/03.

Bio study waiver request for additional (5mg strength, granted on the basis of the acceptable bio study/dissolution data for the previously approved 20mg strength. Dissolution studies on all 3 strengths found acceptable. Office Level bio endorsed 6/3/03. FPL found acceptable 11/9/02. (5mg additional strength). CMC found satisfactory 4/28/03. EES not needed per 2/18/03 e-mail (F. Fajng).

OR

5. Robert L. West Deputy Director, OGD	Date 6/5/03 Initials [illegible]	Date_____ Initials_____

Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐

Comments: Approval of new strength (15mg) based upon approved Suitability Petition (01-P-0108) CP-1 approved 1/9/01. Upsher-Smith made a paragraph III certification to the '243 patent. Upsher-Smith entered into a license agreement with Schering-Plough Corp to provide for the marketing of OS's 10mg and 20mg tablets. In a letter dated 4/29/02 Schering concurred that the 15mg tablet strength is covered by the earlier licensing agreement (6/97).

These supplemental applications (S009, S011, S-015, S016, and S017) are recommended for approval

6. Gary Buehler Director, OGD Comments: 15mg strength (S-016)	Date_____ Initials_____	Date 6/6/03 Initials [illegible] for

First Generic Approval X PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

7. Project Manager, Peter Chen Review Support Br Team	Date 6/4/03 Initials PC	Date 6/6/03 Initials PC

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:

12:21 Time notified of approval by phone 12:47 Time approval letter faxed

FDA Notification:

6/4/03 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

6/4/03 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

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ANDA: 74-726/S-009, S-011, S-015, S-016 and S-017

Upsher-Smith Laboratories, Inc.
Attn: Mark S. Robbins, Ph.D., J.D.
14905 23rd Avenue North
Minneapolis, MN 55447

APR -4 2003

Dear Sir:

This is in reference to your supplemental new drug applications dated February 14, 2001 (S-009 and S-011) and May 6, 2002 (S-015, S-016 and S-017) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Klor-Con® M, Potassium Chloride Extended-Release Tablets, USP 10 mEq and 20 mEq.

Reference is also made to your amendment dated February 7, 2003.

The supplemental applications, submitted as "Prior Approval Supplements" provide for the following changes:

S-009: Reformulation of the 10 mEq and 20 mEq tablets
S-011: Labeling for 10 mEq & 20 mEq tablets
S-015: Manufacturing Revision (Scale-up of (b) (4))
S-016: New Strength (15 mEq tablet)
S-017: Labeling for 15 mEq tablet.

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reason:

> DMF (b) (4) is deficient. The holder has been notified. Please ensure a response.

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw these supplemental applications. Your amendment should respond to all the deficiencies listed. 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 letter will be considered as a MINOR amendment and should be so designated in your cover letter.

If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

M Smela for 4/4/03

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

cc:

ANDA DUP
DIV FILE
Field Copy
Endorsements:

cc: ANDA 74-726 S-009, S-011, S-015, S-016 and S-017CR4
Division File
Field Copy

Endorsements:

HFD-625/APendse/Review chemist/3/27/03 4/3/03
HFD-625/MSmela/Team leader/3/28/03 4/4/03
HFD-617/PChen/Project manager/4/1/03 4/3/03

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F/T by:ard/4/2/03

CHEMISTRY REVIEW: **NOT APPROVABLE - MINOR**

ANDA: 74-726/S-009, S-011, S-015, S-016 and S-017

Upsher-Smith Laboratories, Inc.
Attn: Mark S. Robbins
14905 23rd Avenue North
Minneapolis, MN 55447

- 6 -

Dear Sir:

This is in reference to your supplemental new drug applications dated February 14, 2001 (S-009 and S-011) and May 6, 2002 (S-015, S-016 and S-017) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Klor-Con® M, Potassium Chloride Extended-Release Tablets, USP 10 mEQ and 20 mEQ.

Reference is also made to your amendment dated December 6, 2002.

The supplemental applications, submitted as "Prior Approval Supplements" provide for the following changes:

S-009: Reformulation of the 10 mEQ and 20 mEQ tablets
S-011: Labeling for 10 mEQ & 20 mEQ tablets
S-015: Manufacturing Revision (Scale-up of (b)(4))
S-016: New Strength (15 mEQ tablet)
S-017: Labeling for 15 mEQ tablet.

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reason:

> Bioequivalence has not been established. Please respond to the deficiencies communicated to you by facsimile on February 4, 2003.

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw these supplemental applications. Your amendment should respond to all the deficiencies listed. 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 letter will be considered as a MINOR amendment and should be so

designated in your cover letter. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

M Smela for 2/6/03

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

cc: ANDA 74-726/S-009, S-011, S-015, S-016 and S-017
Division File
Field Copy

Endorsements:

HFD-625/APendse/ 2/5/03
HFD-625/MSmela/ 2/6/03
HFD-617/PChen/ 2/5/03

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F/t by:ard/2/5/03

CHEMISTRY REVIEW: **NOT APPROVABLE - MINOR**

OCT 22 2002

ANDA: 74-726/ S-009, S-011, S-015, S-016 and S-017

Upsher-Smith Laboratories, Inc.
Attn: Mark S. Robbins, Ph.D., J.D.
14905 23rd Avenue North
Minneapolis, MN 55447

Dear Sir:

This is in reference to your supplemental new drug applications dated February 14, 2001 (S-009 and S-011) and May 6, 2002 (S-015, S-016 and S-017) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Klor-Con® M, Potassium Chloride Extended-Release Tablets, USP 10 mEQ and 20 mEQ.

Reference is also made to your amendments dated May 6, 2002 (S-009 and S-011) and July 12, 2002 (S-016).

The supplemental applications, submitted as "Prior Approval Supplements" provide for the following changes:

S-009: Reformulation of the 10 mEQ and 20 mEQ tablets
S-011: Labeling for 10 mEQ & 20 mEQ tablets
S-015: Manufacturing Revision (Scale-up of (b) (4))
S-016: New Strength (15 mEQ tablet)
S-017: Labeling for 15 mEQ tablet.

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

1. Please provide Certificates of Analysis for the lots of drug substance and excipients used in the M15 exhibit batch.

2. Multiple batches of (b) (4) were used for the M15 exhibit batch. Please state the disposition of the unused portions of the (b) (4).

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

1. Your labeling information for S-017 is pending review.

2. Your Bioequivalency information is pending review.

3. Please provide additional stability data for the M10, M15 and M20 exhibit batches, if available.

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw these supplemental applications. Your amendment should respond to all the deficiencies listed. 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 letter will be considered as a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

M Smela for 10/22/02

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

cc:

ANDA DUP
DIV FILE
Field Copy
Endorsements:

cc: ANDA 74-726 S-009, S-011, S-015, S-016 and S-017
Division File
Field Copy

Endorsements:

HFD-625/APendse/10/11/02 10/22/02
HFD-625/MSmela/10/11/02
HFD-617/PChen/10/20/02 10/22/02

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F/t by: gp/10/22/02

Chemistry Review: **Not Approved Minor**
V:\FIRMSNZ\UPSHER\LTRS&REV\74726S09S011.S015,S016,S017CR1.doc
F/T by: gp

CHEMISTRY REVIEW: **NOT APPROVABLE - MINOR**