CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 74-726/S-001 and S-002

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

Sponsor: Upsher-Smith Laboratories, Inc.

Approval Date: August 9, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-001 and S-002

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-001 and S-002

APPROVAL LETTER

ANDA 74-726/S-001,S-002

AUG 9 2000

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

Dear Sir:

This is in reference to your supplemental new drug applications dated August 5, 1999, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Klor-Con® M20 (Potassium Chloride Extended-Release Tablets USP, 20 mEq).

Reference is also made to your amendment dated July 11, 2000.

The supplemental applications provide for:

S-001 Addition of a new strength, 10 mEq,

S-002 Associated labeling revisions.

The listed drug product referenced in your application, K-Dur 10 Extended-release Tablets of Key Pharmaceuticals, Inc., is subject to a period of patent protection that expires on September 5, 2006 (U.S. patent No. 4,863,743). Your application contains a patent certification to patent 4,863,743 under Section 505(j)(2)(A)(vii)(IV) of the Act. Section 505(j)(5)(B)(iii) of the Act provides that approval shall be made effective immediately unless an action is brought for infringement of the patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received. You have notified FDA that Upsher-Smith Laboratories, Inc. has 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 Laboratories, Inc. within the statutory forty-five day period.

We have completed the review of these supplemental abbreviated applications and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the supplemental applications are approved. The

Division of Bioequivalence has determined your KLOR-CON® M10 (Potassium Chloride Extended-release Tablets USP, 10 mEq) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (K-DUR 10® Extended-release Tablets of Key Pharmaceuticals, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

We remind you that you must comply with the requirement for an approved abbreviated 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 which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.
Submit both copies together with a copy of the proposed or 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 our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

for 8/9/00

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

cc: ANDA 74-726
Division File
FIELD COPY
HFD-610/RWest
HFD-92
HFD-210/B.Poole
HFD-330/
HFD-205/F.O.I

Endorsements:

HFD-625/BCai/ 7/31/00
HFD-625/MSmela\ for Mike Smela 8/2/00
HFD-625/MDillahunt PM/7-26-00 MDillahunt 7/27/00
HFD-613/T.Watkins/ T. Watkins 7/27/00
HFD-613/J.Grace/ J Grace 7/28/2000
F/T by: bc/7-27-00

Robert L. West 8/3/00

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PS 8/4/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-001 and S-002

LABELING

5-002

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

05800200

KLOR-CON® M
10 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® 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, Microcrystalline Cellulose, and Sorbitan Monooleate.

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, 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

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.

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

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WARNINGS

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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 matrix or enteric coated products is not available. Klor-Con®M is a tablet formulated to provide an extended rate of release of microencapsulated potassium chloride and thus to minimize the possibility of a high local concentration of potassium near the gastrointestinal wall.

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

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

05800200

KLOR-CON® M
10 mEq and 20 mEq

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

PRECAUTIONS

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

Information for Patients: Physicians should consider reminding the patient of the following:

To take each dose with meals and with a full glass of water or other liquid.

To take each dose without crushing, chewing, or sucking the tablets. If those patients are having difficulty swallowing whole tablets, they 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.

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®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

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®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 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 USL 20 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 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 USL 10.

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

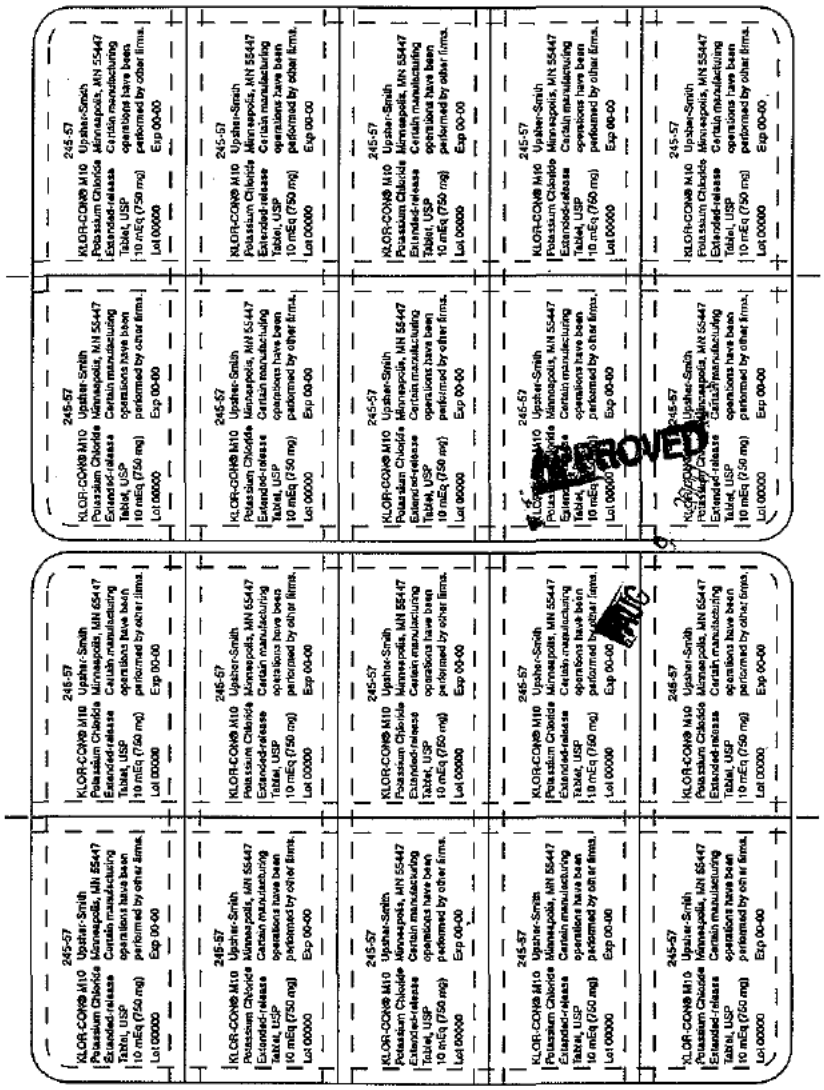
Manufactured by: Upsher-Smith Laboratories, Inc. Minneapolis, MN 55447
Certain manufacturing operations have
been performed by other firms.

Rev. 0200
40-05800

Klor-Con® M (Potassium Chloride Extended-release Tablets, USP), 10 mEq
ANDA 74-726

Unit Dose Card for 10 Tablets (Blister Text)

NOTE: Blister text, including the specific lot number and expiration date, are printed on the paper-backed foil (b) (4)



Klor-Con® M (Potassium Chloride Extended-release Tablets, USP), 10 mEq
ANDA 74-726

Bottle Label for 1000 Tablets

Each extended-release tablet provides 750 mg potassium chloride (equivalent to 10 mEq of potassium).

Usual Dose: See accompanying package insert for full prescribing information.

Dispense in tight, light-resistant container as defined in the USP.

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

Keep out of reach of children.

NDC 0245-0057-10
1000 Tablets

KLOR-CON®M10

Potassium Chloride Extended-release Tablets, USP

MICRO-DISPERSIBLE TECHNOLOGY™

10 mEq K

Rx only

UPSHER-SMITH

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

Certain manufacturing operations have been performed by other firms.

Rev. 0200 42-05710

Lot/Exp.

Klor-Con® M (Potassium Chloride Extended-release Tablets, USP), 10 mEq
ANDA 74-726

Bottle Label for 100 Tablets

n for 10

UPSHER-SMITH

10 mEq K

MICRO-DISPERSIBLE TECHNOLOGY™

Potassium Chloride
Extended-release
Tablets, USP

KLOR-CON® M10

Unit Dose 100 Tablets
NDC 0245-0057-01

N 3 0245-0057-01 7

KLOR-CON®M10

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

Certain manufacturing operations have been performed by other firms.

Rev. 0200

49-05701

[redacted]

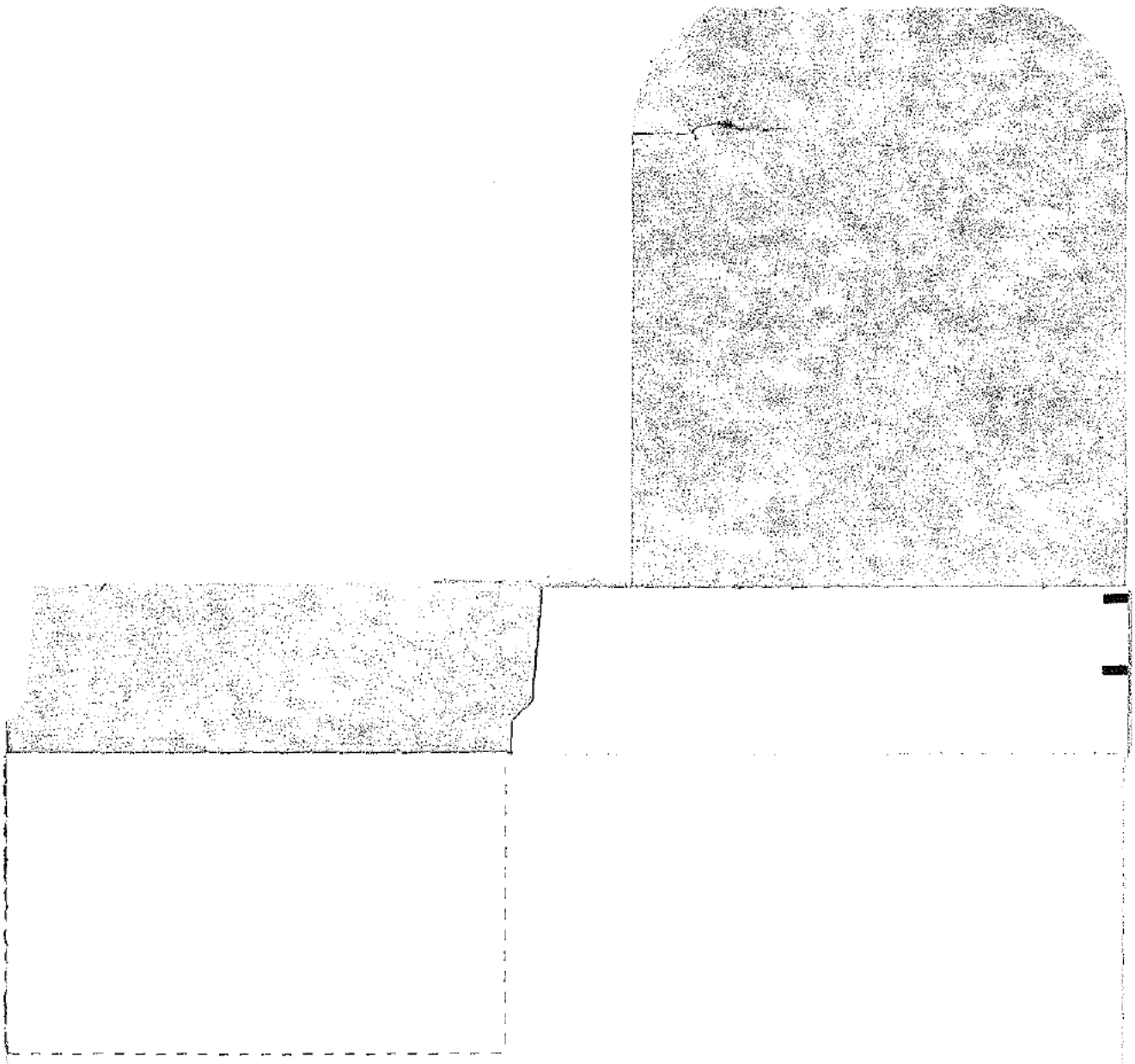
AUG 9 2000

Each extended-release tablet provides 750 mg potassium chloride (equivalent to 10 mEq of potassium).

Usual Dose: See accompanying package insert for full prescribing information.

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

Keep out of reach of children.



NDC 0245-0057-01
Unit Dose 100 Tablets

KLOR-CON® M10

Potassium Chloride Extended-release Tablets, USP

MICRO-DISPERSIBLE TECHNOLOGY ™

10 mEq K

Rx only

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

UPSHER-SMITH

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-001 and S-002

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING #
SUPPLEMENT
FPL

DATE OF REVIEW: April 18, 2000
ANDA #: 74-726/S-002

NAME OF FIRM: Upsher Smith Laboratories, Inc.
NAME OF DRUG: Potassium Chloride Extended-release Tablets USP
DATE OF SUBMISSION: April 11, 2000

COMMENTS:
Container: (10 mEq – 100's and 1000's) Satisfactory as of April 11, 2000 submission.
Unit Dose: (10 mEq) Satisfactory as of August 5, 1999 submission.
Unit Dose Carton: (100's) Satisfactory as of April 11, 2000 submission.
Insert: Satisfactory as of April 11, 2000 submission.

RECOMMENDATIONS:
1. Inform the firm of the above comments.
2. Recommend approve supplement.

FOR THE RECORD:
1. Review based on the labeling of K-DUR® (Schering-Plough; NDA#19-439/S-015; approved December 20, 1990.
2. Patent/ Exclusivities: There is one patent in effect for this product. U-99 – Expires September 5, 2006. For a method of providing potassium to a subject in need of potassium.
3. This is a combined new strength/labeling review for the addition of the 10 mEq strength.

cc: ANDA 74-726/S-002
Dup/Division File
HFD-613/TWatkins/JGrace (no cc:)
V:\FIRMSNZ\UPSHER\LTRS&REV\74726S02.APL
Review

REVIEW OF PROFESSIONAL LABELING #
SUPPLEMENT
DRAFT

DATE OF REVIEW: September 20, 1999
ANDA #: 74-726/S-002

NAME OF FIRM: Upsher Smith Laboratories, Inc.

NAME OF DRUG: Potassium Chloride Extended-release Tablets USP

DATE OF SUBMISSION: August 5, 1999

COMMENTS:

Container: (10 mEq – 100's and 1000's) Satisfactory in draft.

Unit Dose: (10 mEq) Satisfactory as of August 5, 1999 submission.

Unit Dose Carton: (100's) Satisfactory in draft.

Insert: Satisfactory in draft.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm prepare and submit 12 copies of final print labels and labeling.

FOR THE RECORD:

1. Review based on the labeling of K-DUR® (Schering-Plough; NDA#19-439/S-015; approved December 20, 1990.

2. Patent/ Exclusivities: There is one patent in effect for this product. U-99 – Expires September 5, 2006. For a method of providing potassium to a subject in need of potassium.

3. This is a combined new strength/labeling review.

cc: ANDA
Dup/Division File 9/20/99
HFD-613/TWatkins/JGrace (no cc:)
V:\FIRMSNZ\UPSHER\LTRS&REV\74726s02.ael
Review

9/24/1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-001 and S-002

CHEMISTRY REVIEWS

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 3

2. **ANDA #** 74-726/S-001

3. **NAME AND ADDRESS OF APPLICANT:**

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

Telephone: (612) 473-4412

4. **LEGAL BASIS FOR ANDA SUBMISSION:**
Paragraph IV certification
Key Pharmaceutical's K-DUR 20®
(pat. #4863743, exp. Sept. 6, 2006)

5. **Supplement(s):** S-001

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:**
Potassium Chloride Extended-Release Tablets USP

8. **SUPPLEMENT(S) PROVIDE(S) FOR:**
For dosage proportional 10 mEq strength tablets.

9. **AMENDMENTS AND OTHER DATES:**

Upsher-Smith:

08/08/95	Submission of original ANDA.
08/05/99	Submission of current supplement, S-001
04/11/00	Amendment
05/17/00	NC (patent certification)
05/31/00	Patent Information (settlement agreement)
06/02/00	NC (mail receipt to Schering per 5/18/00)
06/30/00	NC (mail receipt to Schering per 6/19/00)
07/11/00	Minor Amendment (45 days period expired)

FDA:

11/20/98	Original ANDA (20 mEq) approved.

09/24/99	Labeling for 10 mEq: Request FPL.
12/22/99	Bio waiver is granted.
02/10/00	CMC NA/minor.
04/20/00	labeling review completed/acceptable
04/18/00	**T-con (re 180days exclusivity & patent certification.**
06/01/00	**OGD internal meeting**
06/09/00	**NA (minor)-re patent issue.**
07/20/00	**N. Mahmud noted "ready to approval"**

10. PHARMACOLOGICAL CATEGORY:
Potassium supplementation.

11. Rx or OTC: Rx

12. RELATED IND/NDA/DMF(s):
See item 37

13. DOSAGE FORM: Tablet

14. POTENCY: 10 mEq

15. CHEMICAL NAME AND STRUCTURE: Potassium Chloride (KCl)

16. RECORDS AND REPORTS: N/A

17. COMMENTS:

- Bio Waiver: Granted based on results from Batch #96828 (20 mEq strength tablets) and acceptable dissolution data from 10 mEq tablet; 12/6/99 (Vol.3.1).
- Stability: Lot#60154. Accel/Full term Data: Acceptable
- EERs: Not required (a new dose proportional strength to ANDA/no biostudy required)
- DMF: Acceptable
- Labeling review: Acceptable per 04/20/00.
- Micro: N/A
- MV: Not required (USP DS/DP)
- CMC Approvable

Note:
On 06/09/00, agency sent a NA minor to the firm asking for patent clarification.

On 07/11/00, Upsher-Smith provided a minor amendment indicating that they have a settlement with Schering/Key

Pharmaceuticals in 1997 (see attachment 1). In addition, Schering/Key Pharmaceuticals were noticed again regarding this patent issue on 05/18/00. The 45 days period has expired. Upsher-Smith now requests the approval of these supplemental applications.

On 07/20/00, N. Mahmud has confirmed that the 45-day period has elapsed without initiation of a lawsuit by the innovator.

All CMC issues were solve in the previous review cycles. These supplemental applications are ready for approval.

18. CONCLUSIONS AND RECOMMENDATIONS:
Approved

19. REVIEWER: Bing Cai, Ph.D. DATE COMPLETED: 07/31/00 DATE REVISED:

cc: ANDA 74-726
Division File
FIELD COPY

Endorsements:

HFD-625/BCai/07/31/00
HFD-625/Msmela/

A:\74726S01.CR3.BBC.DOC
F/T by:

8/2/00
Mujtaba Khaliq for Mike Smela 8/2/00

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

28. **LABORATORY CONTROLS: Satisfactory per CR#2**

Description:	(b) (4) white (b) (4) capsule-shaped uncoated tablet.
	(b) (4)
Identification:	As per USP. Positive for Potassium and for Chloride.
Assay:	As per USP. (b) (4)
	(b) (4)
Uniformity of dose:	As per USP. (b) (4)
Dissolution:	Water at 50rpm; Apparatus 2.

1 Hour	NLT	(b) (4) %	and NMT	(b) (4) %
2 Hours	NLT	%	and NMT	%
6 Hours	NLT	%	and NMT	%
12 Hours	NLT	%		

29. **STABILITY: Satisfactory per CR#2**

Description:	as per release
Assay:	as per release
Dissolution:	Water at 50rpm; Apparatus 2.

1 Hour	NLT	(b) (4) %	and NMT	(b) (4) %
2 Hours	NLT	%	and NMT	%
6 Hours	NLT	%	and NMT	%
12 Hours	NLT	(b) (4) %		

30. **CONTROL NUMBERS:** N/A

31. **SAMPLES AND RESULTS:**
USP DS/DP.

32. **LABELING:** Satisfactory.

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

34. **BIOEQUIVALENCY STATUS:** Satisfactory per CR#1

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

36. **ORDER OF REVIEW:**

The application submission(s) covered by this review was taken in the date order of receipt:

Yes____No__X (MINOR)__Spot? Yes____No__X__

37. DMF CHECKLIST FOR ANDA # 74-726/S-001 REVIEW # 3

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
	(b) (4)	3	Adequate	07/17/00
	(b) (4)	4		
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		4		
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		4		
		4		
		2		
		2		
		2		
		2		

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").

Bing Cai, Ph.D.
Reviewer

Signature

9/7/00
Date

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 2 HBS

2. **ANDA #** 74-726/S-001

3. **NAME AND ADDRESS OF APPLICANT:**

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

Telephone: (612) 473-4412

4. **LEGAL BASIS FOR ANDA SUBMISSION:**
Paragraph IV certification
Key Pharmaceutical's K-DUR 20®
(pat. #4863743, exp. Sept. 6, 2006)

5. **Supplement(s):** S-001

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:**
Potassium Chloride Extended-Release Tablets USP

8. **SUPPLEMENT(S) PROVIDE(S) FOR:**
For dosage proportional 10 mEq strength tablets based on Waiver of in-vivo bioavailability.

9. **AMENDMENTS AND OTHER DATES:**

Upsher-Smith:

08/08/95	Submission of original ANDA.
08/05/99	Submission of current supplement, S-001
04/11/00	Amendment
05/31/00	Patent Information

FDA:

11/20/98	Original ANDA (20 mEq) approved.
09/24/99	Labeling for 10 mEq: Request FPL.
12/22/99	Bio waiver is granted.
02/10/00	CMC NA/minor
04/20/00	labeling review completed/acceptable

10. **PHARMACOLOGICAL CATEGORY:**
Potassium supplementation.

11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):**
See item 37

13. **DOSAGE FORM:** Tablet

14. **POTENCY:** 10 mEq

15. **CHEMICAL NAME AND STRUCTURE:** Potassium Chloride (KCl)

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**

- Bio Waiver: Granted based on results from Batch #96828 (20 mEq strength tablets) and acceptable dissolution data from 10 mEq tablet; 12/6/99 (Vol.3.1).
- Stability: Lot#60154. Accel/Full term Data: Acceptable
- EERs: Not required (a new dose proportional strength to ANDA/no biostudy required)
- DMF: Acceptable
- Labeling review: Acceptable per 04/20/00.
- Micro: N/A
- MV: Not required (USP DS/DP)
- CMC Approvable

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Not Approvable due to patent issues.

19. **REVIEWER:** Bing Cai, Ph.D. **DATE COMPLETED:** 04/21/00 **DATE REVISED:**

cc: ANDA 74-726
Division File
FIELD COPY

Endorsements:

HFD-625/BCai/04/21/00
HFD-625/Msmela/06/08/00
F/t by: gp/06/09/00
V:\FIRMSNZ\UPSHER\LTRS&REV\74726S01.CR2.BBC.DOC
F/T by: gp/06/09/00

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30. **CONTROL NUMBERS:** N/A

31. **SAMPLES AND RESULTS:**
USP DS/DP.

32. **LABELING:** Satisfactory.

Reviewed by chemist: Satisfactory
1. Description Section:
   a. Structures: Satisfactory
   b. Chemical names: Satisfactory
   c. Empirical formulas: Satisfactory
   d. Name of the inactives: Satisfactory
   e. Physical and Chemical properties of DS: Satisfactory
2. How supplied section
   a. Packaging: Available in bottles of 100 tablets. (NDC 0245-0057-11); bottles of 1000 tablets. (NDC 0245-0057-01) and unit dose.

   b. Storage conditions:
   Store between 59-86 °F (15-30 °C).

NOTES/QUESTIONS TO THE CHEMIST/From Labeling reviewer: None

33. **ESTABLISHMENT INSPECTION:** Not needed for this submission.

34. **BIOEQUIVALENCY STATUS:** Satisfactory per CR#1

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

36. **ORDER OF REVIEW:** Satisfactory
The application submission(s) covered by this review was taken in the date order of receipt:
Yes___ No__ X (MINOR) Spot? Yes____ No___ X___

37. **DMF CHECKLIST FOR ANDA # 74-726/S-001 REVIEW # 2**

DMF #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED
	(b) (4)	3	N/A	
	(b) (4)	4		
		4		
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		4		
		2		
		2		
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		2		

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").

Bing Cai, Ph.D.
Reviewer

Signature

6/9/08
Date

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 1

2. **ANDA #** 74-726/S-001

3. **NAME AND ADDRESS OF APPLICANT:**

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

Telephone: (612) 473-4412

4. **LEGAL BASIS FOR ANDA SUBMISSION:**
Paragraph IV certification
Key Pharmaceutical's K-DUR 20®
(pat. #4863743, exp. Sept. 6, 2006)

5. **Supplement(s):** S-001

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:**
Potassium Chloride Extended-Release Tablets USP

8. **SUPPLEMENT(S) PROVIDE(S) FOR:**
For dosage proportional 10 mEq strength tablets based on Waiver of in-vivo bioavailability.

9. **AMENDMENTS AND OTHER DATES:**

Upsher-Smith:

08/08/95	Submission of original ANDA.
08/05/99	Submission of current supplement, S-001

FDA:

11/20/98	Original ANDA (20 mEq) approved.
09/24/99	Labeling for 10 mEq: Request FPL.
12/22/99	Bio waiver is granted.

10. **PHARMACOLOGICAL CATEGORY:**
Potassium supplementation.

11. **Rx or OTC:** Rx

12. **RELATED IND/NDA/DMF(s):**
See item 37

13. **DOSAGE FORM:** Tablet

14. **POTENCY:** 10 mEq

15. **CHEMICAL NAME AND STRUCTURE:** Potassium Chloride (KCl)

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**

- Bio Waiver: Granted based on results from Batch #96828 (20 mEq strength tablets) and acceptable dissolution data from 10 mEq tablet; 12/6/99 (Vol.3.1).
- Stability: Lot#60154. Accel/Full term Data: Acceptable
- EERs: Not required (a new dose proportional strength to ANDA/no biostudy required)
- DMF: Acceptable
- Labeling review: pending for FPL.
- Micro: N/A
- MV: Not required (USP DS/DP)
- Minor CMC deficiencies could be found in item 38.

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Not approvable (MINOR Amendment).

19. **REVIEWER:**	**DATE COMPLETED:**	**DATE REVISED:**
Bing Cai, Ph.D.	01/28/00	02/02/00

cc: ANDA 74-726
Division File
FIELD COPY

Endorsements:

HFD-625/BCai/01/28/00
HFD-625/MSmela\02/02/00

2/10/00
M Smela 2/10/00

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F/T by: gp/02/04/00

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2. Please be advised that it is your responsibility to correspond with USP and have their ANDA approved dissolution test added to the monograph.

30. **CONTROL NUMBERS:** N/A

31. **SAMPLES AND RESULTS:**
USP DS/DP.

32. **LABELING:** Pending for FPL.

Reviewed by chemist: Satisfactory
1. Description Section:
   a. Structures: Satisfactory
   b. Chemical names: Satisfactory
   c. Empirical formulas: Satisfactory
   d. Name of the inactives: Satisfactory
   e. Physical and Chemical properties of DS: Satisfactory
2. How supplied section
   a. Packaging: Available in bottles of 100 tablets. (NDC 0245-0057-11); bottles of 1000 tablets. (NDC 0245-0057-01) and unit dose.

   b. Storage conditions:
   Store between 59-86 °F (15-30 °C).

NOTES/QUESTIONS TO THE CHEMIST/From Labeling reviewer: None

33. **ESTABLISHMENT INSPECTION:** Not needed for this submission.

34. **BIOEQUIVALENCY STATUS:** Satisfactory
Bio Waiver: Granted based on results from Batch #96828 (20 mEq strength tablets) and acceptable dissolution data from 10 mEq tablet; 12/6/99 (Vol.3.1).

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

36. **ORDER OF REVIEW:** Satisfactory
The application submission(s) covered by this review was taken in the date order of receipt:
Yes X No_____Spot? Yes____No___X___

37. **DMF CHECKLIST FOR ANDA # 74-726/S-001 REVIEW # 1**

DMF #	DMF TYPE/SUBJECT/HOLDER (b) (4)	ACTION CODE 3	RESULT OF REVIEW N/A	DATE REVIEW COMPLETED
	(b) (4)	4		
		4		
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		2		

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").

Bing Cai, Ph.D.
Reviewer

Signature 2/10/09
Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-001 and S-002

BIOEQUIVALENCE REVIEWS

Potassium Chloride
Extended Release 10 mEq Tablets
ANDA #74-726; SCQ 001
Reviewer: Sikta Pradhan
V:\firmsnz\Upsher\trs&rev\74726DW.899

Upsher-Smith Laboratories
Minneapolies, MN
Submission Date:
August 5, 1999

REVIEW OF DISSOLUTION DATA AND A WAIVER REQUEST

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 has conducted an acceptable dissolution testing on the test and reference products of 10 mEq tablets.
- ☞ Proportional Compositions of 10 mEq and 20 mEq tablets of the test product.
- ☞ The firm has requested a waiver of in vivo bioequivalence study on its test product, Potassium Chloride Extended Release 10 mEq Tablets.

COMMENTS:

Based on the following reasons the waiver request for in vivo bioequivalence study on Upsher-Smith's 10 mEq Potassium Chloride Extended Release tablets has been found acceptable to the Division of Bioequivalence:

1. The guidance allows waiver of 10 mEq tablet if the product contains slow release beads (encapsulated (b) (4)).
2. Upsher -Smith's products are encapsulated (b) (4) tablet. This is very much like beads in capsules. The mechanism of release is reported to be same. According to the NDA review, the RLDs are also manufactured in a similar fashion.

3. Upsher -Smith's 10 and 20 mEq strengths are compositionally proportional. Formulations for K-Dur's two strengths (10 and 20 mEq) are also proportional in the same way (see Attachment #1).

4. Upsher -Smith's 10 mEq and 20 mEq strengths appear to be manufactured from a (b) (4). This is to be confirmed by the chemistry division.

5. Dissolution profiles for Upsher -Smith's 20 mEq and 10 mEq are similar (f2= 51.1). For 10 and 20 mEq of K-Dur, f2 value is 51.5. Both pass f2 test.

6. Upsher -Smith's 10 mEq strength passes dissolution specifications set for the 20 mEq strength. The 10 mEq strength of RLD is not scored unlike the 20 mEq strength and thus, there is no issue regarding the dissolution of half tablets (see Attachment #2).

7. There was no evidence of dose dumping by the 20 mEq strength. Based on the similarity in the formulation for the two strengths, there is no reason to believe that the in vivo performance of the 10 mEq strength will be different.

RECOMMENDATIONS:

1. The firm had previously conducted acceptable in vitro dissolution testing and in vivo bioequivalence study on its test product, Potassium Chloride Extended Release 20 mEq Tablets. These studies demonstrated that Upsher -Smith's Potassium Chloride Extended Release 20 mEq Tablets are bioequivalent to the reference product, K-Dur 20 mEq tablets, manufactured by Key Pharmaceuticals.

2. The firm has recently conducted acceptable dissolution testing on its 10-mEq Potassium Chloride Extended Release tablets. The formulation of 10-mEq strength of the test product is proportionally similar to the 20-mEq strength of the test product, which underwent bioequivalency testing. The waiver of in vivo bioequivalence study requirements for 10-mEq Potassium Chloride Extended Release tablets of the test product is granted.

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG ---------- 12/6/99

Concur: Barbara M Davit Date: 12/22/99
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 74726DW.899 (original, duplicate), HFD-652 (Huang, Pradhan), HFD-650 (Director), Drug File, Division File

Draft: SP/8-16-99/ V:\firmsnz\Upsher\ltrs&rev\74726DW.899
Pink copy: SP/11-30-99/ V:\firmsnz\Upsher\ltrs&rev\74726DW.899

Attachment #1

0081

Quantitative Composition for Klor-Con® M10

	%W/W	mg/Tablet
Potassium Chloride, USP	75.0	750.0
Croscarmellose Sodium, NF	[redacted] (b) (4)	
Ethylcellulose, NF		
Microcrystalline Cellulose, NF		
Sorbitan Monooleate, NF		
[redacted] (b) (4)		
	100.0	1000.0 mg

Quantitative Composition for Klor-Con® M20

	%W/W	mg/Tablet
Potassium Chloride, USP	75.0	1500.0
Croscarmellose Sodium, NF	[redacted] (b) (4)	
Ethylcellulose, NF		
Microcrystalline Cellulose, NF		
Sorbitan Monooleate, NF		
[redacted] (b) (4)		
	100.0	2000.0 mg

[redacted] (b) (4)

Attachment # 2

Dissolution Specifications for Klor-Con® M10 and Klor-Con® M20:

Apparatus:	USP <711> Apparatus 2 (Paddle)
RPM:	50 rpm
Medium:	Deionized Water
Volume:	900 ml
Sampling:	1, 2, 6 and 12 hours
# Tablets Tested:	Six
Tolerance:	The percent dissolved of each tablet is:

HOUR	NOT LESS THAN	NOT MORE THAN
1 hour	(b)(4)	(b)(4)
2 hour		
6 hour		
12 hour		---

K-Dur® 10 Dissolution
Lot 96828

Media: DI Water
Apparatus: II (Paddles) at 50 rpm

Percent Potassium Dissolved

	Time Points, hours						
Tablet#	1	2	4	6	8	10	12
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Average:	14.8	32.8	63.2	77.0	87.6	94.3	97.1
Minimum:	(b) (4)						
Maximum							
%RSD:	5.7	4.8	2.1	2.5	2.7	5.1	3.0

NB Ref: R-082
Pages: 90-92

052

Klor-Con® M10 Dissolution
Lot 60154

Media: DI Water
Apparatus: II (Paddles) at 50 rpm

Percent Potassium Dissolved

	Time Points, hours						
Tablet#	1	2	4	6	8	10	12
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
Average:	19.0	30.7	50.8	68.9	80.6	90.8	90.6
Minimum:	(b) (4)						
Maximum							
%RSD:	2.2	4.9	3.3	5.6	2.3	1.5	2.8

NB Ref: R-080
Pages: 72-74

051

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA #74-726/SCQ001 APPLICANT: Upsher-Smith Laboratories, Inc.

DRUG PRODUCT: Potassium Chloride Extended Release Tablets, 10-mEq

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

The dissolution testing will need to be incorporated into your stability and quality control programs. The dissolution testing should be conducted in 900 mL of deaerated water at 37°C using USP XXIII apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:

1 Hour	NLT	(b)(4)% and NMT (b)(4)%
2 Hours	NLT	% and NMT %
6 Hours	NLT	% and NMT %
12 Hours	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,

Barbara M Davis

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

CC: ANDA #74-726; SCQ 001
ANDA DUPLICATE
DIVISION FILE
BIO DRUG FILE
FIELD COPY

Endorsements: (Final with Dates)
HFD-652/ S. Pradhan
HFD-650/ Y. Huang 12/6/99
for HFD-617/ E. Hu 12/23/99
for HFD-650/ D. Conner 12/22/99

Printed in draft on 8\16\99\
Printed in final on 11\30\99

V:\firmsnz\Upsher\ltrs&rev\74726DW.899

Bioequivalency Study Waiver on 10-mEq Tablets Submission date: 08-05-99

Dissolution (DIW) 10-mEq tablet o/c Outcome AC

OUTCOME DECISIONS: AC - Acceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 74-726/SCQ001 SPONSOR: Upsher - Smith Lab.

DRUG AND DOSAGE FORM: Potassium Chloride Tab.

STRENGTH(S): 10 mEq.

TYPES OF STUDIES: Dissolution

CLINICAL STUDY SITE(S): N/A

ANALYTICAL SITE(S): N/A

STUDY SUMMARY: p/. See review

DISSOLUTION: acceptable

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
other _____		

PRIMARY REVIEWER: (NAME) BRANCH:

INITIAL: SP (Sekta Pradhan) DATE: 11/30/99

TEAM LEADER: (NAME) BRANCH:

INITIAL: _____ DATE: 12/6/99

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

INITIAL Barbara M Davit DATE: 12/22/99

V:\division\bio\signoff.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-001 and S-002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 74-726/S-001 Applicant: Upsher Smith Laboratories
Drug KLOR-CON M (POTASSIUM CHLORIDE Extended-Release TABLETS USP) Strength 10mEq

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

/IEWER:	DRAFT RECEIPT	FINAL ACTION
1. Project Manager MDillahunt	Date 7/27/99	Date 8/9/99
Review Support Br 2	Initials MD	Initials MD

Application Summary:

Original Rec'd date 8/6/99
Date Acceptable for Filing 8/6/99
Patent Certification (type) 1H
Date Patent/Exclus.expires 9/15/2006
Citizens Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
(If YES, check PETS)
Pediatric Exclusivity Tracking System (PETS)
Date checked NA
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☐ OAI ☐
Date of EER Status NA
Date of Office Bio Review 12/22/99
Date of Labeling Approv. Sum 9/20/99
Date of Sterility Assur. App. NA
Methods Val. Samples Pending Yes ☐ No ☒
30 Day Clock Start _____ End _____
Commitment Rcd. from Firm Yes ☐ No ☐

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

2. Div. Dir./Deputy Dir.	Date 9/1/99	Date 9/9/99
Chemistry Div. I or II	Initials RS	Initials RS
Comments:		

3. Frank Holcombe	Date _____	Date _____
Assoc. Dir. For Chemistry	Initials _____	Initials _____
Comments: (First generic drug review)		

4. Pat Beers Block	Date _____	Date _____
Supv., Review Support Branch	Initials _____	Initials _____
EER Status:		

Bioequivalence sites:

Clinical site:
Inspection needed: ☐ yes ☐ no
Status: ☐acceptable ☐unacceptable ☐ pending
Date of status: _____
Reason:

Analytical site:
Inspection needed: ☐ yes ☐ no
Status: ☐acceptable ☐unacceptable ☐pending
Date of status: _____
Reason:

Bioequivalence office level sign off:

Labeling Status:

Microbiology status:

Patent Certification:
Controlled Correspondence/Cit.Pet:
Comments: RLD =

ANDA 74-726/S-001,S-002

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

JUN 9 2000

Dear Sir:

This is in reference to your supplemental new drug applications dated August 5, 1999, submitted under section 505(j) of the Federal, Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Klor-Con® M20 (Potassium Chloride Extended-Release Tablets USP, 20 mEq).

Reference is also made to your amendments dated April 11, May 17, and May 31, 2000.

The supplemental applications provide for:

S-001 Addition of a new strength, 10 mEq,

S-002 Associated labeling revisions.

Your supplemental application contains a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(4) and Section 505 (j)(2)(A)(vii)(IV) of the Act. An ANDA applicant with a paragraph IV certification must comply with the notice requirements per 21 CFR 314.95.

You have not provided evidence of notice of certification of invalidity or non-infringement to the patent owner of the patent which is the subject of the certification or the representative designated to receive the notice and application holder for the listed drug. The supplemental application is, therefore, deficient and not approvable under 21 CFR 314.127(a)(12).

Please submit an amendment to this supplemental application with the following:

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of certified or registered U.S. Mail return receipt or a letter acknowledging receipt by the person provided the notice.

Your supplemental application can not be considered approvable until such time that you provide this information to the Agency. Your amendment to this supplemental application submitted in response to this "Not Approvable" letter will be considered as a MINOR AMENDMENT. The file is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. If you have substantial disagreement with our reasons for not approving this supplemental application, you may request an opportunity for a hearing.

Sincerely yours,

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

cc: ANDA 74-726
Division File
Field Copy

Endorsements:

HFD-625/B.Cai/ 6/9/00
HFD-625/M.Smela/06/08/00 6/9/00
HFD-617/M.Dillahunt/06/07/00 6/9/00
HFD-615/N.Mahmud/ for 6/9/00
F/t by: gp/06/09/00

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ANDA 74-726/S-001/S-002

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

FEB 10 2000

Dear Sir:

This is in reference to your supplemental new drug application dated August 5, 1999, submitted under section 505(j) of the Federal, Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Klor-Con® M20 (Potassium Chloride Extended-Release Tablets USP).

The supplemental application, submitted as "Prior Approval Supplement", provides for dosage proportional 10 mEq strength tablets.

The supplemental application is deficient and, therefore, Not Approvable under Section 505 of the Act for the following reasons:

> Please acknowledge that you will provide at least three batches of adequate stability data before you extend your expiration period. Your data may be submitted in an Annual Report. The statement provided on page 90 in your supplement is not adequate.

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

1. Please submit 12 copies of final print labeling.

2. We recommend that you correspond with USP and request that the ANDA approved dissolution test be added to the monograph for this product.

The file on this supplemental application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw this supplemental application. 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 a MINOR Amendment and should be so designated in your cover letter.

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

Sincerely yours,

M Smela for 2/10/00

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

cc: ANDA 74-726
Division File
FIELD COPY

Endorsements:

2/9/00

HFD-625/BCai/01/28/00 02/02/00
HFD-625/MSmela\02/04/00
HFD-625/MDillahunt PM/02/04/00 MDillahunt 2/9/00

V:\FIRMSNZ\UPSHER\LTRS&REV\74726S01.NA1.BBC.DOC
F/T by: gp/02/04/00
Not Approved: Minor Deficiency