CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 74-726/S-005, S-006, S-007 and S-008

Name: Klor-Con® M (Potassium Chloride Extended-release Tablets USP)

Sponsor: Upsher-Smith Laboratories, Inc.

Approval Date: June 28, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-005, S-006, S-007 and S-008

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APPLICATION NUMBER:

ANDA 74-726/S-005, S-006, S-007 and S-008

APPROVAL LETTER

ANDA 74-726/S-005, S-006, S-007 and S-008

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

JUN 28 2001

Dear Sir:

This is in reference to your supplemental new drug applications dated September 14, 2000, 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).

Reference is also made to your amendments dated December 22, 2000 and March 22, 2001.

The supplemental applications, submitted as "Supplement-Changes Being Effected in 30 Days", provide for manufacturing scale-up, equipment and process parameter changes, tablet deboss change and addition of a 90-count bottle.

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

Sincerely yours,

6-27-01

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:

HFD-625/BCai/06/25/01
HFD-625/Msmela/6/25/01
HFD-617/MDillahunt PM/
HFD-613/APayne/
HFD-613/JGrace/

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F/T by: DJ 6/25/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-005, S-006, S-007 and S-008

LABELING

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

05800600
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 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

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 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®

05800600
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 be aware 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

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);

c. 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

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 US 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 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 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. 0600
40-05800

Upsher-Smith Laboratories, Inc.
Klor-Con® M (Potassium Chloride Extended-release Tablets, USP)
Supplement to ANDA #74-726

Final Printed Labeling
Klor-Con® M20
90 Tablets/Bottle Label, Rev. 0600

Each extended-release tablet provides 1500 mg potassium chloride (equivalent to 20 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 0245-0058-90
90 Tablets

KLOR-CON® M20

Potassium Chloride Extended-release Tablets, USP

MICRO-DISPERSIBLE TECHNOLOGY®

20 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. 0600 42-05890

N 3 0245-0058-90 8

Lot/Exp.

SAMPLE

Upsher-Smith Laboratories, Inc.
Klor-Con® M (Potassium Chloride Extended-release Tablets, USP)
Supplement to ANDA #74-726

Final Printed Labeling
Klor-Con® M10
90 Tablets/Bottle Label, Rev. 0700

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 0245-0057-90
90 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. 0700 42-05790

N 3 0245-0057-90 1

Lot/Exp

SAMPLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-005, S-006, S-007 and S-008

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING #1

Supplement (FPL)

ANDA #: 74-726/S-008
NAME OF FIRM: Upsher-Smith Laboratories, Inc.
NAME OF DRUG: Potassium Chloride Extended-release Tablets USP, 10 mEq and 20 mEq.
DATE OF SUBMISSION: September 14, 2000
LABELING COMMENTS:

1. CONTAINER: 10 mEq and 20 mEq bottles of 90 mg
   Satisfactory in **final print** as of the September 14, 2000 submission.

2. PACKAGE INSERT:
   Satisfactory in **final print** as of the September 14, 2000 submission.

RECOMMENDATIONS:
Approve the supplement

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. This labeling supplement (SL-008) was submitted in conjunction with supplement SCR-005, and chemistry supplements SCA-006 and SCS-007 for the addition of a new 90 count package size and revised tablet debossing.

3. **The supplement was originally submitted as a CBE, however, this was denied.** Granted Letter accepted

cc: ANDA 74-726/S-008
DUP/Division File
HFD-613/JBarlow/JGrace(no cc:)
V:\FIRMSNZ\UPSHER\LTRS&REV\74726s8.apl
Review

Endorsements:
HFD-613/JBarlow
HFD-613/JGrace

11/7/-
11/13/2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-005, S-006, S-007 and S-008

CHEMISTRY REVIEWS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drug
Chemistry, Manufacturing and Controls Review

ANDA:74-726/S-005, S-006, S-007 and S-008

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

Telephone: (763) 473-4412

PURPOSE OF AMENDMENT/SUPPLEMENT:
To provide for manufacturing scale-up, equipment and process parameter changes, tablet deboss change and addition of a 90-count bottle:

S-005: Manufacturing Scale-Up, Including Equipment and Process Changes.
S-006: Addtion of 90-Count Bottle;
S-007: Tablet Deboss Change; and,
S-008: Labeling related to S-006.

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

09/14/00: Original submission as "Special Supplements, CBE 30";
10/03/00: TelCon
10/06/00: TelCon
10/16/00: CBE was denied by the agency;
11/13/00: Labeling: Acceptable (FPL are acceptable);
12/22/00: Amendment/Re-submission as CBE-30 (accepted)

NONPROPRIETARY NAME:
Potassium Chloride Extended-Release Tablets USP

PHARMACOLOGICAL CATEGORY	**TRADE NAME**
Potassium Supplementation	N/A

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

REMARKS AND CONCLUSION:
CMC Closed. Pending for bio review.

Reviewer: Bing Cai, Ph.D. **Date Completed:** February 16, 2001

SAMPLES: N/A
RELATED IND/NDA/DMF(S): N/A
LABELING: N/A
BIOEQUIVALENCY: Pending
ESTABLISHMENT INSPECTION: N/A
PACKAGING: see below.
STERILIZATION: N/A

COMPONENTS, COMPOSITION, MANUFACTURING PROCESSING & STABILITY:
These supplements (CBE-30) provide for manufacturing scale-up, equipment and process parameter changes, tablet deboss change and addition of a 90-count bottle. They are summarized in below.

Please note that there are two facilities ((b)(4) and USL) utilized for manufacturing of these products as approved in the original ANDA and the previous supplements. (b)(4)

Manufacturing/Controls Changes	Current	Proposed
(b)(4)		
In process control testing modifications for (b)(4) (b)(4)	NO CHANGES ON SPECIFICATIONS (b)(4)	
(b)(4)		
Deboss	"USL 20" "USL 10"	"US 20" (b)(4)
New bottle (90-count bottle for both M10 and M20)	The 90-count bottles will utilize the same C/C used to package the current approved 100-count bottles.	
Labeling Changes	To reflect above changes regarding the addition of 90-count bottle for both strengths, deboss change for Klor-Con® M20 tablet and minor editorial changes	
(b)(4)		

Following this page, 3 Pages Withheld in Full as (b)(4)

cc: ANDA 74-726
Division File
Field Copy

Endorsements:

HFD-625/B. Cai/02/16/01
HFD-625/M. Smela/

2/20/01 revised
M Smela 2/20/01

\\CDS008\WP51F99\FIRMSNZ\UPSHER\LTRS&REV\74726S05.RV1.BBC.DOC

F/t by:

Bio review OK
M Smela
6/25/01

Addendum to Chemistry Review #1

ANDA Number: 74-726/S-005, S-006, S-007 and S-008
Drug: Potassium Chloride Extended-Release Tablets USP
Firm: Upsher-Smith Laboratories, Inc.

These supplements provide for manufacturing scale-up, equipment and process parameter changes, tablet deboss change and addition of a 90-count bottle have been reviewed February 2001. They were Chemistry Closed, pending for bio review.

The Bio review now has completed (signed on 6/25/01) and it is found Acceptable. The review comments included a Telephone Amendment dated 3/22/01 requested by DBE.

The ANDA supplements are approvable.

Bing Cai/01/30/01
Review Chemist

Mike Smela
Team Leader

cc:ANDA #74-726
DUP File
Division File
Field Copy

Endorsements:

HFD-625/BCai/06/25/01/~~6/20/01~~
HFD-625/MSmela/6/25/01

Project Manager:
HFD-625/M.Dillahunt, PM/

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F/T: DJ 6/25/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-005, S-006, S-007 and S-008

BIOEQUIVALENCE REVIEWS

Potassium Chloride Extended Release Tablets, USP
Klor-Con^{R}, 20 and 10 mEq
ANDA #74-726/SCR 005
Reviewer: Nhan L. Tran
File: 74726D.301

Upsher-Smith
Minneapolis, MN
Submission Date:
March 22, 2001

REVIEW OF A SUPPLEMENT

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. 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 was approved on August 9, 2000.

In December 2000, the firm submitted an amendment to the supplements to request package size and process changes. The following information was submitted to support the amendment:

- Multi-media dissolution data comparing data generated in the year 1995 (submitted in the original application) for Klor-Con M20 (bio-lot 15112) to the data generated in the year 2000 for the same bio-lot
- Multi-media dissolution data comparing data generated in the year 2000 for Klor-Con M20 (bio-lot 15112) to the data generated in the year 2000 for the Klor-Con M20, manufactured by the proposed process, Lot 66203
- Multi-media dissolution data comparing Klor-Con M10 manufactured by the approved process (lot 66689) to the data generated for the product manufactured by the proposed process, Lot 66204.

The Division of Bioequivalence has reviewed the data and concluded that dissolution data submitted by the firm were incomplete. The DBE would like the firm to submit additional data using acetate buffer (not phosphate buffer) pH 4.5, since phosphate solution pH 4.5 does not have a good buffer capacity, and dissolution may be affected. Comparative dissolution data performed in acetate buffer pH 4.5, for 20 mEq and 10 mEq, are submitted in this submission.

Review of dissolution data using acetate buffer pH 4.5:

1. Dissolution data comparing Klor-Con M20 bioequivalency Lot 15112 (data generated for the original application in 1995) to data generated in year 2000 and to Klor-Con M20, Exhibit Lot 66203, manufactured via the proposed process.

Method: Paddle at 50 RPM

900 ml of 0.05M acetate buffer pH 4.5

Lot 15112

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	26.0	39.7	60.9	78.6	92.7
Max.					(b) (4)
Min.					
%CV	3.4%	1.4%	3.2%	2.1%	1.4%

Lot 66203

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	18.2	36.1	64.1	82.6	92.6
Max.					(b) (4)
Min.					
%CV	4.2%	1.4%	1.3%	2.4%	1.5%

F2: 67

2. Dissolution data comparing Klor-Con M10, Lot 66689 (old product) and Lot 66204 (new product), manufactured via the proposed process.

0.05M acetate buffer, pH 4.5

Lot 66689

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	24.4	40.8	69.5	92.2	100.6
Max.					(b) (4)
Min.					
%CV	5.2%	6.0%	2.1%	2.6%	2.0%

Lot 66204

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	19.0	33.6	61.7	79.7	91.8
Max.					(b) (4)
Min.					
%CV	4.2%	2.9%	4.8%	3.5%	0.8%

F2: 53

COMMENTS:

Additional data submitted by the firm indicated that:

1. For Klor-Con M20, dissolution data of the bio-lot 15112 and the lot manufactured by the proposed process (lot 66203), in acetate buffer 0.05M pH 4.5, are comparable. f2 = 67.

2. For Klor-Con M10, dissolution data, in 0.05M acetate buffer, pH 4.5, of the lot manufactured by the approved process (lot 66689) and the one manufactured by the proposed process (lot 66204) are comparable. f2 = 53.

RECOMMENDATION:

After reviewing the data submitted by Upsher-Smith, the Division of Bioequivalence has concluded that dissolution data are adequate for approval of Level 2 SUPAC MR Process Changes.

Nhan L. Tran, Ph. D. 6-12
Review Branch II

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR 6/20/2001

Concur: Date: 6/25/01
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

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

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

Endorsements: (Final with Dates)
HFD-655/ Reviewer (tran) 6-12
HFD-655/ Bio team Leader (nerurkar)
HFD-650/ D. Conner 6/25/01

1. **DISSOLUTION DATA** (DIS) All Strengths
Outcome: **AC**

Outcome Decisions: **AC** - Acceptable

WinBio Comments:

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

GENERIC NAME: Potassium Chloride Extended Release Tablets, USP
ANDA # : 74-726 **SPONSOR :** Upsher-Smith
DOSAGE FORM : Extended Release Tablets STRENGTH(S) : 10 &20 MEq
TYPES OF STUDIES : In-vitro Dissolution
CLINICAL STUDY SITE(S) : N/A
ANALYTICAL SITE(S) : N/A

STUDY SUMMARY: N/A

DISSOLUTION : Dissolution data are adequate for approval of Level 2 SUPAC MR Process Changes.

DSI INSPECTION STATUS

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

PRIMARY REVIEWER : Nhan L. Tran, Ph.D. BRANCH: II
INITIAL : _____ DATE : 6-12

TEAM LEADER : Shriniwas Nanurkar, Ph.D. BRANCH: II
INITIAL : _____ DATE : 6/20/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.
INITIAL : _____ DATE : 6/25/01

SCR-005/us

Potassium Chloride Extended Release Tablets, USP
Klor-Con[R], 20 and 10 mEq
ANDA #74-726
Reviewer: Nhan L. Tran

Upsher-Smith
Minneapolis, MN
Submission Date:
December 22, 2000

REVIEW OF A REQUEST FOR A SUPPLEMENT RECLASSIFICATION-- FROM PRIOR APPROVAL TO CHANGES BEING EFFECTED IN 30 DAYS (CBE-30)

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.
The drug products (20 mEq and 10 mEq tablets) have been approved but they have never been marketed. Subsequently, the firm submitted a series of supplements and a summary of those supplements is given below:

Suppl. #	Date submitted	Nature of submission	Approval date	Note
S-003	4/21/2000	In-process accountability specification changes associated with the manufacture of (b) (4) (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	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.	On 10/16/ 2000, the Chemistry Div. of the OGD denied the CBE-30 request and recommended firm to change to Prior Approval Supplement	Submitted to Chem. Division (SUPAC)
S-006	9/14/2000			
S-007	9/14/2000			
S-008	9/14/2000			
S-005/ 006/007 and 008	12/22/2000	Firm submitted amendment to supplements to request for reclassification from Prior Approval to CBE-30	Pending	Referred to DBE for review and comment

The firm submitted the amendment to the supplements to request a reclassification. i.e., from Prior Approval to Changes Being Effected in 30 days (CBE-30) supplements. In a telephone conversation with the firm, Mr. Smela (Chemistry Team Leader) informed the firm that the tablet deboss change and the scale up (level 1 change) were annual reportable, and the new package size and process change (level 2 change) were CBE-30. But since the firm did not submit correct dissolution data, the CBE-30 request was denied. The Chemistry Division (M. Smela) informed the firm in a telephone conversation on October 3, 2000 that a reclassification can be requested if correct data are submitted to the Agency. Correct information should include comparative multimedia dissolution of the approved and proposed products, not the proposed product and RLD product. The firm submitted comparative multimedia dissolution of the proposed and RLD drugs instead of the approved product because the approved product (bio-lot) is expired. In the same telephone conversation, Mr. Smela indicated that if the approved product (bio-lot) is expired, historical data could be used.
In the present submission, the firm has submitted the following:

- Multi-media dissolution data comparing data generated in the year 1995 (submitted in the original application) for Klor-Con M20 (bio-lot 15112) to the data generated in the year 2000 for the same bio-lot
- Multi-media dissolution data comparing data generated in the year 2000 for Klor-Con M20 (bio-lot 15112) to the data generated in the year 2000 for the Klor-Con M20, manufactured by the proposed process, Lot 66203
- Multi-media dissolution data comparing Klor-Con M10 manufactured by the approved process (lot 66689) to the data generated for the product manufactured by the proposed process, Lot 66204. No historical data for Klor-Con M10 are included in this supplement.

Following are the firm's acceptable dissolution method and specifications:
Method: Paddle at 50 RPM
Medium: 900 ml water

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

It should be noted that the official USP Method for potassium chloride extended release tablet is the same as the firm's method and tolerances is not more than (Q) 35% in 2 hours.

Review of dissolution data:

1. **Multi-media dissolution data comparing Klor-Con M20 bioequivalency Lot 15112 (data generated for the original application in 1995) to data generated in year 2000 and to Klor-Con M20, Exhibit Lot 66203, manufactured via the proposed process.**

Method: Firm's acceptable method: Paddle at 50 RPM, using 900 ml of different dissolution medium.

a. pH 0.1 N HCl

Lot 15112 (old data)

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	25.9	39.8	61.1	77.2	86.6
Max.					(b) (4)
Min.					
%CV	3.4%	2.6%	1.0%	1.4%	0.8%

Lot 15112 (new data)

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	26.4	40.5	65.5	81.8	93.8
Max.					(b) (4)
Min.					
%CV	2.7%	2.2%	3.0%	1.7%	1.2%

F2: 68 Lot 15112 (Old data) versus Lot 15112 (new data)

Lot 66203 (proposed)

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	19	34.6	65.8	79.8	91.6
Max.					(b) (4)
Min.					
%CV	3.6%	3.6%	5.2%	4.7%	3.8%

F2: 67 Lot 15112 (new data) versus Lot 66203 (proposed)

b. 0.05M Phosphate buffer, pH 4.4

Lot 15112 (old data)

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	27.1	41.8	61.9	78.2	88.4
Max.					(b) (4)
Min.					
%CV	4.4%	3.4%	2.8%	2.6%	3.1%

Lot 15112 (new data)

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	26.1	40.6	64.8	80.4	90.6
Max.					(b) (4)
Min.					
%CV	5.4%	4.2%	1.7%	1.5%	1.6%

F2: 82 Lot 15112 (Old data) versus Lot 15112 (new data)

Lot 66203 (proposed)

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	19.1	34.7	63.9	81.9	94.0
Max.	(b) (4)				
Min.					
%CV	2.5%	1.8%	2%	2%	1%

F2: 67 Lot 15112 (new data) versus Lot 66203 (proposed)

c. 0.05M Phosphate buffer, pH 6.2

Lot 15112 (old data)

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	26.9	42.5	64.3	81.6	89.2
Max.	(b) (4)				
Min.					
%CV	4.3%	2.9%	1.6%	1.6%	1.0%

Lot 15112 (new data)

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	27.0	39.4	61.4	78.7	87.3
Max.	(b) (4)				
Min.					
%CV	4.5%	3.9%	4.2%	2.4%	1.0%

F2: 79 Lot 15112 (Old data) versus Lot 15112 (new data)

Lot 66203 (proposed)

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	19.7	35.6	60.2	81.1	90.5
Max.	(b) (4)				
Min.					
%CV	3.6%	2.7%	2.6%	0.9%	0.6%

F2: 69 Lot 15112 (new data) versus Lot 66203 (proposed)

d. Phosphate buffer, pH 7.4

Lot 15112 (old data)

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	25.2	39.3	59.1	74.0	84.9
Max.	(b) (4)				
Min.					
%CV	4.4%	5.1%	2.3%	1.8%	1.5%

Lot 15112 (new data)

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	28.9	41.2	63.1	79.4	91.5
Max.	[redacted] (b) (4)				
Min.					
%CV	2.9%	1.2%	1.7%	1.4%	1.5%

F2: 66 Lot 15112 (Old data) versus Lot 15112 (new data)

Lot 66203 (proposed)

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	20.6	37.9	62.6	82.4	93.7
Max.	[redacted] (b) (4)				
Min.					
%CV	3.6%	1.5%	1.5%	2.2%	1.0%

F2: 68 Lot 15112 (new data) versus Lot 66203 (proposed)

e. Water

Lot 15112 (old data)

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	26.5	40.0	59.7	77.8	89.1
Max.	[redacted] (b) (4)				
Min.					
%CV	3.8%	3.3%	2.7%	3.2%	3.4%

Lot 15112 (new data)

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	26.2	39.1	60.0	77.1	88.9
Max.	[redacted] (b) (4)				
Min.					
%CV	3.4%	2.0%	1.7%	1.9%	1.0%

F2: 97 Lot 15112 (Old data) versus Lot 15112 (new data)

Lot 66203 (proposed)

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	19.2	37.0	62.2	82.0	92.7
Max.	[redacted] (b) (4)				
Min.					
%CV	3.8%	1.8%	1.4%	1.1%	1.7%

F2: 67 Lot 15112 (new data) versus Lot 66203 (proposed)

2. Multi-media dissolution data comparing Klor-Con M10 Exhibit Lot 66689, manufactured via the currently approved process to Klor-Con M10 Exhibit Lot 66204, manufactured via the proposed process.

a. pH 0.1 N HCl

Lot 66689

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	23.7	42.1	67.7	86.2	96.8
Max.	(b) (4)				
Min.					
%CV	8.2%	3.2%	2.4%	2.6%	1.2%

Lot 66204

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	20.5	34.1	62.0	79.8	89.7
Max.	(b) (4)				
Min.					
%CV	2.6%	3.7%	3.2%	2.4%	1.4%

F2: 60

b. 0.05M Phosphate buffer, pH 4.4

Lot 66689

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	25.6	42.3	68.7	86.8	96.4
Max.	(b) (4)				
Min.					
%CV	2.3%	2.7%	3.2%	3.4%	2.9%

Lot 66204

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	20.5	35.5	62.7	80.2	91.8
Max.	(b) (4)				
Min.					
%CV	3.1%	3.4%	2.7%	1.6%	2.4%

F2: 61

c. 0.05M Phosphate buffer, pH 6.2

Lot 66689

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	25.5	42.0	69.2	92.6	104.1
Max.	[redacted] (b) (4)				
Min.					
%CV	3.2%	1.7%	0.7%	1.9%	1.8%

Lot 66204

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	21.0	35.5	62.7	81.2	93.0
Max.	[redacted] (b) (4)				
Min.					
%CV	3.3%	3.5%	2.1%	1.7%	1.2%

F2: 53

d. Phosphate buffer, pH 7.4

Lot 66689

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	24.7	43.6	68.4	91.1	98.7
Max.	[redacted] (b) (4)				
Min.					
%CV	4.8%	3.8%	1.5%	1.8%	3.1%

Lot 66204

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	21.6	36.9	65.4	83.5	97
Max.	[redacted] (b) (4)				
Min.					
%CV	7.7%	3.2%	2.1%	2.6%	2%

F2: 65

e. Water

Lot 66689

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	24	39.3	64.8	85	97.2
Max.	[redacted] (b) (4)				
Min.					
%CV	4.1%	4.1%	1.9%	1.4%	2%

Lot 66204

Parameter	1 hour	2 hours	4 hours	6 hours	8 hours
Av. (N=12)	18.9	35.3	62.3	79.4	91.8
Max.	[redacted] (b) (4)				
Min.					
%CV	6.1%	5.4%	3.4%	2.7%	3.5%

F2: 66

COMMENTS:

1. Dissolution data for Klor-Con M20 generated in the year 1995 for the bio-lot 15112 are comparable to the one generated in the year 2000 for the same bio-lot 15112. F2 ranged from 66 to 97.
2. The same observation can be made when compared dissolution data for Klor-Con M20 of the bio-lot 15112 and the lot manufactured by the proposed process (lot 66203). F2 ranged from 67 to 69.
3. Dissolution data for Upsher -Smith's Klor-Con M10 manufactured by the approved process (lot 66689) and the one manufactured by the proposed process (lot 66204) are comparable in all media. F2 ranged from 53 to 66.
4. No historical data for Klor-Con M10 are submitted in this submission.
5. It is known that the range for the phosphate buffer is from 5.8 to 8 (USP 24, page 2232). Can the pH of the phosphate buffer be 4.4 as the firm reported? The Chemistry Division may ask the firm to explain this issue.

RECOMMENDATION:

The Division of Chemistry should be informed of the above comments.

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

for RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR 2/12/01

Concur: Date: 2/26/2001

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

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

CC: ANDA74-726/s005
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Nhan. L. Tran

V:\FIRMSNZ\74-726\ltrs&rev\74726D.d00
Printed in final on 02/26/2001

Endorsements: (Final with Dates)
HFD-655/ N. Tran
HFD-655/ Bio team Leader
HFD-650/ D. Conner

6/22/01

BIOEQUIVALENCY - submission date: December 22, 2000

8. **OTHER** (OTH) INCOMPLETE

Strengths: 20meq and 10meq
Outcome: IC

WinBio Comments: Chemistry consult

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 74-726/S-005, S-006, S-007 and S-008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

MEETING MINUTES

Meeting Date: 9 March 2001 **Time:** 1300

Location: MPN II Conference Room A

Drug Name: Potassium Chloride Extended Release Tablets
ANDA 74-726

Meeting Type: Internal

Meeting Chair: Rabi Patnaik, DBE

Meeting Recorder: Steven Mazzella, R.Ph.

FDA Attendees, titles and offices:

Nhan Tran, Ph.D.	Reviewer, DBE
Kuldeep Dhariwal, Ph.D	Reviewer, DBE
Rabi Patnaik, Ph.D.	Deputy Director, DBE
Michael Smela, Ph.D.	Team Leader, Chemistry Team 2
Bing Cai, Ph.D.	Reviewer, Chemistry Team 2
Steven Mazzella, R.Ph.	Project Manager, DBE

Meeting Objectives:

1. To discuss the dissolution data submitted by Upsher Smith in support of SUPAC MR level II process changes for ANDA 74-726.

Discussion Points:

1. Upsher Smith has submitted a supplement to ANDA 74-726, Potassium Chloride Extended Release Tablets, 20 meq and 10 meq for SUPAC level II process changes. The 20 meq was approved based on acceptable bioequivalence studies and dissolution testing data in three media. A waiver of *in-vivo* bioequivalence studies was granted for the 10 meq based on acceptable bioequivalence studies for the 20 meq and acceptable dissolution testing for the 10 meq in one media. Upsher Smith has not marketed either product. Upsher Smith doesn't have any 20 meq product manufactured under the approved process.

Upsher Smith does have 10 meq product manufactured under the approved process.

2. The use of historical dissolution data from an approved process is permitted.

3. The original dissolution testing used a phosphate buffer pH 4.5. The USP states that a phosphate buffer can't go below pH 5.8.

Decisions (agreements) reached:

1. The Division of Bioequivalence (DBE) can grant a bio waiver under SUPAC MR. Since Upsher Smith doesn't have any 20 meq product from the approved process, they can use historical dissolution data. In addition, the DBE requests that Upsher Smith conduct additional dissolution testing in acetate buffer pH 4.5 for the 10 meq and 20 meq tablets.

Action items:

1. The DBE will inform the firm of the additional dissolution testing requested in acetate buffer pH 4.5 for the 10 meq and 20 meq tablets.

CBE- THIRTY (30) DAY SUPPLEMENT ROUTING FORM

This form is to accompany all CBE-30 Day supplements. Upon completion, return to the OGD Document Room

I. To be completed by the OGD Document Room using information from the applicant Cover letter:

DATE PROCESSED: 1/25/01
APPLICATION # : 74-726 SUPPLEMENT # : S-005

II: To be determined by Chemistry Division Staff.

Date and initial appropriate category.

Thirty (30) Day CBEs:

Chemistry Div. Staff	Qualifies as CBE-30 (GR)	Does Not Qualify. This is a CBE-0. (DC)	Does not Qualify. This is an Annual Report (DA)	Does not Qualify. This is a Prior Approval Supp. (DN)
Chemistry/Micro Project Manager(s)	[signature]			
Micro and/or Labeling Team Leader (as needed)	N/A			
Chemistry Team Leader	[signature] 1/25/01			
Chemistry Div. Dir. Or Deputy* Dir.				

*Div/Deputy Director signature needed only when: 1) CBE elevated to PAS or 2) PM/TM recommend different actions,
COMMENTS: OK as CBE-30 as amended on 12/22/00

III. To Project Manager Chemistry Team 2 :

Prepare letter and notify applicant by telephone when CBE is denied because it is a prior approval supplement.
DATE:_____

Notify applicant by telephone that inappropriate CBE category used. DATE _____

Request that applicant withdraw supplement when CBE qualifies for submssion as an Annual Report DATE _____

IV. To Document Room

Record appropriate CBE Code OK
File in archival submission

CBE- THIRTY (30) DAY SUPPLEMENT ROUTING FORM

This form is to accompany all CBE-30 Day supplements. Upon completion, return to the OGD Document Room

I. To be completed by the OGD Document Room using information from the applicant Cover letter:

DATE PROCESSED: 1/25/01
APPLICATION # : 74-726 SUPPLEMENT # : S-006

II: To be determined by Chemistry Division Staff.

Date and initial appropriate category.

Thirty (30) Day CBEs:

Chemistry Div. Staff	Qualifies as CBE-30 (GR)	Does Not Qualify. This is a CBE-0. (DC)	Does not Qualify. This is an Annual Report (DA)	Does not Qualify. This is a Prior Approval Supp. (DN)
Chemistry/Micro Project Manager(s)	MDellahert			
Micro and/or Labeling Team Leader (as needed)	N/A			
Chemistry Team Leader	M Smyk 1/25/01			
Chemistry Div. Dir. Or Deputy* Dir.				

*Div/Deputy Director signature needed only when: 1) CBE elevated to PAS or 2) PM/TM recommend different actions,

COMMENTS: OK as CBE-30 as amended on 12/22/00

III. To Project Manager Chemistry Team 2 :

Prepare letter and notify applicant by telephone when CBE is denied because it is a prior approval supplement. DATE:_____

Notify applicant by telephone that inappropriate CBE category used. DATE _____

Request that applicant withdraw supplement when CBE qualifies for submssion as an Annual Report DATE _____

IV. To Document Room

Record appropriate CBE Code OK
File in archival submission

CBE- THIRTY (30) DAY SUPPLEMENT ROUTING FORM

This form is to accompany all CBE-30 Day supplements. Upon completion, return to the OGD Document Room

I. To be completed by the OGD Document Room using information from the applicant Cover letter:

DATE PROCESSED: 1/25/01
APPLICATION # : 74-726 SUPPLEMENT # : S007

II: To be determined by Chemistry Division Staff.

Date and initial appropriate category.

Thirty (30) Day CBEs:

Chemistry Div. Staff	Qualifies as CBE-30 (GR)	Does Not Qualify. This is a CBE-0. (DC)	Does not Qualify. This is an Annual Report (DA)	Does not Qualify. This is a Prior Approval Supp. (DN)
Chemistry/Micro Project Manager(s)	HDallakert			
Micro and/or Labeling Team Leader (as needed)	NA			
Chemistry Team Leader	M Smela 1/25/01			
Chemistry Div. Dir. Or Deputy* Dir.				

*Div/Deputy Director signature needed only when: 1) CBE elevated to PAS or 2) PM/TM recommend different actions,
COMMENTS:
OK as CBE-30 as amended on 1/25/01 12/22/00 MSS

III. To Project Manager Chemistry Team 2 :

Prepare letter and notify applicant by telephone when CBE is denied because it is a prior approval supplement.
DATE:

Notify applicant by telephone that inappropriate CBE category used. DATE

Request that applicant withdraw supplement when CBE qualifies for submssion as an Annual Report DATE

IV. To Document Room

Record appropriate CBE Code GR
File in archival submission

CBE- THIRTY (30) DAY SUPPLEMENT ROUTING FORM

This form is to accompany all CBE-30 Day supplements. Upon completion, return to the OGD Document Room

I. To be completed by the OGD Document Room using information from the applicant Cover letter:

DATE PROCESSED: 9-19-00
APPLICATION # : 74726 SUPPLEMENT # : SCR 005 SCS007 SCA006

II: To be determined by Chemistry Division Staff.

Date and initial appropriate category.

Division/Deputy Director decision is to be used for final classification:

Thirty (30) Day CBEs:

Chemistry Div. Staff	Qualifies as CBE-30 (GR)	Does Not Qualify. This is a CBE-0. (DC)	Does not Qualify. This is an Annual Report (DA)	Does not Qualify. This is a Prior Approval Supp. (DN)
Chemistry/Micro Project Manager(s)				M Dellaherd 9/28/00
Micro Team Leader (as needed)				N/A
Chemistry Team Leader				M Smola 9/29/00
Chemistry Div. Dir. Or Deputy Dir.				GR 9/29/00

COMMENTS: debossa change is AR. New pack size is CBE-30. appears to be Level 1 scale up and Level 1 equip change which is AR. Process change appears to be Level 2. Needs multimedia dissolution profiles vs. current product. Applicant has provide case B profile vs. RLD. Needs Bio Assignment

III. To Project Manager Chemistry Team 2 :

Prepare letter and notify applicnt by telephone when CBE is denied because it is a prior approval supplement.
DATE:_____

Notify applicant by telephone that inappropriate CBE category used. DATE _____

Request that applicant withdraw supplement when CBE qualifies for submssion as an Annual Report **DATE** _____

IV. To Document Room

Record appropriate CBE Code DN
File in archival submission

RECORD OF TELEPHONE CONVERSATION

Upsher-Smith submitted a supplement-Changes being effected in 30 days to the Agency on September 14, 2000 to provide for manufacturing scale up, equipment and process parameter changes, tablet deboss change and addition of a 90 count bottle. Mr. Smela and Michelle Dillahunt called the firm and explained why their CBE was denied. The firm was informed that the data package should include comparative multimedia dissolution data v. approved product.

The firm requested another telecon to go over the data, which they can submit to the Agency.

The firm stated for the M20 tablets, they have multimedia dissolution data at different pH in phosphate buffer and water and [redacted] (b) (4). However, for the M10 tablets, they only have data in water. The data for [redacted] (b) (4) [redacted] (b) (4) was never submitted to the Agency.

Mr. Smela informed the firm, the Agency requires data for all strengths for which the change is being performed. The requirements for SUPAC-MR must be followed for both strengths.
Mr. Smela informed the firm historical data is needed for the M10 strength to make sure there is not a change in profile.
The firm stated they had spoken to Melissa Maust regarding this submission.
Mr. Smela stated he had spoken with Melissa Maust and the Agency did not provide the firm with a formal response to their inquiry. There may have been a misunderstanding on the firm's end.

The firm wants to discuss this issue further as it relates to the SUPAC-MR guidance.

Mr. Mike Smela informed the firm they can submit information to the Division of Bioequivalence and obtain concurrence as a control document or they can consult with Nancy Sager of the Office of Pharmaceutical Science.

DATE
October 6, 2000

ANDA NUMBER
74-726/S-005,006,007

IND NUMBER

TELECON

INITIATED BY

SPONSOR

FDA X

PRODUCT NAME
Klor-Con® M10 an M20 Tablets, 10 mEq & 20 mEq

FIRM NAME
Upsher-Smith Laboratories, Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Michael Poirier
Mark Halvorsen
[redacted] (b) (6)

TELEPHONE NUMBER
(612) 449-7261

SIGNATURE
M.Smela
M.Dillahunt
M Smela 10/10/00
M Dillahunt 10/10/00

Mr. Smela suggested the firm make it clear to the above offices that they are looking for CBE-30 approval.

The firm will submit correspondence to the Division of Bioequivalence and the Office of Pharmaceutical Science and include a cc to each office.

Mr. Smela informed the firm that they will be receiving a CBE-denial letter, however they can submit an amendment to their supplemental applications with the data required in SUPAC-MR or the outcome of their discussions with the above offices and request classification back to CBE-30.

V:\FIRMSNZ\UPSHER\TELECONS\74726.tcon5.doc
CC: ANDA 74-726
Chem Div I, T-con Notebook

RECORD OF TELEPHONE CONVERSATION

Upsher-Smith submitted a supplement-Changes being effected in 30 days to the Agency on September 14, 2000 to provide for manufacturing scale up, equipment and process parameter changes, tablet deboss change and addition of a 90 count bottle. I called the firm on September 29,2000 and informed them that their CBE-30 had been denied and that it is a prior approval supplement. The firm requested a telecon to discuss this issue.

Mr. Smela informed the firm that the tablet deboss change and the level one scale up change is annual reportable. The new package size and process change is level 2 which is CBE-30. Mr. Smela stated that the incorrect data package was included with the submission. The data should include comparative multimedia dissolution data v. approved product.

The firm stated that could not provide data on the approved product because they have not started marketing the product.

The firm request to use the original lots.

Mr. Smela stated the original lots could be used if f_2 of original lots based on current testing are still OK past expiry when compared to the historical data.

The firm agreed to submit current dissolution data v. original data and new process material data v. original batches.

Mr. Smela informed the firm that they will be receiving a CBE-denial letter, however they can submit an amendment to their supplemental applications with the above data and request classification back to CBE-30.

DATE
October 3, 2000

ANDA NUMBER
74-726/S-005,006,007

IND NUMBER

TELECON

INITIATED BY

SPONSOR

FDA X

PRODUCT NAME
Klor-Con® M10 an M20 Tablets, 10 mEq & 20 mEq

FIRM NAME
Upsher-Smith Laboratories, Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Michael Poirier
Mark Robbins
Mark Halvorsen
(b) (6)

TELEPHONE NUMBER
(612) 449-7261

SIGNATURE
M. Smela M Smela 10/6/00
M. Dillahunt
M Dillahunt 10/6/00

V:\FIRMSNZ\UPSHER\TELECONS\74726.tcon4.doc
CC: ANDA 74-726
Chem Div I, T-con Notebook

ANDA 74-726/S-005,S-006,S-007,S-008

OCT 16 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 September 14, 2000, 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).

The supplemental applications, submitted as "Supplement-Changes Being Effected in 30 Days", provide for manufacturing scale-up, equipment and process parameter changes, tablet deboss change and addition of a 90-count bottle.

Reference is made to the telephone conversation on October 3, 2000, between Mike Smela and Michelle Dillahunt of the Office of Generic Drugs and Michael Poirier, Mark Robbins, Mark Halvorsen and [redacted] (b) (6) of Upsher-Smith Laboratories, Inc. in which you were informed that incorrect data were submitted in your supplemental applications. The data should include comparative multimedia dissolution data versus your approved product. You have provided Case B dissolution profile data versus the Reference Listed Drug.

The changes that you have submitted are not, in our opinion, the kind permitted by regulation to be put into effect in advance of approval of the supplements. The changes require approval of a supplement before a product made with the changes can be distributed.

This letter is to notify you that an approved supplement is required for the proposed changes and that the supplements are under review. Please do not implement the proposed changes until you receive notification that the supplemental applications are approved. Alternatively, you may amend these supplements with the appropriate information and re-institute their CBE-30 status.

Sincerely yours,

10/13 cc

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:

HFD-625/MSmela/10/6/00 MSmela 10/10/00
HFD-617/MDillahunt PM/10/3/00 MDillahunt 10/10/00
V:\FIRMSNZ\UPSHER\LTRS&REV\74726S05.CBE.DOC

DRAFTED by: MDillahunt
F/T by: