MICRO-K LS.RSP
(19-561)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-561

AUG 26 1988

A.H. Robins Company
Research Laboratories
Attention: Emily M. Morley, M.D.
1211 Sherwood Avenue
P.O. Box 26609
Richmond, VA 23261-6609

Dear Dr. Morley:

Please refer to your December 30, 1985 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Micro-K LS (potassium chloride for liquid suspension) 1.5 g (20 mEq) Packets.

We also acknowledge receipt of your amendments dated August 5 and 22, 1988.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed package insert and draft carton and container labels submitted on August 24, 1988. Accordingly, the application is approved effective on the date of this letter.

As requested in our August 1, 1988 letter, please submit legible introductory promotional material that you propose to use for this product. Please submit one copy to this division and a second, along with a copy of the package insert, directly to:

Division of Drug Advertising and Labeling, HFD-240
Room 10B-04
5600 Fishers Lane
Rockville, Maryland 20857

Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

As soon as they are available please submit one market package of the drug and twelve copies of the final printed container and carton labels, seven of which are individually mounted on heavy weight paper or similar material.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Virginia O'Hagan
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

Ray Lipicky

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

A·H·ROBINS

August 1988

MICRO-K® LS

brand of **Potassium Chloride**
Extended-Release Formulation
for Liquid Suspension

U.S. Patent 4,259,315

APPROVED
AUG 26 1988

Labeling:
NDA No: 19
Reviewed by:

Working Copy
561 Rec'd. Aug 24, 1988

Pharmaceutical Division
A. H. Robins Company
Richmond, VA 23220

A·H·ROBINS

Front Page 2

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

To take each dose with meals mixed in water or other suitable liquid.

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 inform patients that this product contains as a dispersing agent the stool softener, docusate sodium, which may change stool consistency, or rarely produce diarrhea or cramps.

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

Laboratory Tests: Regular serum potassium determinations are recommended, especially in patients with renal insufficiency or diabetic nephropathy.

When blood is drawn for analysis of plasma potassium, it is important to recognize that artifactual elevations can occur after improper venipuncture technique or as a result of *in vitro* hemolysis of the sample.

Drug Interactions: Potassium-sparing diuretics, angiotensin converting enzyme inhibitors: see WARNINGS.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity, mutagenicity, and fertility studies in animals have not been performed. Potassium is a normal dietary constituent.

Pregnancy Category C. Animal reproduction studies have not been conducted with Micro-K LS. 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 children have not been established.

Adverse Reactions: One of the most severe adverse effects is hyperkalemia (see CONTRAINDICATIONS, WARNINGS, AND OVERDOSAGE).

Gastrointestinal bleeding and ulceration have been reported in patients treated with microencapsulated KCl (see WARNINGS).

In addition to bleeding and ulceration, perforation and obstruction have been reported in patients treated with solid KCl dosage forms, and may occur with Micro-K LS.

The most common adverse reactions to the 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 taking the dose with meals, or reducing the amount taken at one time.

Skin rash has been reported rarely with potassium preparations.

In a controlled clinical study Micro-K LS was associated with an increased frequency of gastrointestinal intolerance (e.g., diarrhea, loose stools, abdominal pain, etc.) compared to equal doses (100 mEq/day) of Micro-K Extencaps (see WARNINGS, Diarrhea or Dehydration). This finding was attributed to an inactive ingredient used in the Micro-K LS formulation that is not present in the Micro-K Extencaps formulation.

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-wave, 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 solution 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 potassium intake 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 are given such that no more than 20 mEq is given in a single dose.

Usual Adult Dose—One Micro-K LS 20 mEq packet 1 to 5 times daily, depending on the requirements of the patient. This product must be suspended in a liquid, preferably water, or sprinkled on food prior to ingestion.

Suspension in Water: Pour contents of packet slowly into approximately 2–6 fluid ounces (¼–¾ glassful) of water. Stir thoroughly for approximately 1 minute until slightly thickened, then drink. The entire contents of the packet must be used immediately and not stored for future use. Any microcapsule/water mixture should be used immediately and not stored for future use.

Suspension in Liquids other than Water: Studies conducted using orange juice, tomato juice, apple juice and milk as the suspending liquid have shown that the quantity of fluid used to suspend one Micro-K LS packet MUST be limited to 2 ***fluid ounces (¼ glassful)***. The use of volumes greater than 2 fluid ounces substantially reduces the dose of potassium chloride delivered. If a liquid other than water is used to suspend Micro-K LS then the contents of the packet should be slowly poured into **2 *fluid ounces (¼ glassful)*** of liquid. Stir thoroughly for approximately 1 minute, then drink. The entire contents of the packet must be used immediately and not stored for future use. Any microcapsule/liquid mixture should be used immediately and not stored for future use.

Sprinkling Contents on Food: Micro-K LS may be given on soft food that may be swallowed easily without chewing, such as applesauce or pudding. After sprinkling the contents of the packet on the food, it should be swallowed immediately without chewing and followed with a glass of cool water, milk, or juice to ensure complete swallowing of all the microcapsules. Do not store microcapsule/food mixture for future use.

How Supplied: Micro-K LS containing 1.5 g microencapsulated potassium chloride (equivalent to 20 mEq K) per packet in cartons of 30 (NDC 0031-5760-56) and 100 packets (NDC 0031-5760-63).

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

CAUTION: Federal law prohibits dispensing without prescription.

August 1988

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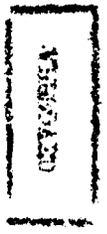
Package Outsert



Printed in U.S.A.

Description: Micro-K LS is an oral dosage form of microencapsulated potassium chloride. Each packet contains 1.5 g of Potassium Chloride, USP equivalent to 20 mEq of potassium. Micro-K LS is comprised of specially formulated granules. After reconstitution with 2–6 fl oz of water and 1 minute of stirring, the suspension is odorless and tasteless.

Each crystal of potassium chloride (KCl) is microencapsulated with an insoluble polymeric coating which functions as a semipermeable membrane; it allows for the controlled release of potassium and chloride ions over an eight-ten hour period. The controlled release of K^+ ions by the microcapsular membrane is intended to reduce the likelihood of a high localized concentration of potassium chloride at any point on the mucosa of the gastrointestinal tract. Fluids pass through the membrane and gradually dissolve the potassium chloride within the microcapsules. The resulting potassium chloride solution slowly diffuses outward through the membrane.

Micro-K LS is an electrolyte replenisher. The chemical name of the active ingredient is potassium chloride and the structural formula is KCl. Potassium Chloride, USP occurs as a white, granular powder or as colorless crystals. It is odorless and has a saline taste. Its solutions are neutral to litmus. It is freely soluble in water and insoluble in alcohol.

Inactive Ingredients: Docusate Sodium, Ethylcellulose, Povidone, Silicon Dioxide, Sucrose, and another ingredient.

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

back Page

CONTROLLED RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE IMMEDIATE RELEASE LIQUIDS/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, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium losing nephropathy, and certain diarrheal states.

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

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

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

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

Warnings: *Hyperkalemia* (see OVERDOSAGE). In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage 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 sustained release wax matrix formulations (less than one per 100,000 patient years). Because of the lack of extensive marketing experience with microencapsulated products, a comparison between such products and wax matrix or enteric coated products is not available. Micro-K LS is administered as a liquid suspension of microencapsulated potassium chloride formulated to provide a controlled rate of release of 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 controlled release formulation under conditions which did not resemble usual or recommended clinical practice (i.e., 96 mEq per day in divided doses of potassium chloride administered to fasted patients, in the presence of an anticholinergic drug to delay gastric emptying). The upper gastrointestinal lesions observed by endoscopy were asymptomatic and were not accompanied by evidence of bleeding (hemoccult testing). The relevance of these findings to the usual conditions (i.e., non-fasting, no anticholinergic agent, smaller doses) under which controlled release potassium chloride products are used is uncertain; epidemiologic studies have not identified an elevated risk, compared to microencapsulated products, for upper gastrointestinal lesions in patients receiving wax matrix formulations. Micro-K LS should be discontinued immediately and the possibility of ulceration, obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Diarrhea or Dehydration. Micro-K LS contains, as a dispersing agent, docusate sodium, which also increases stool water and is used as a stool softener. Clinical studies with Micro-K LS indicate that minor changes in stool consistency may be common, although usually are well-tolerated. However, rarely patients may experience diarrhea or cramping abdominal pain. Patients with severe or chronic diarrhea or who are dehydrated ordinarily should not be prescribed Micro-K LS.

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.

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60% Screen of BLUE

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DIRECTIONS FOR USE: Pour contents of packet slowly into approximately 2–6 fl oz (¼–¾ glassful) of water while stirring. Stir thoroughly for approximately 1 minute until slightly thickened, then drink.

DOSAGE: As directed by physician. Consult physician or pharmacist for use in other liquids.

PHARMACEUTICAL DIVISION
A. H. ROBINS COMPANY, RICHMOND, VA. 23220

LOT

EXP.

MICRO-K® LS
(Potassium Chloride)
Extended-Release Formulation
For Liquid Suspension

DIRECTIONS FOR USE: Pour contents of packet slowly into approximately 2–6 fl oz (¼–¾ glassful) of water, while stirring. Stir thoroughly for approximately 1 minute until slightly thickened, then drink. Consult physician or pharmacist for use in other liquids.

KEEP THIS AND ALL MEDICINES OUT OF REACH OF CHILDREN.

Store at Controlled Room Temperature, Between 15°C and 30°C (59°F and 86°F).

U.S. Patent 4,259,315

PATIENT INSTRUCTIONS

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PHARMACEUTICAL DIVISION 8.88
A. H. ROBINS COMPANY, RICHMOND, VA. 23220

MICRO-K® (Potassium Chloride) LS
Extended-Release Formulation For Liquid Suspension
Each packet contains 1.5 g KCl (20 mEq K)
4 PACKETS

PROFESSIONAL SAMPLES—
NOT FOR SALE
NDC 0031-5760-32

A·H·ROBINS

MICRO-K® LS
(Potassium Chloride)
Extended-Release Formulation
For Liquid Suspension
Each packet contains 1.5 g KCl (20 mEq K)

[redacted]

CAUTION: Federal law prohibits dispensing without prescription.

4 PACKETS

MICRO-K® (Potassium Chloride) LS Extended-Release Formulation For Liquid Suspension
Each packet contains 1.5 g KCl (20 mEq K)
4 PACKETS

MICRO-K® (Potassium Chloride) LS Extended-Release Formulation For Liquid Suspension

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A.H. ROBINS

NDC 0031-5760-56

MICRO-K® LS

(Potassium Chloride)

Extended-Release Formulation

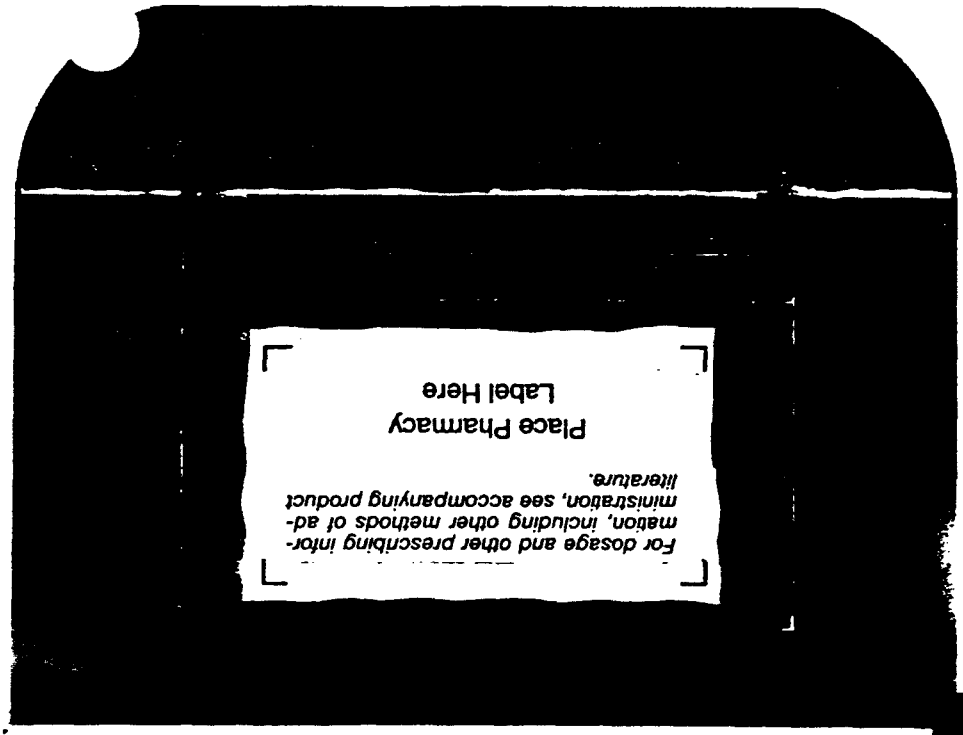
For Liquid Suspension

Each packet contains 1.5 g KCl (20 mEq K)

CAUTION: Federal law prohibits dispensing without prescription.

30 PACKETS

MICRO-K® LS
(Potassium Chloride)
Extended-Release Formulation
For Liquid Suspension
Each packet contains 1.5 g KCl (20 mEq K)
30 PACKETS



MICRO-K® LS
(Potassium Chloride)
Extended-Release Formulation
For Liquid Suspension

DIRECTIONS FOR USE: Pour contents of packet slowly into approximately 2–6 fl oz (¼–¾ glassful) of water, while stirring. Stir thoroughly for approximately 1 minute until slightly thickened, then drink. Consult physician or pharmacist for use in other liquids.

KEEP THIS AND ALL MEDICINES OUT OF REACH OF CHILDREN.

Store at Controlled Room Temperature, Between 15°C and 30°C (59°F and 86°F).

U.S. Patent 4,259,315

PHARMACEUTICAL DIVISION 8.88
A. H. ROBINS COMPANY, RICHMOND, VA. 23220

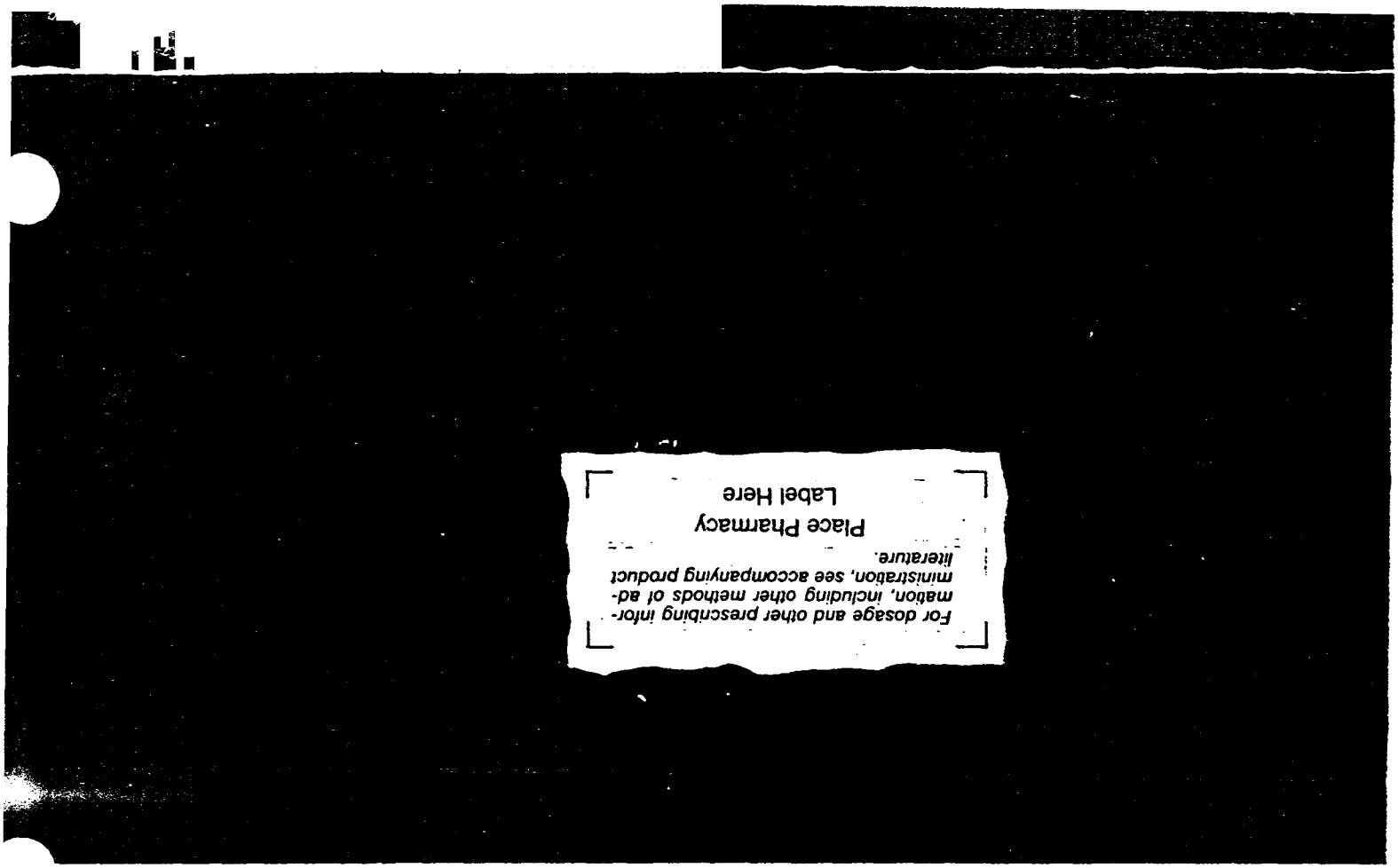
MICRO-K® LS
(Potassium Chloride)
Extended-Release Formulation
For Liquid Suspension

Each packet contains 1.5 g KCl (20 mEq K)

LOT

EXP.

30 PACKETS



MICRO-K® LS
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Extended-Release Formulation
For Liquid Suspension

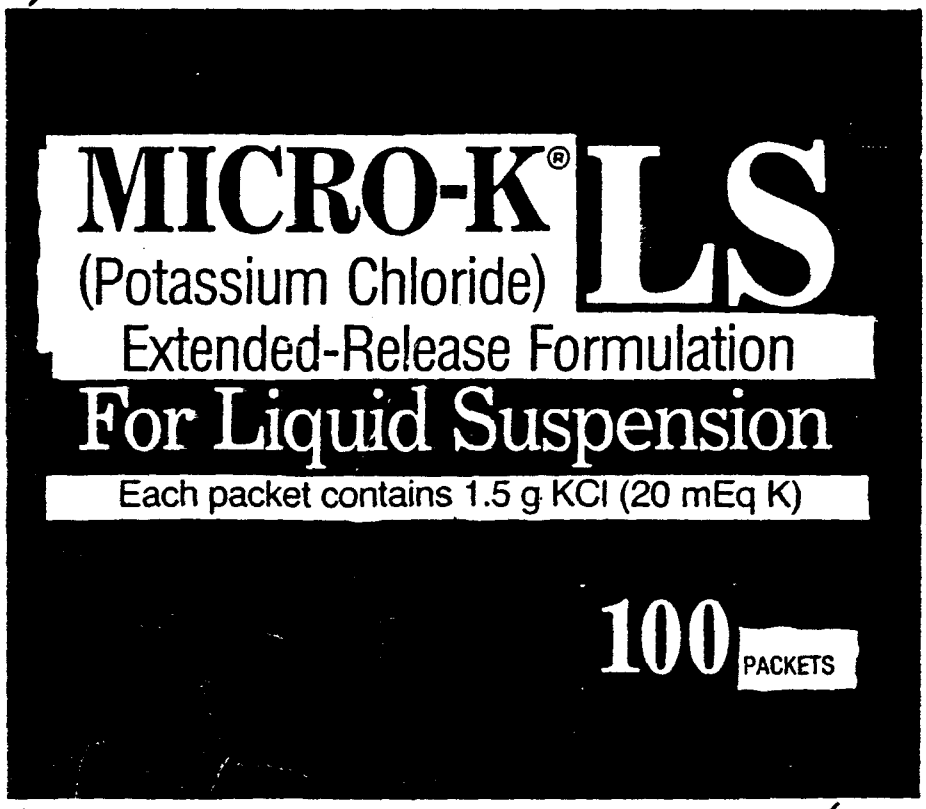
DIRECTIONS FOR USE: Pour contents of packet slowly into approximately 2–6 fl oz (¼–¾ glassful) of water, while stirring. Stir thoroughly for approximately 1 minute until slightly thickened, then drink. Consult physician or pharmacist for use in other liquids.

KEEP THIS AND ALL MEDICINES OUT OF REACH OF CHILDREN.

Store at Controlled Room Temperature, Between 15°C and 30°C (59°F and 86°F).

U.S. Patent 4,259,315

PHARMACEUTICAL DIVISION 8.88
A. H. ROBINS COMPANY, RICHMOND, VA. 23220


MICRO-K® LS
(Potassium Chloride)
Extended-Release Formulation
For Liquid Suspension
Each packet contains 1.5 g KCl (20 mEq K)
100 PACKETS

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A.H. ROBINS

NDC 0031-5760-6

MICRO-K® LS

(Potassium Chloride)

Extended-Release Formulation

For Liquid Suspension

Each packet contains 1.5 g KCl (20 mEq K)

[redacted]

CAUTION: Federal law prohibits dispensing without prescription.

100 PACKETS

MICRO-K® LS

(Potassium Chloride)

Extended-Release Formulation

For Liquid Suspension

Each packet contains 1.5 g KCl (20 mEq K)

LOT

EXP.

100 PACKETS

AUG 1 1988

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

FROM: Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Micro-K LS, NDA 19-561

TO: The File

The saga of NDA 19-561 is of interest. In my judgement, Micro-K LS is a product suitable for marketing and may even represent a "break-through" in administering supplemental KCl to patients.

The product is a slightly modified formulation of Micro-K, which is approved and, by formal studies and moderate marketing history, no more unsafe than any other solid oral dosage form of KCl.

Since the disintegration time constant of Micro-K capsules is measured in minutes and the potassium release from the encapsulated granules has a time constant of 10 s of minutes (i.e., release of potassium from the micro capsules is at least an order of magnitude slower than the release of the microcapsules from the dosage form capsule), the fact that Micro-K LS is administered as a suspension (i.e., bypassing disintegration time) seems to be irrelevant with respect to the expected biological effects of Micro-K LS.

Because it is a new dosage form (i.e., Micro-K microcapsules suspended in a user selected aqueous medium) we were careful to document

a) The suspension can be easily made, is stable and is uniform,

b) The labeled contents can be expected to be delivered,

c) The dose delivered systemically (i.e., bioavailability) is unchanged from similar doses of Micro-K,

d) The differences in formulation (i.e., Docusate) do not have detectable biological effects in man, and

e) The new product can be manufactured and distributed in conformance with usual quality and accuracy.

Of particular note is that there was no experiment (animal, clinical trial or other conventional source) that added to or detracted from the necessity of making our clinical judgement regarding safety and efficacy from the knowledge derived from previous studies and marketing history related to Micro-K capsules. There is no data which indicate that Micro-K LS differs in safety (particularly GI) from Micro-K LS. In passing, I note that we have just concluded that Micro-K and other solid oral dosage forms of potassium chloride are not to be distinguished with respect to known or speculative safety or efficacy.

Additionally, the 2 solid oral dosage forms which employ "explo" technology (i.e, the Key-now-Schering product and the Netherlands product), disintegrate with a time constant of seconds. Hardly different from a suspension of microencapsulated granules. Yet, they share labeling with wax-matrix formulations. This sharing is explicitly because we concluded we could not make a data dependant judgement that they were safer in any clinically relevant way.

In spite of all the above, the current Micro-K LS container and carton labels and package insert lead one to the conclusion that Micro-K LS is expected to be as safe as an oral solution of KCl. I don't see where any data allow such an inference.

I agree with Dr. Graham's concern related to packaging (which starts the whole conception, in my interpretation). Container and package labels can easily be modified by replacing "(Potassium Chloride)" with "(Controlled-Release KCl)." The substitution requires only 4 additional characters.

The package insert may be changed by changing the title from "Micro-K LS, brand of, Potassium Chloride for Liquid Suspension" to "Micro-K LS, brand of Controlled-Release Potassium Chloride for Liquid Suspension."

There is no reason the package insert should not conform exactly to the proposed generic labeling. Although Micro-K LS is swallowed as a suspension, the safety and efficacy of the KCl part is not significantly different from Micro-K Capsules.

Since the class labeling for solid oral dosage form KCl has not been fully implemented, if Robins wishes to go with the currently submitted insert, that is O.K. However, the initial portion of the Gastrointestinal Lesions section must be deleted. I cannot see why one would speculate that Micro-K LS is as safe as an oral solution. Micro-K LS, as far as the characteristics of KCl release, are identical to those of Micro-K capsules. If this were not true, Micro-K LS would not be approvable. As far as I can tell, the "unsafety" of solid oral dosage forms of KCl relate to the release characteristics of KCl, not to the dispersibility of the dosage form.

My understanding of the current status of this application is that it, unfortunately, has received an approvable letter and ther indicated agreement with container and package insert format. As a consequence, bulk printing has already occurred. That is unfortunate but as it stands now it cannot be approved.

Paragraph 1 - O.K.

Paragraph 2 - O.K.

Paragraph 3

We have completed our review of this application and have concluded the product is approvable provided that there are substantive changes in labeling.

Your application contains no data comparing the safety of Micro-K LS to that of an oral solution, Micro-K or any other orally administered KCl formulation. In fact, the entire safety assessment rests upon the data base which supports your Micro-K product.

As you know, we have (after long and intensive deliberation, which included consultants and an Advisory Committee meeting) concluded that Micro-K has not established that there is any clinically relevant extrapolation from the McMahon type human endoscopy studies nor from the animal toxicology.

Micro-K LS and Micro-K, from the risk of gastrointestinal risks, do not differ substantively. Since Micro-K is not devoid of gastric irritation (as has been demonstrated by the McMahon type studies) it is logical to conclude that the rate at which potassium chloride is released is an important feature of the gastrointestinal irritant potential of the dosage form. Since Micro-K LS and Micro-K are similar in this regard, Micro-K LS and Micro-K are not to be differentiated in any regard (except for the physical characteristics that differentiate their identification and/or mode of administration).

In this regard, the final printed labeling submitted on July 27, 1988 is not acceptable and misrepresents the product which we find approvable, provided the following labeling changes are made.

1) Package Container and Carton Labeling.

   Change "(Potassium Chloride)" to "(Controlled-Release KCl)." It is our understanding that, based upon verbal agreements with the staff to the Division of Cardio-Renal Drug Products, you have printed substantial quantities of these items.

   If such is the case, the changes can be made at next printing. However, submit the new samples in your response to this letter.

2) Package Insert.

   There is no reason that the labeling of Micro-K LS and Micro-K should differ expect as pertinent to the physical properties of the two formulations. Nor is there any reason to depart from the class labeling we sent to you on August 19, 1987. Any suggestion that Micro-K LS and Micro-K might differ with respect to clinical safety is totally unacceptable.

The initial promotional campaign is essentially not evaluable. Please submit copy that is readable. Then we can respond to the thrust of your campaign, if necessary.

Raymond J. Lipicky, M.D.

cc
Orig.
HFD-110
/HFD-110/CSO
HFD-110/RLipicky;7/31/88
sb/7/31/88;7/31/88/1160S

AUG 1 1988

NDA 19-561

A.H. Robins Company
Attention: Ms. Frances Aaroe
1211 Sherwood Avenue
P.O. Box 26609
Richmond, VA 23261-6609

Dear Ms. Aaroe:

Please refer to your December 30, 1985 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Micro-K LS (potassium chloride for liquid suspension) 20 mEq.

We also acknowledge receipt of your correspondence and amendments dated April 20 and 27, June 7 and July 27, 1988.

We have completed our review of this application and once again conclude the product is approvable but there must be substantive changes in labeling. Our previous communication with you regarding approvability, unfortunately, was a gross oversight with respect to appropriate labeling of your product.

Your application contains no data comparing the UGI irritant potential of Micro-K LS to that of an oral solution, Micro-K or any other orally administered KCl formulation. In fact, the entire safety assessment in this regard, rests upon the data base which supports your Micro-K product. The one comparison provided (Micro-K LS vs. Micro-K) showed Micro-K LS to be somewhat less tolerated, in general, than Micro-K.

As you know, we have (after long and intensive deliberation, which included consultants and an Advisory Committee meeting) concluded that data obtained from studies of Micro-K has not established that there is any clinically relevant extrapolation from McMahon type human endoscopy studies nor from animal toxicology and that the epidemiology studies available to date are also not convincing.

Micro-K LS and Micro-K, from an apriori risk of gastrointestinal irritation, do not logically differ substantively. Since Micro-K is not devoid of gastric irritation (as has been demonstrated by the McMahon type studies) it is logical to conclude that the rate at which potassium chloride is released is an important feature of the gastrointestinal irritant potential of the dosage form. Since Micro-K LS and Micro-K are similar in this regard, Micro-K LS and Micro-K are not to be differentiated in any regard in labeling (except for the physical characteristics that differentiate their identification and/or mode of administration).

In this regard, the final printed labeling submitted on July 27, 1988 is not acceptable and misrepresents the product which we find approvable. The following labeling changes would be acceptable.

1) Package Container and Carton Labeling.

Change "(Potassium Chloride)" to "(Controlled-Release KCl)." It is our understanding that you have already printed substantial quantities of these items.

If such is the case, the changes can be made at next printing. However, submit new container and carton labeling in your response to this letter.

2) Package Insert.

There is no reason that the labeling of Micro-K LS and Micro-K should differ except as pertinent to the physical properties of the two formulations. Nor is there any reason to depart from the class labeling we sent to you on August 19, 1987. Any suggestion that Micro-K LS and Micro-K might differ with respect to clinical safety is totally unacceptable, except in regard to the sections that deal with the results of trial number 31.

The initial promotional campaign is essentially not evaluable. Please submit copy that is readable. Then we can respond to the thrust of your campaign, if necessary.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact:

Ms. Virginia O'Hagan
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA
HFD-110
HFD-110/CSO
HFD-80/DDIR
HFD-232 (with labeling)
HFD-102/LCarter
HFD-110/SBenton
HFD-110/VO'Hagan/6/27/88;7/28/88
sb/6/27/88;7/27/88;7/28/88;7/28/88;7/31/88/8/1/88/11625
R/D: AThompson/7/22/88
RWolters/7/22/88;7/26/88;7/28/88;7/28/88
WVanArsdel/7/25/88
CResnick/7/25/88;7/28/88
CGraham/7/16/88
MMorgenstern/7/28/88;7/28/88
Revised by RLipicky/7/31/88

APPROVABLE

JUN - 9 1988

Division of Cardio-Renal Drug Products
Medical Officer's Review

Number: NDA 19-561
Drug Name: Micro-K LS
Sponsor: AHRobins

Submission Type: FPL
Submission Date: 7 June 1988
Date of Receipt: 9 June 1988
Review Complete: 9 June 1988

Content:

MOR #3 dated 31 March 1988 contains the marked-up labeling for this approvable application. The sponsor has incorporated most of the changes into the labeling with a few minor editorial changes. The one exception is the use of "extended release" to describe the formulation.

Assessment:

The omission of the extended-release description for the potassium chloride formulation is not a critical concern from the FDA viewpoint, because it permits labeling that appears very similar to that already used by the immediate-release potassium chloride products. It does not, however, permit a NEW category of potassium chloride products to be identified. Micro-K LS is different in formulation and final product packaging from either the immediate-release products and the solid oral extended-release products. Therefore, it would seem reasonable to include descriptive wording in the product labeling that would make this differentiation. Discussions of this issue have been held with the Chemistry staff and some resolution will most likely be reflected in the approval letter to the sponsor.

Plan:

CSO should make certain that approval letter does not issue without a note in the file that either the issue identified above had been resolved and/or included in the approval letter.

Cheryl Fossum Graham, M.D.

cc:
Orig NDA 19-561
HFN-110
HFN-110/CSO
HFN-110/CGRAHAM

MM# N1956113/cfg/9jun88

APR 25 1988

NDA 19-561

A.H. Robins Company
Research Laboratories
Attention: Ms. Frances Aaroe
1211 Sherwood Avenue
P.O. Box 26609
Richmond, VA 23261-6609

Dear Ms. Aaroe:

Please refer to your December 30, 1985 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Micro-K LS (potassium chloride for liquid suspension), 1.5 g (20 mEq).

We also acknowledge receipt of your amendments dated November 3, 1986; February 9, 1987; and January 7 and 27 and March 25, 1988.

We have completed the review of this application as submitted with draft labeling. Before the application may be approved, however, it will be necessary for you to submit final printed labeling for the drug. The labeling should be identical in content to the enclosed marked-up draft. If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

In addition, we would appreciate your submitting copies of the introductory promotional material that you propose to use for this product. Please submit one copy to this division and a second, along with a copy of the package insert, directly to:

Division of Drug Advertising and Labeling, HFN-240
Room 10B-04
5600 Fishers Lane
Rockville, Maryland 20857

Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

Please submit twelve copies of the printed labels and other labeling seven of which are individually mounted on heavy weight paper or similar material.

The Division of Biopharmaceutics requests that you submit detailed methodology on the sampling technique, the filtering of samples, and the accounting for microencapsulated particles lost while sampling.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Ms. Virginia O'Hagan
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Original NDA
HFN-110
HFN-110/CSO
HFN-240 (with draft labeling)
HFN-80/DDIR
HFN-110/VO'Hagan/4/5/88;4/14/88
sb/4/5/88;4/6/88;4/14/88;4/21/88;4/22/88/0732S
R/D: AThompson/4/7/88
RWolters/4/7/88;4/15/88
CResnick/4/8/88;4/14/88
WVanArsdel/4/7/88
MRose/4/12/88
NMorgenstern/4/13/88;4/15/88
CGraham/4/11/88

APPROVABLE

Top

Lot No.
Exp. Date:

Place Pharmacy Label Here

Front

Professional Sample — 4 Packets
NDC 0031-5760-56 — 30 Packets
NDC 0031-5760-63 — 100 Packets

Micro-K® LS

(Potassium Chloride for Liquid Suspension)

1.5g (20 mEq K)
in each packet

CAUTION: Federal law prohibits dispensing without prescription.

Back

Directions for use: Pour contents of packet slowly into approximately ~~2~~ 2-6 fl. oz. (1/4 - 3/4 glassful) of water, ~~milk, or favorite juice~~ while stirring. Stir thoroughly for approximately 1 minute until slightly thickened, then drink.

For dosage and other prescribing information, see accompanying product literature.

Keep this and all medicines out of reach of children.

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

U. S. Patent 4,259,315

Pharmaceutical Division
A. H. Robins Company, Richmond, Virginia 23220

Sides

30 Packets
100 Packets

Micro-K® LS

(Potassium Chloride for Liquid Suspension)

1.5g (20 mEq K)
in each packet

IMMEDIATE CONTAINER LABEL FOR 20 mEq PACKET

FRONT PORTION

Micro-K® LS

(Potassium Chloride for Liquid Suspension)

1.5g (20 mEq K)

CAUTION: Federal law prohibits dispensing without prescription.

A. H. ROBINS

BACK

Directions for use: Pour contents of packet slowly into approximately 2 fl. oz. (1/4 glassful) of water, milk, or favorite juice while stirring. Stir thoroughly for approximately 1 minute until slightly thickened, then drink.

to color

to previous page

DOSAGE: As directed by physician.

for other methods of administration, see accompanying product literature

Lot Number
Expiration Date

Pharmaceutical Division
A. H. Robins Company, Richmond, VA 23220

PROPOSED MICRO-K LABELING

Micro-K® LS

Brand of Potassium Chloride for Liquid Suspension → Extended-release

DESCRIPTION

Micro-K LS is an oral dosage form of microencapsulated potassium chloride. Each packet contains 1.5 g of potassium chloride USP equivalent to 20 mEq of potassium. Micro-K LS is comprised of specially formulated granules for reconstitution which will remain suspended in a liquid ~~imparting virtually no taste to the liquid.~~ → after reconstitution with 4 oz of water and 1 minute of stirring, the suspension is odorless and tasteless.

Each crystal of potassium chloride (KCl) is microencapsulated by a patented process with an insoluble polymeric coating which functions as a semi-permeable membrane; it allows for the controlled release of potassium and chloride ions over an eight ~~to ten~~ hour period. The controlled release of K^+ ions by the microcapsular membrane is intended to reduce likelihood ~~avoid the possibility that excessive amounts of KCl can be~~ localized at any point on the mucosa of the gastrointestinal tract. → of a high localized concentration of potassium chloride

Fluids pass through the membrane and gradually dissolve the potassium chloride within the microcapsules. The resulting potassium chloride solution slowly diffuses outward through the membrane.

Micro-K LS is an electrolyte replenisher. The chemical name of the active ingredient is potassium chloride and the structural formula is KCl. Potassium chloride USP occurs as a white, granular powder or as colorless crystals. It is odorless and has a saline taste. Its solutions are neutral to litmus. It is freely soluble in water and insoluble in alcohol.

Inactive Ingredients: Docusate Sodium, Ethylcellulose, Povidone, Silicon Dioxide, Sucrose, and another ingredient.

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 [illegible], 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

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

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

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

CONTRAINDICATIONS

Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis,

acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene, amiloride) (see OVERDOSAGE).

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 controlled release Micro-K Extencaps (<0.1 per 100,000 patient years). ~~Micro-K~~/Micro-K LS is administered as a liquid suspension, it is expected that the frequency of small bowel lesions would be no greater than and possibly less than the frequency reported with ~~Micro-K Extencaps~~ sustained release wax matrix formulations.

One Micro-K LS Packet contains approximately 20,000 microcrystals individually coated with an insoluble, semi-permeable membrane formulated to provide a controlled rate of release of potassium chloride solution and thus to avoid the possibility that excessive amounts of potassium chloride can be localized at any one point on the mucosa of the gastrointestinal tract.

The relative risk of gastrointestinal tract bleeding due to potassium preparations was assessed in a large, retrospective, epidemiological study, and the incidence of gastrointestinal bleeding from Micro-K Extencaps was approximately 33% lower than from a wax-matrix preparation.

Solid oral dosage forms of potassium chloride can produce ulcerative and/or stenotic lesions of the gastrointestinal tract. Based on spontaneous adverse reaction reports, enteric coated preparations of potassium chloride are associated with an increased frequency of small bowel lesions (40-50 per 100,000 patient years) compared to sustained release wax matrix formulations (less than one per 100,000 patient years). Because of the lack of extensive marketing experience with microencapsulated products, a comparison between such products and wax matrix or enteric coated products is not available.

start here

Data regarding the safety of long-term therapy with Micro-K LS are not available. However, because it is administered as a liquid suspension, it is expected that the frequency of ulcerative and stenotic lesions of the gastrointestinal tract would be ~~lower than with solid oral dosage~~ forms of potassium chloride, and possibly as low as with potassium chloride solution.

(see below)

spective trials, in which the upper gastrointestinal tract was evaluated by
oscopic inspection before and after one week of solid oral potassium
loride therapy, have been conducted in normal volunteers. Results of these
prospective studies demonstrated that an injury to the upper gastrointes-
nal mucosa occurred much less frequently with Micro-K Extencaps than with a
ix-matrix preparation. The lower incidence of gastric lesions with the
icroencapsulated product was observed whether or not gastric motility was
lowed by a concomitantly administered anticholinergic. Delayed gastric
mptying often exists in the elderly who are frequent users of potassium supple-
ents. In these trials, the upper gastrointestinal lesions were asymptomatic
and were not accompanied by evidence of bleeding on Hemoccult® testing.

-K LS should be discontinued immediately and the possibility of ulcera-
tion, obstruction, or perforation considered if severe vomiting, abdominal
pain, distention, or gastrointestinal bleeding occurs.

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

Diarrhea or Dehydration

Micro-K LS contains, as a dispersing agent, docusate sodium, which also increases stool water and is used as a stool softener. Clinical studies with Micro-K LS indicate that minor changes in stool consistency may be common, although usually well-tolerated. However, rarely patients may experiece diarrhea or cramping abdominal pain. Patients with severe or chronic diarrhea or who are dehydrated ordinarily should not be prescribed Micro-K LS.

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 mixed in water or other suitable liquid.

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.

as a dispersing agent

To ~~remind~~ inform patients that this product contains the stool softener sodium docusate, which may ~~cause loose or unformed stools~~, or ~~occasionally~~ diarrhea or uterus rarely produce

change stool consistency

Laboratory Tests:

Regular plasma potassium determinations are recommended, especially in patients with renal insufficiency or diabetic nephropathy.

When blood is drawn for analysis of plasma potassium, it is important to recognize that artifactual elevations can occur after improper venipuncture technique or as a result of *in vitro* hemolysis of the sample.

Drug Interactions:

Potassium-sparing diuretics, angiotensin converting enzyme inhibitors: see WARNINGS.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

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

Pregnancy Category C:

Animal reproduction studies have not been conducted with Micro-K LS. 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 children have not been established.

ADVERSE REACTIONS

It is one of the most severe adverse effects is hyperkalemia (see CONTRAINDICATIONS, WARNINGS, AND OVERDOSAGE). → associated with oral potassium chloride treatment.

Bleeding, ulceration, perforation and obstruction have been reported in patients treated with ~~other~~ solid KCl dosage forms, and may occur with Micro-K LS (see WARNINGS, Gastrointestinal lesions)

The most common adverse reactions to the 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 taking the dose with meals, or reducing the amount taken at one time.

Skin rash has been reported rarely with potassium preparations.

(See Warning)

Add →

In a controlled clinical study Micro-K LS was associated with an increased frequency of gastrointestinal intolerance (e.g., diarrhea, loose stools, abdominal pain, etc.) compared to equal doses (100 mEq/day) of Micro-K Extencaps. This finding was attributed to the inactive ingredients used in the Micro-K LS formulation that are not present in the Micro-K Extencap formulation.

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-wave, 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 solution 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 potassium intake 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.

Usual Adult Dose - One Micro-K LS 20 mEq packet 1 to 5 times daily, depending on the requirements of the patient.

Pour contents of packet slowly into approximately 2 fl. oz (¼ glassful) of water, milk, or favorite juice while stirring. Stir thoroughly for approximately 1 minute until slightly thickened, then drink. The entire contents of the packet must be used immediately and not stored for future use. Any microcapsule/liquid mixture should be used immediately and not stored for future use.

Suspension in Water: Pour contents of packet slowly into approximately 4 fluid ounces (1/2 cup) of water. Stir thoroughly for approximately 1 minute until slightly thickened, then drink. The entire contents of the packet must be used immediately and not stored for future use. Any microcapsule/water mixture should be used immediately and not stored for future use.

Suspension in Other Liquids: Studies conducted using orange juice, tomato juice, apple juice and milk as the suspending liquid have shown that the quantity of fluid used to suspend one Micro-K LS packet MUST be limited to 2 fluid ounces (1/4 cup). The use of volumes greater than 2 fluid ounces substantially reduces the dose of potassium chloride delivered. If a liquid other than water is used to suspend Micro-K LS then the contents of the packet should be slowly poured into 2 fluid ounces (1/4 cup) of liquid. Stir thoroughly for approximately 1 minute, then drink. The entire contents of the packet must be used immediately and not stored for future use. Any microcapsule/liquid mixture should be used immediately and not stored for future use.

Sprinkling Contents on Food:

Micro-K LS may be given on soft food such as applesauce or pudding. After sprinkling the contents of the packet on the food, it should be swallowed immediately without chewing and followed with a glass of cool water, milk, or juice to ensure complete swallowing of all the microcapsules. Do not store microcapsule/food mixture for future use.

How Supplied: Micro-K LS containing 1.5 g microencapsulated potassium chloride (equivalent to 20 mEq K) per packet in cartons of 30 (NDC 0031-5760-56) and 100 packets (NDC 0031-5760-63).

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

CAUTION: Federal law prohibits dispensing without prescription.

U.S. Patent 4,259,315

Pharmaceutical Division
A. H. Robins Company
Richmond, VA 23220

Division of Cardio-Renal Drug Products
Medical Review of an Original NDA

NDA Number: 19-561 **Medical Review Number:** 3
Drug Name: Micro-K LS
Applicant: AHRobins **Date Review Completed:** 31 Mar 88

Primary Source Document for Review:
NDA Amendment dated 7 January 1988

Additional References:
Medical Review #1 dated 24 June 1986; Medical Review #2 dated 23 July 1987; Chemistry Review #2 completed 12 February 1988; IND [redacted] - Review of Protocol #31 dated 16 September 1987 and revision dated 22 September 1987.

---

1. General Information: (Based on Amendment dated 7 January 1988)
   a. NAME OF DRUG: Micro-K LS (Brand of Potassium Chloride for Liquid Suspension)

   b. PHARMACOLOGIC CLASS: electrolye replenisher

   c. DOSAGE FORM AND STRENGTH: Packets for reconstitution containing 1.5 g of potassium chloride USP equivalent to 20 mEq of potassium.

   d. ROUTE OF ADMINISTRATION: oral

   e. PROPOSED DOSING REGIMEN: Usual Adult Dose: One Micro-K LS 20 mEq packet 1 to 5 times daily, depending on the requirements of the patient. 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.

   f. PROPOSED INDICATION:
      1. For the treatment of patients with hypokalemia, with or without metabolic alkalosis; in digitalis intoxication; and in patients with hypokalmic familial periodic paralysis.
      2. For the prevention of hypokalemia in patients who would be at particular risk if hypokalemia were to develop, e.g., digitalized patients or patients with significant cardiac arrhythmias; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy; and certain diarrheal states.

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

g. PROPOSED INSTRUCTIONS FOR ADMINISTRATION:

Pour contents of packet slowly into approximately 2 fl. oz. (1/4 glassful) of water, milk, or favorite juice while stirring. Stir thoroughly for approximately 1 minute until slightly thickened, then drink. The entire contents of the packet must be used immediately and not stored for future used. Any microcapsule/liquid mixture should be used immediately and not stored for future use.

Micro-K LS may be given on soft food, such as applesauce or pudding. After sprinkling the contents of the packet on the food, it should be swallowed immediately without chewing and followed with a glass of cool water, milk, or juice to ensure complete swallowing of all the microcapsules. Do not store microcapsule/food mixture for future use.

2. Chemistry, Manufacturing and Quality Control Information:

The composition of the finished product in a typical unit dose packet weighing 6 g (approx.) is:

potassium chloride	1.5 g
ethylcellulose	[redacted]
sucrose	
povidone	
[redacted]	
docusate sodium	
[redacted]	

The release rate specifications for the finished dosage form determined in the USP Dissolution Test Apparatus, Method 2 using 900 ml distilled water at 37 degrees and 75 RPM for the paddle speed is:

[redacted]

Additional details can be found in the Chemistry Reviews.

3. Nonclinical Pharmacology and Toxicology Information:

No studies submitted.

4. Human Pharmacokinetics and Bioavailability Information:

The results of Study 2601 - "Report #85-0472, Comparison of the Bioavailability of Potassium from a Microencapsulated Potassium Chloride Suspension with that from Orally Administered Micro-K Extentabs and a Potassium Chloride Solution" - was reviewed in Medical Review #1 dated 24 June 1986. Several amendments to the report are included as part of the 7 January 1988 submission. These amendments do not influence the previous conclusions based on this study.

As of the date of this Medical Review the results of the Biopharmaceutics Review have not been received.

5. Clinical Information:

The results of one clinical safety study are included in this NDA amendment. The primary objective of this study was to demonstrate that the LS formulation of Micro-K did not have any significant differences in safety and tolerability compared to the Extencap formulation. After the initial review of this NDA, the question of the safety and tolerability of the inactive ingredients in the LS formulation could not be satisfactorily resolved by a review of the FDA archives or the medical literature. Likewise, it did not seem appropriate to assume that the safety profile of the LS formulation would be entirely similar to the Extencap formulation because the LS formulation contains a number of ingredients not found in the Extencap formulation including an known stool softener, docusate sodium. Therefore this study was requested by the FDA to provide some information about the potential differences between the two Micro-K formulations.

Study Number: 31 (Report # 87-0424)

Source Materials for MOR: Volume 2.6 of NDA

Study Title:
A Study to Determine the Safety, Tolerance and Stool Softening Potential of Micro-K LS Compared to Micro-K 10 in Healthy Male Subjects

Investigator:
Sheldon Zuckerman, M.D.; Westbury NY (Contracted by Pharmaceutical Food and Drug Associates, Roslyn Heights NY)

Study Dates: September 1987 - October 1987

Objectives:
To evaluate the safety and tolerance, and to compare the stool-softening potential of the new formulation, Micro-K LS, to the already marketed product, Micro-K 10.

Study Plan:

This was a single center, open label, randomized, parallel group study to be conducted in healthy adult males. After screening and collecting diary cards on fecal frequency and consistency for a 14 day baseline, eligible subjects were randomly assigned to receive either Micro-K LS, one 20 mEq packet suspended (by stirring for 1 minute) in 4 oz. water at 7 AM, 11 AM, 3 PM, 7 PM and 11 PM; or Micro-K 10 Extencaps, two extencaps with 4 oz. of water at 7 AM, 11 AM, 3 PM, 7 PM and 11 PM. Total daily dose was 100 mEq for 14 days. Subjects could not take any concomitant drugs. Besides routine monitoring of clinical laboratory values and ECG, daily diary cards on fecal frequency and consistency were collected for Day 1-7 and Day 7-14 of treatment.

Patient Disposition and Eligibility Determination:

A total of 114 subjects were screened, and 106 were randomized to one of the treatment groups - 52 to Micro-K LS and 54 to Micro-K Extencaps. One subject in the Extencap group did not return for the appropriate visits at Day 7 and 14 and was not included in the analysis. One subject in the LS group (No. 179) had severe stomach pain and discontinued treatment. The analysis of safety was based on 53 subjects in the Extencap group and 51 subjects in the LS group.

Quality Assurance:

The section in the sponsor's study report titled "...Data Quality Assurance" contained no information on how the recorded measurements were verified, transferred to a database and checked for accuracy.

Results, Population Profile:

All subjects were white male adults. The baseline comparability measurements for the two treatment groups are shown below.

BASELINE VARIABLE	LS (N=51)	EXTENCAPS (N=53)
MEAN STOOL FREQUENCY (FROM BASELINE DAYS 1-14)	1.45 (0.48)	1.53 (0.66)
MEAN STOOL CONSISTANCY (FROM BASELINE DAYS 1-14)	1.97 (0.21)	2.06 (0.29)
AGE	25.90 (5.88)	25.77 (6.31)
HEIGHT (IN)	70.17 (3.62)	70.50 (2.50)
WEIGHT (LB)	181.06 (27.01)	181.83 (35.74)
SITTING SBP	124.45 (11.38)	126.26 (12.91)
SITTING DBP	77.76 (6.98)	76.94 (9.08)
SITTING PULSE	70.51 (8.87)	71.61 (9.27)

* STANDARD DEVIATION IN PARENTHESES

No concomitant prescription medications were allowed; however, a record of OTC drugs was part of the case report form. No listing or tabulation of concomitant drugs was included in the sponsor's study report. In information (the informed consent form for this study) provided by the sponsor on 3 March 1988 it was ascertained that NO concomitant OTC drugs were allowed during the study.

Results, Efficacy:

This was a normal healthy population, therefore no measurement of the efficacy of potassium treatment was possible.

Results, Safety:

Primary Endpoints:

It was determined that the measurement of stool frequency and stool consistency through the use of a daily diary would be an adequate measure of the comparative safety and tolerability of equal doses of the LS and the Extencap formulations of Micro-K. The inactive ingredients in the LS formulation includes docusate sodium, a stool softener, as well as a number of other ingredients not found in the Extencap formulation. The table below summarizes the results of the data recorded in the daily diaries. The baseline was determined by calculating the mean for stool frequency and stool consistency on pre-treatment Days 1-14. This baseline was then incorporated into the ANOVA analysis of the means for these two variables for Day 8-14 of active treatment.

	Adjusted* Mean Daily Stool Frequency (No. of Bowel Movements ± SE)	
Micro-K LS	1.63 ± 0.07	p = 0.3895
Micro-K 10 Extencaps	1.72 ± 0.07	

	Adjusted* Mean Daily Stool Consistency (Rating ± SE)	
Micro-K LS	1.76 ± 0.05	p = 0.0286
Micro-K 10 Extencaps	1.92 ± 0.05	

(Rating: 1=Loose, 2=Formed, 3=Hard)

*Means adjusted for baseline.

Secondary Endpoints:

Compliance

There was one dropout in the LS group attributable to an adverse gastrointestinal effect of the treatment (Subject # 179). After one day of treatment (4 doses) the patient discontinued the treatment due to severe abdominal pain. Three other subjects in the LS group were known to be non-compliant with the dosing regimen because of intolerable gastrointestinal side effects. Subject # 116 reduced the number of daily doses due to nausea and sour stomach. Subject # 138 decreased the number of daily doses due to severe stomach pain, burning sensation and an increase in salivation. Subject # 192 decreased intake due to vomiting on Days 2, 4, 5, 6, & 7. There were no reports of non-compliance in the Extencap group.

Reports of Adverse Effects

Only the gastrointestinal system had a significant number of reports such that a reasonable comparison of the two formulations could be made. The table below summarizes the number of patients with each complaint.

BODY SYSTEM	ADVERSE EXPERIENCES	NUMBER OF SUBJECTS LS	NUMBER OF SUBJECTS EXTENCAPS	NUMBER OF ADVERSE EXPERIENCES LS	NUMBER OF ADVERSE EXPERIENCES EXTENCAPS
GASTRO-INTESTINAL SYSTEM DISORDERS	ABDOMINAL PAIN	7(13 %)	4(7 %)	7(20 %)	4(17 %)
	DIARRHEA	3(6 %)	2(4 %)	3(9 %)	2(9 %)
	DYSPEPSIA	7(13 %)	5(9 %)	8(23 %)	5(22 %)
	FLATULENCE	6(12 %)	4(7 %)	6(17 %)	4(17 %)
	GASTRITIS	1(2 %)	0(0 %)	1(3 %)	0(0 %)
	NAUSEA	3(6 %)	2(4 %)	3(9 %)	3(13 %)
	RECTAL DISORDER	1(2 %)	0(0 %)	1(3 %)	0(0 %)
	VOMITING	1(2 %)	0(0 %)	1(3 %)	0(0 %)
	TOTALS FOR BODY SYSTEM	21 •	16 •	30	18
	Total N	51	53	99	23
METABOLIC AND NUTRITIONAL DISORDERS	THIRST	1(2 %)	0(0 %)	1(3 %)	0(0 %)
	TOTALS FOR BODY SYSTEM	1 •	0 •	1	0
RESPIRATORY SYSTEM DISORDERS	COUGHING	0(0 %)	1(2 %)	0(0 %)	1(4 %)
	RHINITIS	0(0 %)	1(2 %)	0(0 %)	1(4 %)
	TOTALS FOR BODY SYSTEM	0 •	1 •	0	2
SKIN AND APPENDAGES DISORDERS	PRURITUS	1(2 %)	0(0 %)	1(3 %)	0(0 %)
	TOTALS FOR BODY SYSTEM	1 •	0 •	1	0

• - TOTAL NUMBER OF SUBJECTS WITH BODY SYSTEM DISORDERS

Clinical Laboratory and Electrocardiogram Results

In general there were no clinically significant findings in either the routine clinical laboratory screen or the ECGs. Several of the parameters did show some shifts that occurred in both treatment groups and may reflect the effect of high doses of potassium chloride. A significant shift in any clinical laboratory measurement was identified by a formula that calculated an increase from baseline that was greater than 1/2 of the normal range. Using this criteria, the clinical laboratory measurements that had more than 5% of the population (N=104) changing in either an upward or downward fashion during the course of the study are indicated below.

alkaline phosphatase - 12/104 had increase, 1/104 had decrease
calcium - 14/104 had decrease, 2/104 had increase
chloride - 13/104 had increase, 4/104 had decrease
carbon dioxide - 36/104 had increase, 21/104 had decrease
monocytes - 14/104 had a decrease, 4 had an increase
potassium - 11/104 had an increase, 4/104 had a decrease
SGOT - 9/104 had an increase, 1/104 had a decrease
sodium - 22/104 had an increase, 4/104 had a decrease
total protein - 11/104 had decrease, 2/104 had increase
triglycerides - 61/104 had decrease, 21 had increase

Conclusions:

The use of a daily diary to record fecal frequency and consistency was accepted as the best possibility for detecting a difference between the two formulations of Micro-K. The results of the baseline/treatment comparisons for the two treatment groups based on mean data showed no statistically significant difference between the two groups with regard to stool frequency, and a statistically significant difference in stool consistency with the LS treatment group having "looser" stools. Using the data listings provided by the sponsor a categorical analysis of the change (decrease, increase, no difference) from baseline for the stool frequency and stool consistency during Day 8-14 of treatment was done. Those results are shown below.

Stool Frequency

	Number of Patients with INCREASE	DECREASE	NO CHANGE
LS group	28 (55%)	19	4
Extencap group	36 (69%)	15	2

Stool Consistency

	Number of Patients with DECREASE	INCREASE	NO CHANGE
LS group	35 (67%)	9	7
Extencap group	29 (55%)	16	8

These categorical data show that the Extencap formulation increased the stool frequency while the LS formulation tended to decrease the consistency of the stool compared to baseline. However, in the statistical analysis where the baseline measurements are used to adjust the end of treatment measurements, the two treatments are indistinguishable with regard to stool frequency, but a significant difference in stool consistency is found.

Based on the data for stool consistency the Micro-K LS formulation should contain appropriate information in the labeling indicating that the product contains a stool softener and may produce loose stools/diarrhea in susceptible patients. This is supported by the additional data collected in this study regarding compliance with the LS dosing regimen and the adverse reaction profile. This latter information comparing the adverse reaction reporting rate for the LS and the Extencap formulation should be included in the Adverse Reaction section of the labeling for the product.

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6. In Vitro Studies:

Background:

In MOR #2 dated 23 July 1987, there is data for the residual potassium chloride resulting from the admixture of 20 mEq Micro-K LS

On the basis of this data the sponsor requested labeling in the Dosage and Administration section that included not only water as the suspending liquid, but also juice. The sponsor was asked to supply supporting data for the juice recommendation as well as additional data regarding the effect of standing time on the amount of residual KCl.

In the present submission the sponsor has extended the original in vitro studies to include a variety of commonly consumed juices (tomato, orange and apple) as well as milk and water.

Results, Residual KCl:

Conclusions:

On the basis of these in vitro results the sponsor is recommending that the Dosage and Administration section of the label contain the following recommendations for administration of Micro-K LS:

> Pour contents of packet slowly into approximately 2 fl. oz. (1/4 glassful) of water, milk, or favorite juice while stirring. Stir throroughly for approximately 1 minute until slightly thickened, then drink. The entire contents of the packet must be used immediately and not stored for future use. Any microcapsule/liquid mixture should be used immediately and not stored for future use.

The sponsor's explanation for the increasing residual potassium chloride content seen with increasing fluid quantity is reasonable. It suggests that fluids other than water are likely to interfere with the suspending agents in Micro-K LS such that the quantity of liquid used to suspend Micro-K LS must be kept very small, about 2 oz, or the delivered dose will be decreased significantly from the labeled amount. Water as a suspending agent does not appear to interfere with with the suspending agents at quantities up to 6 oz for a 20 mEq Micro-K LS packet.

Therefore, it is recommended that the labeling for Micro-K LS contain water as the liquid of choice for preparation and administration of the product. The instructions for reconstitution should resemble the "traditional" recommendations for administration of a potassium chloride supplement, i.e. 3-4 oz of water with stirring. The labeling for the preparation of Micro-K LS in juice will need to be much more restrictive and contain additional wording indicating that quantities of juice in excess of 2 oz are not recommended because of the reduction in the delivered dose of potassium chloride.

7. Labeling:

The current guidelines for labeling extended-release potassium chloride products were used as a basis for commenting on the sponsor's proposed labeling for this product. Several important changes were made in the Micro-K LS labeling that are at variance with the standard KCl labeling and/or the sponsor's proposed labeling for Micro-K LS. They are noted below along with comments by this Reviewer.

"Tasteless" claim: This claim was included in the Description section of the labeling by the sponsor and modified by this reviewer. The modification is patterned after the usual wording for the physical description of a solution/suspension.

Bold-type Warning in the Indications and Usage section: The solid extended-release dosage forms of potassium chloride contain an introductory statement in the Indications and Usage section that recommend using a solid dosage form ONLY IF the patient cannot tolerate or refuses to take the liquid preparations. In essence the statement makes the solid dosage forms a second line dosage form. Micro-K LS is a liquid dosage form and therefore the bold-type warning is inappropriate. Micro-K LS should be considered a first line dosage form for potassium supplementation.

Gastrointestinal Lesions subsection of the WARNING section: The standard "first" paragraph of this section has been used to replace the version proposed by the sponsor with the addition of a concluding sentence that reads as follows:

> Because Micro-K LS is administered as a liquid suspension, it is expected that the frequency of small bowel lesions would be no greater than and possibly less than the frequency reported with sustained release wax matrix formulations.

The remainder of the sponsor's proposed wording for this subsection with the exception of the last sentence was deleted in accordance with other meetings and discussions held with the sponsor regarding the labeling for Micro-K Extencaps. Furthermore, the "second" paragraph of the standard wording for this subsection was not included because it applies entirely to studies done comparing the wax matrix and microencapsulated solid oral dosage forms.

Adverse Reactions section and "gastrointestinal intolerance": As recommended elsewhere in this MOR, the results of the Micro-K LS vs Micro-K Extencap study should be incorporated into the labeling. It is recommended that the following paragraph be added to the Adverse Reaction Section.

> In a controlled clinical study Micro-K LS was associated with an increased frequency of gastrointestinal intolerance (e.g., diarrhea, loose stools, abdominal pain, etc.) compared to equal doses (100 mEq/day) of Micro-K Extencaps. This finding was attributed to the inactive ingredients used in the Micro-K LS formulation that are not present in the Micro-K Extencap formulation.

Instructions for Reconstitution of Micro-K LS: The paragraph in the Dosage and Administration section containing the instructions for reconstitution of this product should be clearly identified. The instructions, as indicated by the results of the *in vitro* studies, should differentiate between aqueous suspensions and those for juices. The following paragraphs are recommended for inclusion in the Dosage and Administration Section in place of the paragraph proposed by the sponsor.

> Suspension in Water: Pour contents of packet slowly into approximately 4 fluid ounces (1/2 cup) of water. Stir thoroughly for approximately 1 minute until slightly thickened, then drink. The entire contents of the packet must be used immediately and not stored for future use. Any microcapsule/water mixture should be used immediately and not stored for future use.

Suspension in Other Liquids: Studies conducted using orange juice, tomato juice, apple juice and milk as the suspending liquid have shown that the quantity of fluid used to suspend one Micro-K LS packet MUST be limited to 2 fluid ounces (1/4 cup). The use of volumes greater than 2 fluid ounces substantially reduces the dose of potassium chloride delivered. If a liquid other than water is used to suspend Micro-K LS then the contents of the packet should be slowly poured into 2 fluid ounces (1/4 cup) of liquid. Stir thoroughly for approximately 1 minute, then drink. The entire contents of the packet must be used immediately and not stored for future use. Any microcapsule/liquid mixture should be used immediately and not stored for future use.

Labeling on Foil Packets: It is recommended that only the directions for suspension in water be included on the foil packet with reference to the package insert for alternative methods of administration.

A "marked-up" copy of the sponsor's proposed labeling is attached to this review as Attachment I. It includes all of the above changes as well as some editorial and clarification changes.

8. Conclusions:

The results of one controlled clinical trial are included in this amendment to NDA 19-561. This open-label, parallel group comparison between Micro-K LS and Micro-K Extencap was intended to investigate any differences in the safety and tolerability between the two formulations at maximum recommended doses of 100 mEq per day. The study was conducted in normal male volunteers who kept daily diaries on stool frequency and stool consistency for 28 days. The first 14 days were a baseline period followed by a 14 day active treatment period. Results of the study showed that Micro-K LS was associated with a significant decrease in stool consistency compared to Micro-K Extencaps and that Micro-K LS was less well tolerated than the Extencap. The labeling for Micro-K LS has been revised to include the results of this study.

The results of a series of in vitro studies are reported in this amendment. The studies were intended to serve as a subsitute for additional clinical studies that would demonstrate the efficacy of Micro-K LS when it is administered in a variety of different suspending liquids under varying conditions of mixing and standing. The results of these studies showed that Micro-K LS is least likely to show variation in dosage delivery when WATER is the suspending liquid. If the conditions of reconstitution for Micro-K LS in liquids other than water are clearly specified, e.g. quantity of liquid should not exceed 2 fluid ounces, then it appears that Micro-K LS can also be administered with a full dose delivered to the patient. The Dosage and Administration section of the labeling has been revised to reflect the results of these studies.

9. Recommendation:

With the additional information about Micro-K LS included in this amendment to NDA 19-561, the NDA for Micro-K LS is considered approvable. The labeling revisions discussed in this review and included on the "marked-up" copy in Attachment I are a key determinant of this approvable recommendation and therefore must be included in the final determination of approvability.

Cheryl Fossum Graham

cc:
Original NDA 19-561
HFN-110
HFN-110/mrose
HFN-110/cgraham
HFN-110/athompson
HFN-110/cso

with 1 (one) Attachment - Labeling

MM# N1956112/cfg/31mar88

Division of Cardio-Renal Drug Products
Medical Review of an Original NDA

NDA Number: 19-561 **Medical Review Number:** 2

Applicant: AHRobins **Date Completed:** DRAFT-19 May 1987
FINAL-21 July 87

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1. General information:

a. Name of Drug: Micro-K LS (potassium chloride for liquid suspension)

b. Pharmacologic Class: electrolyte replenisher, potassium supplement

c. Dosage Form and Strength: Packet of a granular powder for reconstitution with water or juice containing 20 mEq of potassium chloride. (Amended in the 7 February 1987 submission)

d. Route of Administration: Oral

e. Dosing Regimen: Adults - One Micro-K LS 20 mEq packet 2 to 4 times daily, depending on the requirements of the patient. (Revised per change in dosage strength - see above.)

f. Proposed Indication:

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy; and certain diarrheal states.

g. Related Documents:

NDA 18-238; Micro-K Extencaps
IND [redacted] potassium chloride (AHRobins)
MOR #1 for NDA 19-561 completed 28 May 1986

2. Chemistry, manufacturing and quality control information:

3. Nonclinical pharmacology and toxicology information:

As with the original submission, the sponsor has not submitted the results of any animal testing with this product.

4. Human pharmacokinetics and bioavailability information:

The single clinical study submitted in this NDA was Study 1206 titled "Comparison of the Bioavailability of Potassium from a Microencapsulated Potassium Chloride Suspension with that from Orally Administered Micro-K Extencaps and a Potassium Chloride Solution." The results of this study demonstrated that the Micro-K LS product was similar to the solution with regard to extent of availability based on net urinary excretion after 24 hours - 63% of administered dose for solution vs 57% for the Micro-K LS suspension. The rate of availability was compatible with a controlled release product for the Micro-K LS and was similar to the release rate profile for Micro-K extencaps. No questions with regard to this study were directed to the sponsor and therefore no further review of this study is necessary.

5. Clinical information:

a. Background

The safety and efficacy of the Micro-K LS product must be inferred from the results of the bioavailability study discussed above and in vitro measurements such as dissolution. No additional clinical studies have been conducted with this product. As a result of the initial review of this NDA several issues with regard to the safety of this product were identified.

1. The largest approved strength for a controlled release potassium chloride product is 20 mEq while the sponsor was proposing packets of 25 mEq and 50 mEq.

2. The Micro-K LS formulation is substantially different from Micro-K extencaps. About 75% of the suspendable material consists of inactive ingredients including sucrose, povidone, [redacted] and docusate. In addition the quantity of docusate in the formulation was of special concern because it is marketed as a stool softener/laxative in recommended doses about 5 times greater than the amount contained in the proposed 50 mEq packet.

3. The intended population of use was not clear from the materials and labeling provided by the sponsor.

In addition there was at least one issue pending with regard to the efficacy of this product.

4. No information was provided with regard to the behavior of the suspension under the recommended conditions of use. Specifically there was no information about the loss of product in the container used for suspending the product, nor was there any information about the loss of potassium chloride to the suspending agent, e.g., water or other liquids. Temperature and pH of the suspending liquid were also not characterized.

b. Issue # 1 - Strength of dosage form

In response to this issue the sponsor has limited the size of the proposed packaging to 20 mEq packets of Micro-K LS. At this dosage strength the product will contain 4.2 mg of docusate per packet.

c. Issue #2 - Product formulation

The sponsor's response to this issue refers extensively to the OTC panel review of docusate as part of the overall OTC review of laxative products. The Tentative Final Monograph for the laxatives was published in the Federal Register on January 15, 1985 without a section on docusate. The docusate recommendation was delayed due to new information regarding the potential teratogenicity of docusate. A separate TFM addressing docusate has yet to be published. The prevailing regulatory status of docusate is found in the notice of proposed rulemaking published on March 21, 1975 in which the docusate salts were classified as Category I at a recommended adult daily dose of 50-360 mg.

In discussions with other FDA personnel familiar with the docusate review, the following impressions were collected:

- The data filed during the OTC review (DOC # 78N036L) does not contain any dose response information that would demonstrate a no effect dose to be 20 mg or less, nor does the data show that the recommended dose of 50-360 mg is any different from a 20 mg dose of docusate.

- The issue of teratogenicity is still under consideration by the Agency and is currently under review by the nutritional staff of CFSAN. They have recently completed a memo [a copy of which was mailed to this Division on 20 May 1987] that basically states that the use of docusate in food products is safe.

- Of primary concern within CDB is the use of docusate as part of prenatal vitamin/mineral combinations in which the stool softener was added to counteract the constipating effects of the iron supplements. At the time of this review the status of the use of docusate in these drug products has yet to be resolved by CDB.

- Both the CFSAN and the CDB position on docusate are necessary to reply to a Citizen's Petition (CP006, DOC# 78N036L) filed on behalf of American Cyanamid.

It appears from this quick survey of the Agency experts on docusate that the food additive issue has been resolved and that the drug product issue and inactive ingredient issue has yet to be resolved. The amount of docusate in the Micro-K LS preparation is more than that allowed in foods and less than the recommended drug dose thus placing it in the category of an 'inactive ingredient'.

In the proposed strength of 20 mEq KCl per packet the amount of docusate is [redacted] per packet. At this amount as an inactive ingredient, the Micro-K LS 20 mEq packet is within the range of amounts for docusate already allowed in other approved oral products. However, at the maximal recommended doses of 100 mEq KCl per day, the patient taking Micro-K LS would also receive 20+ mg of docusate.

That there is no laxative effect of docusate at the doses proposed in the Micro-K LS formulation as well as any other potentially unique safety problems should be demonstrated prior to approving this product formulation. The occurrence of docusate-related effects and/or other product-related problems could be adequately demonstrated if the sponsor were to conduct a controlled clinical trial in the expected user population.

d. Issue # 3 - Who is the intended user population

The sponsor seems to be suggesting, although not directly stating it as such, that Micro-K LS is intended for the same population that currently receives the immediate release liquids and effervescent formulations of potassium chloride. Specifically, their labeling has excluded all references to gastrointestinal ulcerations and bleeding associated with solid oral dosage forms of potassium chloride and thereby any reference to the "second line" status of these solid dose form products. Therefore it is assumed that they would market/promote Micro-K LS as a sustained release liquid to be used in a manner similar to the immediate release liquids and effervescent tablets, i.e., as primary therapy in patients requiring additional potassium not available from standard diet therapy.

Because Micro-K LS would seem to combine the safety advantages of both the liquid KCl and the sustained release dosage formulations, it is reasonable to permit a less restrictive labeling than that required for solid oral dosage forms. However, the labeling for the liquid KCl formulations is not subject to the NDA approval process and therefore it should not be used as the model for developing the labeling for Micro-K LS. The model labeling that should be used to develop the Micro-K LS labeling is the proposed "class" labeling for solid oral dosage forms of KCl recently finalized for release by this Division.

The proposed labeling for Micro-K LS contains no mention of the gastrointestinal lesions associated with other controlled release products of KCl. Since Micro-K LS is a sustained release formulation it is reasonable to refer in the labeling to the safety problems encountered with another dosage form, i.e., the solid sustained release dose form. Although bold-faced warnings in the Indication section and a paragraph in the Warning section about gastrointestinal lesions is probably not appropriate for the Micro-K LS labeling, it is appropriate to have a paragraph in the Precaution section that informs the prescribing physician about the problems previously encountered with solid sustained release dose forms of KCl. The paragraph could be worded in a manner similar to that currently proposed for the Warning section of the solid dose form products. By placing it in the Precaution section the information would be included but de-emphasized compared to the placement of the same information in a solid dose form preparation.

This Medical Reviewer does not disagree with the sponsor's desire to de-emphasize the association of gastrointestinal lesions with sustained release solid oral dosage forms of KCl. However, the complete exclusion of this information from the labeling of Micro-K LS is inappropriate and should not be allowed. It is hoped that the above compromise will be acceptable with regard to including relevant information in the Precaution section of the label.

e. Issue # 4 - Efficacy of Micro-K LS when administered as recommended.

The final issue raised in the 24 October 1986 deficiency letter to the sponsor related to the lack of evidence that their dosing recommendations would result in the delivery of a full dose of potassium chloride to a patient. In response the sponsor has conducted two in vitro studies in which the 20 mEq packet of Micro-K LS was used. The dissolution rates for this new dosage form were determined and reported as follows:

DISSOLUTION DATA FOR MICRO-K LS PACKETS 20 mEq

Clinical Lot No. 3547

Conditions: Paddle Method; Medium - Purified Water, USP; 900 mL; 37°C; 75 rpm
Dissolution Procedure Number 167
Dissolution Assay Procedure Number 95

	% Label Claim Potassium Chloride Dissolved				
	0.5 Hour	1 Hour	4 Hours	8 Hours	10 Hours
Packet 1					
Packet 2					
Packet 3					
Packet 4					
Packet 5					
Packet 6					
Mean					
Standard Deviation					

In vitro Study # 1

METHODS: In this study the 20 mEq packet of Micro-K LS was placed in 120 ml of water and stirred for a variable period of time with a teaspoon. Aliquot samples of the suspension were taken at various intervals ranging from 5 minutes to 2 hours. The aliquot was filtered, diluted and potassium content was determined using a spectrophotometric procedure.

RESULTS

Table 1

KCl in Solution

Prior to Admixture				After adding Micro-K LS to water											
Water		Water Plus Base Granules[1]		Immediately following stirring		After standing for __ minutes									
						5		10		15		30		60		120	
mEq per 4 oz	% of dose	mEq per 4 oz	% of dose[2]	Stirring time (sec)	mEq per 4 oz	% of dose	mEq[3]	%[4]	mEq	%	mEq	%	mEq	%	mEq	%	mEq	%

COMMENTS: The sponsor does not mention whether or not the suspension was stirred again prior to the aliquot determinations. If no stirring was done prior to the analysis for potassium, there could be a wide variation in results depending on where in the solution the aliquot sample was taken. This situation needs to be clarified by the sponsor.

The results obtained with the solutions after 45 seconds of stirring indicate that this amount of agitation may affect the integrity of the microcapsules such that more of the potassium chloride leaks out. In order to further explore this possibility it may be necessary to do some additional studies. On the other hand it may be possible to restrict the labeling instructions such that stirring is recommended for no more than 30 second.

The sponsor suggests in their proposed labeling that this product may also be reconstituted in juice. There is no data about the behavior of this product in varying pH solutions or in liquids such as orange or apple juice. Before any recommendation can be made about the use of Micro-K LS in juice additional studies would be necessary.

In vitro Study # 2

METHODS: In this study the contents of the Micro-K LS packet was suspended in 60, 120 or 240 ml (2, 4, or 6 oz) of water and stirred for 30 seconds. After stirring the suspension was poured out and the residue analyzed for potassium.

RESULTS: A summary table of results is included below.

Amount of KCl remaining in container following dosage delivery

Volume of Water (Fluid ounces)	Trial	Amount KCl Remaining mEq	% of Dose

COMMENTS

6. Labeling

This amendment does not contain a revised proposed label for Micro-K LS, therefore the following comments are based on the label as it was presented in the original submission. The label needs revisions and/or additional supportive data in the following areas:

1. The 20 mEq dosage strength of Micro-K LS was not among the originally proposed strengths and so all references to a dosage strength need to be changed.
2. All references to gastrointestinal ulcers and bleeding associated with solid oral dosage forms of potassium chloride have been deleted in the Indication section, the Contraindication section, the Warnings section and the Adverse Reaction section. It is unacceptable to exclude all references to the safety problems associated with solid dosage forms of KCl, therefore it is recommended that a paragraph of information about these safety concerns be included in the Precaution section of the label.
3. The Dosage and Administration section makes the following recommendation for use of the product;

> Pour contents of packet slowly into appropriate quantity of water or favorite juice while stirring. Stir thoroughly for approximately 30 seconds until slightly thickened, then drink.

These recommendations are not fully supported by the <u>in vitro</u> data reviewed in this document and thus revisions are necessary depending on whether additional studies are conducted by the sponsor. If no further studies are done then any reference to "favorite juice" must be deleted and the directions for suspension preparation and ingestion need to be more explicit.

7. Overall summary and conclusions:

This amendment provides new information in two areas: 1.) the dosage strength has been reduced to 20 mEq per package, and 2.) additional <u>in vitro</u> data is provided to support the administration instructions.

The information provided in this amendment and the original submission do NOT support the approval of Micro-K LS for the following reasons:

1. Micro-K LS is substantially different from Micro-K Extencaps and therefore the safety of the Micro-K LS formulation cannot be extrapolated from the data collected on Micro-K Extencaps. Additional clinical studies are necessary to establish the safety of Micro-K LS in the intended user population.

2. The labeling for Micro-K LS must be revised to include the recommendations made in the Labeling section of this review.

3. The in vitro studies supporting the recommendations for administration of Micro-K LS are inadequate. [redacted]

4. The question regarding the amount of docusate in Micro-K LS and its potential teratogenic effect is still under consideration by the Agency. If the amount of docusate per packet were within the regulatory limits for food products then it would be reasonable to conclude that this product could be considered safe for general consumption. However, the amount of docusate is greater than the food limit and therefore falls under the jurisdiction of CDB as an inactive ingredient. At this time CDB is reviewing the use of docusate both as an inactive ingredient and as an approved stool softener. Further recommendations on the safety of this amount of docusate as an inactive ingredient await CDB action.

8. Recommendations:

For the reasons stated in the above section, I continue to recommend that Micro-K LS NOT be approved. The sponsor should be requested to conduct a controlled clinical study for the purpose of demonstrating the safety of this product in the intended user population. In addition the sponsor should be requested to conduct additional in vitro studies supporting the proposed administration instructions.

These recommendations were communicated to the sponsor in a meeting held on 29 June 1987 and agreed to in principle at that time.

Cheryl Fossum Graham, M.D.

cc.
HFN-110
HFN-110/VO'Hagen
HFN-110/AThompson
HFN-110/MRose
HFN-110/CGraham

IM# N1956108/cfg/22may87
DRAFT to MRose for concurrence on 22may87
revised/MRose/20jul87
revised/CGraham/21jul87

Division of Cardio-Renal Drug Products
Medical Review of an Original NDA

NDA Number: 19-561 Medical Review Number: 1

Applicant: AH Robins Date Completed: 14 May 86
Addendum added: 28 May 86

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1. General Information:

a. Name of Drug: Micro-K LS (potassium chloride for liquid suspension)

b. Pharmacologic Class: Electrolyte replenisher, potassium supplement

c. Dosage Form and Strength: Packets of a granular powder for reconstituion with water or juice. Packets contain either 1.875g (equivalent to 25mEq) of potassium chloride and weigh 7.5g, or [redacted] of potassium chloride and weigh [redacted]

d. Route of Administration: Oral

e. Dosage Regimen: Adults - One Micro-K LS [redacted] packet 1 to 2 times daily depending on the requirements of the patient. One Micro-K LS 25 mEq packet 2 to 4 times daily, depending on the requirements of the patient.

f. Proposed Indication:
1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.

g. Related Documents: NDA 18,238 (Micro-K Extencaps)
IND [redacted]
Additional Agency documents on approval policies for potassium chloride products

2. Chemistry and Manufacturing Controls:

a. Composition (Information on the composition was provided by the sponsor in a telephone conversation from F.Aaroe on 8 May 86):

The content of the final packaged dose form is:

	25 mEq packet	50 mEq packet
Micro-K LS Blend (Grams)	7.5	15 (100%)
Microcaps of potassium chloride	2.07	4.14 (27.6%)
[redacted]	[redacted]	[redacted]
Granulate		
Sucrose		
Povidone		
[redacted]		
Docusate		

The components of the granulate portion of the product formulation are included as 'inactive ingredients' in the labeling of the final dosage form along with ethylcellulose which is the coating material for the potassium chloride crystals.

b. Dissolution specifications:

c. Reviewer's Comments:

Micro-K LS and Micro-K Extencaps are NOT the same formulation in two different dose forms. Although the microencapsulated potassium chloride crystals (microcaps) are derived from the same process and constitute nearly 100% of the Micro-K Extencaps, the microcaps constitute only about 25% of the Micro-K LS product. The remaining portion of the Micro-K LS formulation imparts the suspending/emulsifying properties necessary for producing a pharmaceutically acceptable 'powder for reconstitution'. These latter components of the Micro-K LS formulation are referred to as the 'granulate' portion and are listed as inactive ingredients in the product labeling.

The potassium chloride microcaps in Micro-K LS are identical to the ones used in the Micro-K Extencaps with one exception, the formulation in Micro-K LS is subjected to an extra sieving process to remove the ethylcellulose residue left after coating the KCl crystals. This modification in the processing increases the potency range of the microcaps from [redacted] for Micro-K Extencaps to [redacted] for Micro-K LS.

The Micro-K Extencaps contain no granular component. The granular component of the Micro-K LS formulation contains ingredients that are commonly considered suspending and/or emulsifying agents. The purpose of all the components of the granulate is not stated anywhere in the submission. The granulate contains four listed ingredients: docusate, povidone, sucrose and [redacted].

One 50 mEq dose of Micro-K LS provides the labeled dose of potassium chloride as well as [redacted] of sucrose (equal to [redacted] Calories) and [redacted] of docusate (doses of 50mg of docusate are recommended as a stool softener). These ingredients may be inactive with regard to potassium supplementation, but they are not inert. The label of the powder packet as well as the other packaging/labeling information needs to contain information about the activity of these other ingredients and appropriate precautionary statements where necessary. In a formulation where 75% of the final packaged dose form is 'inactive', the label should contain more than just a line listing of the other ingredients because any one of the other ingredients could be present in an amount that is 'therapeutic' for another indication and/or contraindicated in certain patients. Both the prescribing physician and the patient deserve access to this additional information about the 'inactive ingredients' if they are to make a reasonable decision about the appropriateness of this product in a therapeutic regimen.

Since this is the first application (that I am aware of) for a sustained release potassium chloride preparation packaged as a powder for reconstitution, there are no comparable products or NDAs for comparison. Among the immediate release potassium chloride preparations there are a number of powder packet dose forms, effervescent tablets and effervescent granules. The formulation for the majority of the effervescent preparations is substantially different from Micro-K LS containing only potassium chloride with an artificial flavor, artificial color and saccharin. Only the K-Lyte/Cl and K-Lyte/Cl-50 products by Mead Johnson Labs appear to have a similar formulation to the Micro-K LS product.

The K-Lyte/Cl 50 product contains 2.24g of potassium chloride, [redacted] of potassium bicarbonate, [redacted] of L-lysine monhydrochloride and [redacted] of citric acid. The product is an effervescent tablet and lists as inactive ingredients undisclosed amounts of docusate sodium, natural and/or artificial flavors, light mineral oil, saccharin and talc and D & C Yellow No. 10 or FD&C Yellow No. 6. Discussions with both the Division of Generic Drugs and the Division of Drug Labeling Compliance revealed that the actual quantitative content of this product was not known by the Agency. The product is not the subject of any approved application and is subject only to GMPs and a judgment that the labeling is adequate.

The claim by the sponsor that the formulation of the Micro-K LS product is identical to the Micro-K Extencaps is true only with regard to the microencapsulated potassium chloride. The tests of comparability of the microcaps in Micro-K Extencaps and Micro-K LS include the clinical bioavailability and the dissolution tests. The comparative dissolution information on the two formulations is tabulated below.

Dissolution (Mean % Dissolved) of Micro-K Dosage Forms

Dosage form	Date of Test	Time (hr)				
		0.5	1	4	8	10
Suspension*	November 85					
Capsules**	May 84					
Capsules**	December 85					
Capsules*	December 85					

*U.S.P. Paddle Apparatus, 75 rpm, 900 ml Purified Water, 37 degrees
**U.S.P. Basket Apparatus, 100 rpm, 900 ml Purified Water, 37 degrees

ccording to the FDA reviewing chemist for this application, Dr. Thompson, he sponsor has a supplement pending with this Division that would eliminate the 0.5 hour data point. If this supplement is considered approvable then the specifications for Micro-K LS should be revised to match the specs for the Micro-K Extencaps. The specifications for the two products should be the same with regard to dissolution rate and the suggestion in this application that a different set of specs should be applied to the Micro-L LS formulation should not be allowed.

The conclusions based on this selective review of the Chemistry and Manufacturing Section of this application can be stated as follows:

1. The final packaged dose form of Micro-K LS is substantially different form Micro-K Extencaps.

2. The 'inactive ingredients' in the Micro-K LS product contain components known to be biologically and therapeutically active.

3. The proposed labeling for Micro-K LS does not provide adequate information about the quantity and the activity of the 'inactive ingredients'.

4. The microencapsulated potassium chloride (microcaps) in Micro-K Extencaps and Micro-K LS have similar dissolution profiles.

5. Micro-K LS should be subject to the same dissolution specifications as Micro-K Extencaps (NDA 18-238).

3. Pharmacology

There were no animal pharmacology studies done with the Micro-K LS formulation. All requirements for animal studies were supported by references to NDA 18,238 for the Micro-K Extencaps.

4. Clinical Background:

The rationale for developing a suspension (liquid formulation) of sustained release potassium chloride depends on the arguments that favor a sustained release formulation and those in favor of a palatable, easy to ingest dosage form. No other sustained release potassium chloride preparation is available in a liquid/suspension dosage form. There are numerous immediate release formulations that are marketed as powder packets, effervescent tablets and effervescent granules as well as the classic solution of KCl. Thus this product proposes to include both the putative safety advantages of a sustained release formulation with the compliance advantages of an easy to use, palatable dosage form.

The choice of dosage strengths, 25 and 50 mEq packets, exceeds the strength of any approved potassium chloride supplement. The highest dose presently approved as a sustained release solid oral dosage form is 10 mEq. Approval is pending for a 20 mEq microencapsulated tablet (NDA 19,439), however, there are no other products that this reviewer is aware of that exceed 20 mEq in a sustained release and/or solid oral dosage form. Immediate release potassium chloride supplements are available in units of administration that exceed 20 mEq. Because the immediate release potassium chloride supplements are not subject to the NDA/ANDA process, the information regarding their safety both under the supervised conditions of a clinical trial and as a marketed product is not collected or reviewed by the FDA. Therefore the rationale for a 50 mEq dose form of Micro-K LS is not supported by any previously documented experience with a dose this large. A recent review of S015, a supplement to the Micro-K Extencaps NDA 18,238, contains a more extensive discussion on the approvability of a unit of administration containing more than 20 mEq of potassium chloride.

The therapeutic rationale for using potassium supplements has been adequately discussed in other reviews and documents prepared by this Division and so will not be reiterated here.

5. Clinical Studies:

The results of one clinical study are included in this application. A bioavailability study comparing Micro-K LS to Micro-K Extencaps and a potassium chloride solution was conducted. The results of this study show that the extent of absorption of potassium from a 40 mEq single dose of Micro-K LS was 57%, compared to 63% for an equivalent amount of liquid potassium chloride (based on the net increase of urinary potassium excretion during the 24 hours after dosing compared to the control period). The extent of absorption for the Micro-K Extencaps was 47%. After 48 hours the extent of absorption for the Micro-K LS, KCl solution and Micro-K Extencaps was 65%, 76% and 58% respectively. The extent of availability of the Micro-K LS formulation is within the acceptable range of variability (20%) compared to the reference standard for this drug (potassium chloride solution). The Micro-K Extencaps produced availability results outside the usual acceptable range.

The rate of excretion for Micro-K LS and Micro-K Extencaps was similar and occurred at a rate that was slower initially than that recorded for the potassium chloride solution. Peak excretion of potassium in the urine (based on the net increase over control) occurred during the 0-2hour period after the dose of KCl solution, and at the 4-6hour period for both Micro-K LS and Micro-K Extencaps. This observation was interpreted as differentiating between an immediate release product and a slow release product.

The results of this bioavailability study demonstrate that the extent of absorption of potassium from the Micro-K LS formulation is similar to a solution of potassium chloride and that the rate of absorption is slower with a lower peak rate and longer duration than that of a similar amount of potassium chloride solution. The comparison of Micro-K LS to Micro-K Extencaps shows the former to be more bioavailable, but with similar rates of absorption. The detailed review of this study is included below.

Title of Study: Comparison of the Bioavailability of Potassium from a Microencapsulated Potassium Chloride Suspension with that from Orally Administered Micro-K Extencaps and a Potassium Chloride Solution

Protocol Number: Study 2601

Investigator(s): Albert Cohen, M.D.; Peninsular Testing Corporation; 20215 NW Second Avenue; Miami FL 33169.

Dates of the Study: September 1985

Objective of the Study:

(From the Protocol) The objective of this study was to assess the relative rate and extent of absorption of potassium from an experimental microencapsulated formulation of KCl in suspension compared with that from Micro-K taken as capsules and from a liquid KCl formulation. Since food contains potassium, control phases where the same meals will be served with and without the drug will be used to correct for the contribution of the diet to the potassium excretion.

Study Plan:

The study was designed as a non-blinded, single-dose, 4-period crossover investigation using confined healthy male volunteers assigned to randomly ordered treatment sequences. Each period lasted 5 days with the first 3 days being used for stabilization of potassium intake and output followed by a single dose of test drug and 1 day of fractional urine collections. Treatment consisted of either 40mEq of Micro-K LS, 5 capsules of Micro-K Extencaps 8mEq, potassium chloride 1.33mEq/ml (30ml)liquid, or no treatment (control). The same five day diet regimen was followed for each of the treatment periods based on a daily intake of 60mEq of potassium and 160-180mEq of sodium. Fluid intake was 2500ml per day. On the day of the test drug dose fractional urines were collected at intervals of 0-2, 2-4, 4-6, 6-8, 8-12, and 12-24 hours after dosing. Each of the other days had 24 hour urine collections.

Study Population:

Subjects were eligible for this study if they were healthy males between the ages of 18 and 40 and not more than 15% above or below the range of desirable weight. No evidence of a systemic or organ specific disease or condition was allowed after history, physical examination, laboratory screening, electrocardiogram and medication history was completed.

Quality Assurance:

A total of 28 subjects were enrolled in the study and all 28 completed the 4 periods of treatment. All subjects were male and ranged in age from 20 to 40. Twenty-seven were white and one was black. There were 19 smokers. As each subject was enrolled in the study he was assigned to one of four randomly ordered treatments. All subjects received their first treatment on 7 September 85 and the last treatment on 22 September 85 so no treatment blocks were necessary. No tests of the randomization scheme were done by the sponsor's statistician; however, a review of the tabulations on treatment assignments and demographics did not reveal any obvious discrepancies between the groups assigned to the four different treatment schemes.

The case report form conformed adequately to the protocol although there was no 'intake' flow sheet to match the output portion of the data collection forms. Thus there is no documentation on the fluid intake on the non-testing days or any record of the forced hydration described for the test day. There is also no record of food intake so the dietary potassium content, although known for the meals as provided, is not evaluated with regard to the amount of the meal the subject actually consumed.

Efficacy Results:

The protocol called for analyzing cumulative excretion and excretion rates of potassium for all four treatment periods. Comparisons were to be based on between treatment analyses for total potassium excretion. This is different from the analysis of data most frequently requested by the Division of Biopharmaceutics which ordinarily prefers an analysis based on the net increase over baseline. Therefore the data from the tabulations of mean potassium excretion are summarized below for each five day, 24 hour urine collection period as a basis for determining extent of absorption/excretion. A second table has been derived from the 24 hour fractional urines collected on the test dose day. This table will be used as a basis for determing rate of absorption. The original tabulations from which these summary tables are derived are attached to this review.

Extent of Absorption

The mean urinary potassium excretion in a 24 hour period for all subjects (N=28) for each treatment is summarized below.

Mean amounts of potassium excreted in urine (mEq)

	Day 1	Day 2	Day 3	Day 4	Day 5
Control Period	49.4	48.6	44.1	43.9	47.3
KCl solution	46.2	46.7	42.1	69.2	52.5
Micro-K Extencaps	46.6	46.4	42.6	62.8	51.6
Micro-K LS (suspension)	47.5	49.4	43.1	66.6	50.7

The change in the mean amount of potassium excreted base on the control period and the active treatment period for each five day treatment cycle is summarized in the table below.

Change in mean excretion (treatment minus control) in mEq

	Day 1	Day 2	Day 3	Day 4	Day 5
KCl solution	-3.2	-1.9	-2	+25.3	+5.2
Micro-K Extencaps	-2.8	-2.2	-1.5	+18.9	+4.3
Micro-K LS(suspension)	-1.9	+0.8	-1.0	+22.7	+3.4

All treatments contained 40 mEq of potassium. The percent of the dose excreted in 24 hours was 63% for the solution, 57% for the suspension and 47% for the capsules. Using the solution as the reference standard this represents 91% of the standard for Micro-K LS and 75% of the standard for the Micro-K Extencaps. The same order and degree of difference exists if the 48 hour excretion of potassium is the basis of analysis. The differences do not change if the actual measured amount of potassium in each treatment is used instead of the theoretical content, i.e the 5 capsules of Micro-K Extencaps delivered a dose of 40.1 mEq, the KCl solution delivered a dose of 39.5mEq and the suspension contained 38.5mEq of potassium chloride.

These results demonstrate that the Micro-K LS suspension is within an acceptable range of the standard solution with regard to extent of absorption/excretion. The results with regard to Micro-K Extencaps are not within the usual acceptable range.

Rate of Availability

The mean urinary excretion of potassium for all subjects (N=28) for each treatment during the 24 hours after dosing based on the fractional urines collected is summarized below.

Mean amount of potassium excreted (mEq)

	0-2	2-4	4-6	6-8	8-12	12-24	0-24
Control period	6.6	4.5	4.2	4.8	9.1	14.7	43.9
KCl solution	16.8	9.4	7.1	6.9	10.7	18.3	69.2
Micro-K Extencaps	8.0	8.1	8.5	8.5	12.6	18.3	62.8
Micro-K LS suspen.	9.0	9.2	9.7	8.7	12.0	18.6	66.6

The change of the means between the baseline/control period and the active treatment period is summarized here.

Change in the mean potassium excretion (treatment minus control) in mEq

	0-2	2-4	4-6	6-8	8-12	12-24	0-24
KCl solution	10.2	4.9	2.9	2.1	1.6	3.6	25.3
Micro-K Extencaps	1.4	3.6	4.3	3.7	3.5	3.6	18.9
Micro-K LS suspen.	2.4	4.7	5.5	3.9	2.9	3.9	22.7

The results from the fractional urines collected and analyzed for potassium demonstrate a substantial difference between the peak time for excretion and the rate of excretion for the solution and the sustained release formulations. The solution has a high (5.1mEq/h) and early peak excretion at 0-2 hours with a rapid tapering to 0.4mEq/hour by the 8-12 hour collection. Both the Micro-K capsules and suspension peaked at the same collection period (4-6 hours) but the suspension had a slightly higher rate at 2.75mEq/h compared to 2.15mEq/h for the capsule. By the 12-24 hour collection all three formulations had similar rates of excretion. Therefore the rate of availability for the solution is substantially different than the rate for the Micro-K products.

Safety Results:

There were no deaths or withdrawals from the study. There were 7 patients who reported an adverse effect that was possibly related to the test treatment and they accounted for 8 different treatments. The majority of adverse effects were gastrointestinal and involved 2 reports associated with the solution, 3 reports with the capsules, and 3 reports with the suspension. Two of the subjects were hypokalemic at the end of the study reflecting an overall trend toward lower post-treatment serum potassiums. No other clinically significant laboratory or ECG changes were noted.

Sponsor's Conclusions: The sponsor makes the following conclusions based on the results of this study:

1. The rate of excretion of potassium from the Suspension and the Capsule were initially less than that for the Liquid which was indicative of the potassium content of the Suspension not being "dumped".
2. The rates of excretion of potassium from the Suspension and Capsule were similar to one another and slowed with respect to the rate of the Liquid.
3. The extent of the absorption of potassium from the Suspension was equal to that from the Capsule and the Liquid.
4. The Suspension was fully bioavailable when compared to the Liquid.
5. The Suspension was bioequivalent to the Capsule in that both the extent of the absorption and the rate at which excretion occurred was similar.

Reviewer's Conclusions:

The results of this study with regard to the comparison between the Micro-K LS suspension and the KCl solution show that the sponsor's product is within the limits of acceptability for the extent of bioavailability and that the rate of availability is substantially different such that one can conclude that the solution is likely to be an immediate release product and the suspension is likely to be a sustained release product.

Even though the extent of availability of the Micro-K Extencaps used in this study produced results that were below the limits of acceptability, the rate of availability showed a similar trend to that produced by the suspension and therefore the two products can be considered comparable with regard to the bioavailability profile produced by the microencapsulated portion of the formulation.

The study provides no information about the safety of the granulate portion of the Micro-K LS formulation.

Recommendations:

Micro-K LS has a bioavailability profile that is characteristic of a sustained release potassium chloride formulation. Therefore this study is considered an adequate demonstration of the sustained release and availability of Micro-K LS.

No other clinical studies with Micro-K LS were submitted as part of this application.

6. Labeling:

The labeling submitted for this product is a hybrid of the currently approved labeling for Micro-K and the generic immediate release products. Since this product represents some unique formulation problems not previously presented by an applicant for NDA approval, the label provides an opportunity to set a precedent for future products of this type. Therefore a thorough review of the label is suggested at such time the product is considered approvable.

7.Overall Summary and Conclusions:

This application is based on Chemistry and Manufacturing information and the demonstration of 'bioequivalence' to an already marketed product. On this basis the sponsor has waived the usual requirements for approval of a sustained release oral dosage form of potassium chloride. Therefore no animal pharmacology studies were done nor were any clinical studies on the safety of chronic use or the gastric irritation potential using the McMahon model.

The only dosage strength that could be considered for approval at this time would be the 25 mEq packet, since an adequate amount of exposure information is available for units of administration of this size. [redacted] exceeding the 25 mEq unit could be safely recommended.

As stated in the concluding comments in the Chemistry and Maunfacturing Section of this review:

1. The final packaged dose form of Micro-K LS is substantially different form Micro-K Extencaps.

2. The 'inactive ingredients' in the Micro-K LS product contain components known to be biologically and therapeutically active.

3. The proposed labeling for Micro-K LS does not provide adequate information about the quantity and the activity of the 'inactive ingredients'.

4. The microencapsulated potassium chloride (microcaps) in Micro-K Extencaps and Micro-K LS have similar dissolution profiles.

5. Micro-K LS should be subject to the same dissolution specifications as Micro-K Extencaps (NDA 18-238).

As stated in the concluding remarks on the single clinical study submitted in this application:

> The results of this study with regard to the comparison between the Micro-K LS suspension and the KCl solution show that the sponsor's product is within the limits of acceptability for the extent of bioavailability and that the rate of availability is substantially different such that one can conclude that the solution is like an immediate release product and the suspension is like a sustained release product.

Recommendation:

I recommend that this application NOT be approved. This recommendation is based on the following deficiencies:

1. the formulation contains quantities of docusate that exceed the usual acceptable limits for either foods or drugs (see Addendum for discussion of these limits).

2. the Micro-K LS formulation is substantially different from the parent NDA 18,238 for Micro-K Extencaps and therefore requires additional safety studies in humans.

3. in addition to the above deficiencies the [redacted], NDA 18-238).

Cheryl Fossum Graham, M.D.

[redacted]
HFN-110
HFN-110/CSO
HFN-110/C GRAHAM

N1956102/cfg/14may86
revised/cfg/28may86

)ate: 28 May 86

The presence of docusate (dioctyl sodium sulfosuccinate) in the Micro-K LS formulation raises an interesting problem. Docusate is approved as a single entity and in fixed dose combination drug products as a stool softener in doses beginning at 50 mg per unit of administration. It is also considered a food additive and is specifically regulated for use and amount in 21 CFR 172.810. Paragraph (c) of this regulation is pertinent to the use of docusate in food products that are formulated in a manner similar to Micro-K LS. That paragraph specifies that docusate may be safely used "...as a solubilizing agent on gums and hydrophilic colloids to be used in food as stabilizing and thickening agents, when standards of identity do not preclude such use. The additive is used in an amount not to exceed 0.5 percent by weight of the gums or hydrophilic colloids."

If one were to apply the food standard to the Micro-K LS formulation, the allowable amount of docusate would be 5.9mg per 50 mEq packet based on 1.1727 grams of xanthan gum or 6.8mg if povidone and xanthun gum are both included under the category of "gums and hydrophilic colloids". The formulation composition reported by the sponsor of Micro-K LS contains 10.9 mg of docusate per 50 mEq packet.

A review of drug products containing docusate as an inactive ingredient was done using a printout from the ASTRO IV drug file (19 May 1986). With a few exceptions the usual amount of docusate per unit of administration is 2 mg or less for approved drug products intended for oral ingestion. Products intended for external application contain amounts that would exceed this depending on how the product were used.

Potassium chloride supplements are subject to either food or drug regulations depending on the amount per unit of administration. Under the food regulations the Micro-K LS formulation would be unacceptable as presently compounded. Since there is no comparable set of drug product standards, the prevailing use in other products appears to be the best standard. Using this criteria the Micro-K LS formulation again would appear to be unacceptable. The most comparable formulation of a potassium chloride supplement is K-Lyte Cl/50 which was reported by the manufacturer (Mead-Johnson) to contain 0.8 mg of docusate per 50 mEq effervescent tablet.

It is the opinion of this reviewer that a potassium supplement such as Micro-K LS should not contain docusate, or any other inactive ingredient, in amounts that may be therapeutic for some other indication. In the case of drug products used in life-threatening situations where no other additive was suitable, the use of docusate might be justified, but such is not the case with this product and therefore its use in such a high concentration should not be allowed.

N1956106/cfg/28may86

TABLE V

AMOUNTS (MEQ) OF POTASSIUM EXCRETED IN URINE IN THE SUSPENSION TREATMENT GROUP

SUBJECT NUMBER	DAY 1	DAY 2	DAY 3	DAY 4 (TREATMENT DAY)							DAY 5
	0-24	0-24	0-24	0-2	2-4	4-6	6-8	8-12	12-24	0-24	0-24
1											
2											
3											
4											
5											
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N	28	28	28	28	26	28	28	28	28	28	28
MEAN	47.46	49.39	43.12	9.00	9.16	9.73	8.72	12.01	18.60	66.57	50.66
SD	10.90	8.96	6.71	3.04	2.60	3.18	2.44	4.49	5.43	10.39	7.82
CV%	23.0	18.1	15.6	33.8	28.4	32.7	27.9	37.4	29.2	15.6	15.4

N=NO URINE COLLECTED

TABLE VI

AMOUNTS (MEQ) OF POTASSIUM EXCRETED IN URINE IN THE CAPSULE TREATMENT GROUP

SUBJECT NUMBER	DAY 1	DAY 2	DAY 3	DAY 4 (TREATMENT DAY)							DAY 5
	0-24	0-24	0-24	0-2	2-4	4-6	6-8	8-12	12-24	0-24	0-24
1											
2											
3											
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5											
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26											
27											
28											
N	28	28	28	27	25	28	28	28	28	28	28
MEAN	46.59	46.41	42.63	8.01	8.12	8.45	8.45	12.56	18.32	62,76	51,60
SD	15.97	8.55	6.05	2.47	2.79	4.34	2.83	3.60	5.32	9.51	7.01
CV%	34.3	18.4	14.2	30.9	34.3	51.3	33.5	28.7	29.0	15.1	13.6

N=NO URINE COLLECTED

TABLE VII

AMOUNTS (MEQ) OF POTASSIUM EXCRETED IN URINE IN THE SOLUTION TREATMENT GROUP

SUBJECT NUMBER	DAY 1	DAY 2	DAY 3	DAY 4 (TREATMENT DAY)							DAY 5
	0-24	0-24	0-24	0-2	2-4	4-6	6-8	8-12	12-24	0-24	0-24
1											
2											
3											
4											
5											
6											
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22											
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25											
26											
27											
28											
N	28	28	28	28	28	28	28	28	28	28	28
MEAN	46.23	46.69	42.08	16.75	9.43	7.09	6.93	10.68	18.32	69.20	52.46
SD	12.03	11.70	7.62	5.23	2.93	2.46	2.43	3.49	5.81	9.99	9.05
CV%	26.0	25.1	18.1	31.2	31.0	34.7	35.0	32.7	31.7	14.4	17.2

TABLE VIII

AMOUNTS (MEQ) OF POTASSIUM EXCRETED IN URINE IN THE CONTROL TREATMENT GROUP

SUBJECT NUMBER	DAY 1	DAY 2	DAY 3	DAY 4 (TREATMENT DAY)							DAY 5
	0-24	0-24	0-24	0-2	2-4	4-6	6-8	8-12	12-24	0-24	0-24
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
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17											
18											
19											
20											
21											
22											
23											
24											
25											
26											
27											
28											
N	28	28	28	28	28	28	28	28	28	28	28
MEAN	49.40	48.59	44.09	6.63	4.49	4.23	4.83	9.06	14.70	43.93	47.31
SD	12.38	7.60	8.53	2.30	1.52	1.64	1.85	3.72	5.38	7.95	5.79
CV%	25.1	15.6	19.3	34.7	33.9	38.8	38.3	41.1	36.6	18.1	12.2