CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-238/S011, S013

Trade Name: Micro-K

Generic Name: (potassium chloride)

Sponsor: A.H. Robins Company

Approval Date: May 14, 1984

Indications: For the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-238/S011, S013

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-238/S011, S013

APPROVAL LETTER

9.1

NDA 18-238/S011

MAY 14 1984

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

Dear Ms. Aaroe:

We acknowledge receipt of your resubmitted supplemental application for the following:

Name of Drug: Micro-K

NDA Number: 18-238

Supplement Number: S011

Date of Resubmitted Supplement: April 2, 1984

Date of Receipt: April 2, 1984

The supplemental application provides for a new dosage strength, Micro K-10 mEq (750 mg)..

We have completed the review of this supplemental application and it is approved. Our letter of October 17, 1980 detailed the conditions relating to the approval of this application.

Sincerely yours,

RJ 5/11/84

Raymond J. Lipicky, M.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc: RIC-DD
Original NDA
HFN-110
HFN-110/CSO
HFN-616
HFN-110/JKnight/4/26/84
sh/4/26/84/5903c

Knight 4/26/84

APPROVAL

9.1

NDA 18-238/S-011, S-013

JUL 25 1985

A.H. Robins Company
Attention: Ms. Frances Aaroe
1211 Sherwood Avenue
Richmond, VA 23220

Dear Ms. Aaroe:

Please refer to your supplemental new drug applications of April 22, 1983 (S-011) and December 19, 1983 (S-013) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Micro-K (potassium chloride) Capsules, 600 mg (8 mEq) and 750 mg (10 mEq).

We also acknowledge receipt of your additional communications dated October 23 and October 24, 1984.

The supplemental applications provide for

We have completed the review of these supplemental applications, as amended, and they are approved. Our letter of October 17, 1980 detailed the conditions relating to the approval of these applications.

Sincerely yours,

7/24/85

Stewart J. Ehrreich, Ph.D.
Deputy Director
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Original NDA
HFN-110
HFN-110/CSO
HFN-83
HFN-232 (with labeling)
HFN-110/AThompson/7/16/85
sb/7/23/85/1566s
R/D: CResnick/7/19/85
RWolters/7/17/85

7/24/85

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-238/S011, S013

LABELING

ORIGINAL

18-238 4/2/84

Package Outsert

Printed in U.S.A.

Description: Micro-K Extencaps are pale orange, hard gelatin capsules, each containing 600 mg of dispersible, small crystalline particles of potassium chloride (equivalent to 8 mEq K), monogrammed Micro-K and AHR/5720

Micro-K 10 Extencaps are pale orange and opaque white, hard gelatin capsules, each containing 750 mg of dispersible, small crystalline particles of potassium chloride (equivalent to 10 mEq K) monogrammed Micro-K 10 and AHR/5730. Each particle of potassium chloride (KCl) is microencapsulated by a patented process with a polymeric coating which allows for the controlled release of potassium and chloride ions over an eight- to ten-hour period. The dispersibility of the microcapsules and the controlled release of ions are intended to minimize the likelihood of high localized concentrations of potassium chloride and resultant mucosal ulceration within the gastrointestinal tract.

The polymeric coating forming the microcapsules functions as a water-permeable membrane. 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.

Actions: Potassium ion is the principal intracellular cation of most body tissues. Potassium ions participate in a number of essential physiological processes, including the maintenance

2 of intracellular tonicity, the transmission of nerve impulses, the contraction of cardiac, skeletal, and smooth muscle and the maintenance of normal renal function.

Potassium depletion may 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 slowly as a consequence of prolonged therapy with oral diuretics, primary or secondary hyperaldosteronism, diabetic ketoacidosis, severe diarrhea, or inadequate replacement of potassium in patients on prolonged parenteral nutrition. Potassium depletion due to these causes is usually accompanied by a concomitant deficiency 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.

Potassium depletion associated with metabolic alkalosis is managed by correcting the fundamental causes of the deficiency whenever possible and administering supplemental potassium chloride, in the form of high potassium food or potassium chloride solution, capsules or tablets. 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, or potassium acetate.

INDICATIONS: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COM-

3 PLIANCE WITH THESE PREPARATIONS.

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.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. 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, 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).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

Warnings: *Hyperkalemia.* In patients with impaired mecha-

4 nisms 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 adjustments.

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 or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions. Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths, in addition to upper gastrointestinal bleeding. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation.

Micro-K Extencaps contain microcapsules which disperse upon dissolution of the hard gelatin capsule. The microcapsules are formulated to provide a controlled release of potassium chloride. The dispersibility of the microcapsules and the controlled release of ions from the microcapsules are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of KCl into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated KCl), but have not eliminated them. The frequency of GI lesions with Micro-K Extencaps is,

ORIGINAL
18-238 4/2/84
Mailed 4/20/84

at present, unknown. Micro-K Extencaps should be discontinued immediately and the possibility of bowel 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, or potassium acetate.

Precautions: 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.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and may be minimized by taking the dose with meals or by reducing the dose.

Intestinal bleeding, ulceration, perforation and obstruction have been reported in patients treated with solid dosage forms of potassium salts and may occur with Micro-K Extencaps (see Contraindications and Warnings).

One of the most severe adverse effects of potassium supplementation is hyperkalemia (see Contraindications, Warnings, and Overdosage).

Skin rash has been reported rarely with potassium preparations.

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 and characteristic electrocardiogram 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.

Treatment measures for hyperkalemia include the following: (1) elimination of foods and medications containing potassium and of potassium-sparing diuretics; (2) intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml; (3) correction of acidosis, if present, with intravenous sodium bicarbonate; (4) use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

Dosage and Administration: The usual dietary intake of potassium by the average adult is 40 to 80 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, but typically is around 20 mEq per day for the prevention of hypokalemia and 40 to 100 mEq per day for the treatment of potassium depletion.

	For Prevention	For Treatment
Micro-K Extencaps (8 mEq K)	2 or 3 Extencaps/day (16–24 mEq K)	5 to 12 Extencaps/day 40–96 mEq K)
Micro-K 10 Extencaps (10 mEq K)	2 Extencaps/day (20 mEq K)	4 to 10 Extencaps/day 40–100 mEq K)

If more than 2 Extencaps are prescribed per day, the total daily dosage should be divided into two or more separate doses. Those patients having difficulty swallowing the capsules may be advised to sprinkle the contents onto a spoonful of soft food to facilitate ingestion.

How Supplied: Micro-K Extencaps® are pale orange capsules monogrammed Micro-K and AHR/5720, each containing 600 mg microencapsulated potassium chloride (equivalent to 8 mEq K), in bottles of 100 (NDC 0031-5720-63), 500 (NDC 0031-5720-70) and Dis-Co® unit dose packs of 100 (NDC 0031-5720-64).

Micro-K 10 Extencaps® are pale orange and opaque white capsules monogrammed Micro-K 10 and AHR/5730, each containing 750 mg microencapsulated potassium chloride (equivalent to 10 mEq K), in bottles of 100 (NDC 0031-5730-63), 500 (NDC 0031-5730-70), and Dis-Co® unit dose packs of 100 (NDC 0031-5730-64).

Animal Toxicology: The ulcerogenic potential of microencapsulated KCl was studied in anesthetized cats by direct applications on exteriorized gastric mucosa. The microcapsules of KCl were found to be non-ulcerogenic and significantly less irritating than wax-matrix tablets and 20% solution of KCl.

In groups of monkeys (up to 8 monkeys per group) receiving different formulations of potassium chloride at equivalent daily dosage (2400 mg KCl) for four and one-half days, Micro-K Extencaps showed no tendency to cause intestinal ulceration (similar to liquid KCl and a wax-matrix preparation but in contrast to an enteric-coated KCl tablet) and minimal gastric irritation (less than a wax-matrix preparation). Rev. April 1984

A·H·ROBINS

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

Rev. April 1984

Micro-K Extencaps®
Micro-K 10 Extencaps®
brand of
Potassium Chloride

U.S. Patent 4,259,315

A·H·ROBINS

18238 4/2/84

Hospital Unit Dose: 4/20/84

Micro-K 10 Extencap®

(Potassium Chloride)

750 mg
(10 mEq K)

PEEL

A. H. Robins Company
Richmond, Virginia 23220

Lot No.
Exp. Date:

Dis-Co® UNIT DOSE PACK
NDC 0031-5730-64 **100 Capsules**

Micro·K 10 Extencaps®

brand of
Potassium Chloride
750 mg (10 mEq K)
in each Extencaps capsule

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
For dosage and other prescribing information, see accompanying product literature.
Micro-K 10 Extencaps contain microencapsulated KCl and are designed to release the active ingredient over an 8-to 10-hour period.

A·H·ROBINS

Dis-Co® UNIT DOSE PACK
NDC 0031-5730-64 **100 Capsules**

Micro·K 10 Extencaps®

brand of
Potassium Chloride
750 mg (10 mEq K)
in each Extencaps capsule

CAUTION: Federal law prohibits dispensing without prescription.

INTENDED FOR INSTITUTIONAL IN-PATIENT DISPENSING. IF OTHERWISE DISPENSED, AN APPROPRIATE CHILD-RESISTANT CONTAINER SHOULD BE USED.

PHARMACEUTICAL DIVISION 4.84
A. H. ROBINS COMPANY, RICHMOND, VA. 23220

18-238 4/2/84
4/20/84

will be blue

Micro-K 10 Extencap®
(Potassium Chloride)

750 mg
(10 mEq K)

PEEL

A. H. Robins Company Lot No.
Richmond, Virginia 23220 Exp. Date:

BREAK APART

Micro-K 10 Extencaps®
brand of Potassium Chloride
A·H·ROBINS

Micro-K 10 Extencaps®
brand of Potassium Chloride

Controlled-Release Capsules

PROFESSIONAL SAMPLE
4 Capsules

Micro-K 10 Extencaps®
brand of
Potassium Chloride
750 mg (10 mEq K)
in each Extencaps capsule

CAUTION: Federal law prohibits dispensing without prescription.

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

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

A·H·ROBINS

ORI

18-

4/30/84

NDC0031-5730-63 100 Capsules

Micro-K 10 Extencaps®

brand of

Potassium Chloride

750 mg
(10 mEq K)
in each Extencaps capsule

CAUTION: Federal law prohibits dispensing without prescription.

A·H·ROBINS

Bulk Container–Not For Household Dispensing
Store at Controlled Room Temperature, Between 15°C and 30°C (59°F and 86°F).
Dispense in tight container.

U.S. Patent 4,259,315
DOSAGE: For dosage and other prescribing information, see accompanying product literature.
Micro-K 10 Extencaps contain microencapsulated KCl and are designed to release the active ingredient over an 8- to 10-hour period.
PHARMACEUTICAL DIVISION
A. H. ROBINS COMPANY, RICHMOND, VA. 23220

NDC0031-5730-70 500 Capsules

Micro-K 10 Extencaps®

brand of

Potassium Chloride

750 mg
(10 mEq K)
in each Extencaps capsule

CAUTION: Federal law prohibits dispensing without prescription.

A·H·ROBINS

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

U.S. Patent 4,259,315
DOSAGE: For dosage and other prescribing information, see accompanying product literature.
Micro-K 10 Extencaps contain microencapsulated KCl and are designed to release the active ingredient over an 8- to 10-hour period.
PHARMACEUTICAL DIVISION
A. H. ROBINS COMPANY, RICHMOND, VA. 23220

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-238/S011, S013

APPROVABLE LETTER

NDA 18-238/S-011

MAR 16 1984

A. H. Robins Company
Attention: Ms. Frances Aaroe
1211 Sherwood Avenue
Richmond, Virginia 23220

Dear Ms. Aaroe:

Please refer to your supplemental new drug application of April 22, 1983 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Micro-K-10 (potassium chloride) Capsules.

We also acknowledge receipt of your additional communication dated May 20, 1983 providing for the use of an alternate ink to print the product identification on the capsules.

The supplemental application provides for a new dosage size, namely a 750 mg (10 mEq K) of potassium chloride.

We have completed the review of this supplemental application. Before we are able to reach a final conclusion, however, the following information is necessary:

1. It will be necessary for you to submit accelerated stability data on the 750 mg capsule.

2. Submit twelve copies of the final printed labeling identical in content to the draft copy.

Further action on this supplemental application will await our receipt and review of your response to this request.

We also acknowledge receipt of your submission dated October 19, 1983. This submission requests a waiver of the bioavailability/bioequivalence requirement. We have reviewed this submission and your request for a waiver is granted.

Sincerely yours,

Raymond J. Lipicky, M.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Research and Review
National Center for Drugs and Biologics

cc: BLT-DO
Original NDA
HFN-110
HFN-110/CSO
HFN-110:RWolters:2/13/84
Revised:JKnight:3/14/84
sie:3/3/84:3/14/84:5228c
R/D init: RLipicky:3/1/84

REVIEW WAITING

5 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-238/S011, S013

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: HFN-110

2. NDA NUMBER: 18-238

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
A.H. Robins Company
1211 Sherwood Avenue
Richmond, Virginia 23220

MAR 16 1984

4. AF NUMBER: 6-375

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S-011	4-22-83
S-012	5-20-83

6. NAME OF DRUG: Micro-K

7. NONPROPRIETARY NAME: Potassium Chloride

8. SUPPLEMENT(S) PROVIDES FOR: S-011 provides for a 750 mg capsule
S-012 Provides for a new ink to print the product identitfcation number for the 600 mg capsules.
The AM to S-011 contained the same information for the new 750 mg capsules.

9. AMENDMENTS AND OTHER *(Reports, etc.)* DATES
AM to S-011-5-20-83

10. PHARMACOLOGICAL CATEGORY: Potassium electrolyte replenisher.

11. HOW DISPENSED: [X] RX [ ] OTC

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM (S): Capsules

14. POTENCY *(fos)*
600 mg (approved)
750 mg to be approved

15. CHEMICAL NAME AND STRUCTURE
USP XX

16. RECORDS AND REPORTS
CURRENT: [X] YES [ ] NO
REVIEWED: [X] YES [ ] NO

17. COMMENTS S-012 and S-011 AM: The new ink for these two potencies consist of [redacted] FD&C Blue 2, [redacted] and Yellow 6. All the dyes are as aluminium lakes. Specifications are included. The ink, Black Edible [redacted] is purchased from [redacted]. This is an alternate ink. b(4) b(4)

S-011 Stability-The protocols for testing pilot-scale btahces, production batches, clinical batches, and evaluation of new packaging materials are included. Times and conditions are chosen to adequately characterize the product and and new packaging material. b(4)
Stability data on the 600 mg capsule packaged in amber glass and HDPE bottles for up to 36 months/RT and 6 months/65% RH, in 7.5 ml unit dose for 18 months/RT, 10.0 ml unit dose for 24 months/RT, and physican samples package for 12 months/RT. Assay and dissolution data are satisfactory.
b(4) [redacted] for the capsules packaged in amber glass, HDPE (100's and 500's), physican samples, and unit dose containers. Before the date can be approved, it is necessary for Robins to submit accelerated studies on the 750 mg capsules.

18. CONCLUSIONS AND RECOMMENDATIONS

Approved S-012
REV W/F S-011

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
R.J. Wolters	RJWolt 3/15/84	2-13-84

DISTRIBUTION: [X] ORIGINAL JACKET [ ] REVIEWER [ ] DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED. 1

HFN-110/CSO

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION	HFN-110
2. NDA NUMBER	18-238
3. NAME AND ADDRESS OF APPLICANT (City and State)	A.H. Robins Company 1211 Sherwood Avenue Richmond, Virginia 23220 MAY 14 1984
4. AF NUMBER	6-375
5. SUPPLEMENT (S) NUMBER(S)	S-011
5. SUPPLEMENT (S) DATE(S)	4-22-83
6. NAME OF DRUG	Micro-K
7. NONPROPRIETARY NAME	Potassium Chloride
8. SUPPLEMENT(S) PROVIDES FOR:	Provides for a 750 mg (10 mEq) of KCl. Amendment provides for different color capsule, stability data, and FPL.
9. AMENDMENTS AND OTHER (Reports, etc.) DATES	4-2-84
10. PHARMACOLOGICAL CATEGORY	Potassium electrolyte replenisher
11. HOW DISPENSED	[X] RX [ ] OTC
12. RELATED IND/NDA/DMF(S)	
13. DOSAGE FORM (S)	Capsules
14. POTENCY (less)	600 mg (approved) 750 mg
15. CHEMICAL NAME AND STRUCTURE	USP XX
16. RECORDS AND REPORTS CURRENT	[X] YES [ ] NO
16. RECORDS AND REPORTS REVIEWED	[X] YES [ ] NO

17. COMMENTS

b(4)

The new capsule will be ——— b(4) ——— It will be supplied by ——— Specifications for the capsule shell are included. Stability data were submitted on the capsules stored for one month at 50°C/80% RH, 37°C,/80%RH for three months,and RT for six months. The capsules were stored in HDPE bottles with a metal screw cap. Assay and dissolution data were staisfactory. These data along with the data submitted in the original submission are adequate for the 36 month expiration data. I called Ms. Aaroe and told her that the data are marginal. She should have included data in the physican sample and unit dose conatiner. However since the product is KCl and there is not a stability problem and the dissolution is confirmed by the results from the 600 mg capsule, the data are adequate. FPL is satisfactory insofar as the technical aspects are concerned.

18. CONCLUSIONS AND RECOMMENDATIONS

Approve supplement.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
R.J. Wolters		4-20-84

DISTRIBUTION [ ] ORIGINAL JACKET [ ] REVIEWER [ ] DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

HFN-110/CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-238/S011, S013

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ORIGINAL

A. H. Robins Company
Research Laboratories
1211 Sherwood Avenue
P. O. Box 26609
Richmond, Virginia 23261-6609
Telephone (804) 257-XXX2546

A-H-ROBINS

RESUBMISSION

RS

Division of Cardio-Renal Drug Products
HFN-110, Room 16B-30
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RECEIVED
1984
BUREAU OF DRUGS

April 2, 1984

RE: NDA 18-238/S-011
Micro-K-10

Gentlemen:

Reference is made to your letter of March 16, 1984 regarding Supplement 011 to our New Drug Application for Micro-K, in which you requested final printed labeling and accelerated stability.

The supplement provides for b(4) hard gelatin capsules. Our Marketing Office has decided that Micro-K-10 should be in orange and white, hard gelatin capsules.

We, herewith, submit the following:

NDA PART	DESCRIPTION
4	Labeling: Immediate container labels for 100's Immediate container labels for 500's Cartons for 4's (Professional sample) Labels for Dis-Co Pack Cartons of 100 Package Insert (Identical except for description of Micro-K-10 Extencaps under Description and How Supplied)
6	List of components which substitutes the white body for the natural transparent body of the hard gelatin capsules
7	Composition which substitutes the white body for the natural transparent body of the hard gelatin capsule

NDA PART	DESCRIPTION
8(d)	Raw material specifications and test procedures for capsules, hard gelatin empty
8(h)	Manufacturing, processing, packaging and labeling description changed to reflect the white body of the capsule
8(n)	Product Specifications and Test Procedures which have been changed to reflect the white body of the capsule
8(p)	6-month stability data for Micro-K-10 capsules including 3-months accelerated stability

Twelve copies of the final printed labeling are included with this submission.

Sincerely,

Frances Aaroe

Frances Aaroe, Manager
Special Regulatory Projects

jlc

Enclosures

9.1

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics
Office of Drug Standards

DATE : MAY - 2 1984

MAY 9 1984

TO : Dr. Raymond Lipicky
Acting Director, Division of Cardio-Renal
Drug Product (HFN-110)

FROM : Jerome P. Skelly, Ph.D.
Acting Director, Division of Biopharmaceutics (HFN-520)

SUBJECT: Waiver of in vivo Bioavailability Study
Potassium Chloride — NDA 18-238
A.H. Robins — October 19, 1983

Background:

A.H. Robins currently markets a 600 mg potassium chloride capsule, Micro-K Extencaps. A satisfactory comparative bioavailability was conducted on this product and the results were presented in a submission to the Agency on December 29, 1978.

Discussion:

The firm is now preparing to market a new capsule strength, 750 mg Micro-K-10 Extencaps. Micro-K-10 Extencaps are identical to Micro-K Extencaps with the exception that each capsule contains 750 mg of dispersible small crystalline particles of potassium chloride (equivalent to 10 mEq K^+). b(4) b(4) The 750 mg formulation is placed in a conventional shaped, hard gelatin capsule with b(4) while the 600 mg material is placed in a b(4) with Therefore the firm has requested a waiver for a bioavailability study on its 750 mg capsule formulation.

b(4)

Conclusion:

The Division of Biopharmaceutics agrees that the information submitted by A.H. Robins, demonstrates that 750 mg Micro-K-10 Extencaps capsules falls under Section 320.22 (D)(#2) of the bioavailability regulations in the Code of Federal Regulations. The Division of Biopharmaceutics recommends that the waiver of an in vivo bioavailability study be granted. Accordingly, a bioavailability study should not be undertaken.

Jerome P. Skelly

Jerome P. Skelly, Ph.D.

Prepared by: Donald L. Heald, Ph.D.

Initialed by: HJMalinowski, Ph.D.
cc: HFN-110 (Lipicky), HFN-520 (Skelly), HFN-525 (Heald), Chron File, Drug File, Review File, Division File
DLH/dea/0987x:4/5/84

Potassium Chloride
750 mg capsules
NDA 18-238
Reviewer: Donald L. Heald, Ph.D.
Wang: 0987x

A.H. Robins
Richmond, VA. 23220
Submission Date:
October 19, 1983

MAY - 2 1984

Request for a Waiver of a Bioavailability Study

A.H. Robins currently markets a 600 mg potassium chloride capsule, Micro-K Extencaps. A satisfactory comparative bioavailability study was conducted on this product and the results were presented in a submission to the Agency on December 29, 1978.

The firm is now preparing to market a new capsule strength, 750 mg Micro-K-10 Extencaps. Micro-K-10 Extencaps are identical to Micro-K Extencaps with the exception that each capsule contains 750 mg of dispersible small crystalline particles of potassium chloride (equivalent to 10 mEq K^+). b(4)

b(4)

The 750 mg formulation is placed in a conventional shaped, hard gelatin capsule with b(4) b(4) while the 600 mg material is placed in a b(4) with Therefore the firm has requested a waiver for a bioavailability study on its 750 mg capsule formulation.

Recommendation:

The Division of Biopharmaceutics agrees that the information submitted by A.H. Robins, demonstrates that 750 mg Micro-K-10 Extencaps capsules falls under Section 320.22 (D) (#2) of the Bioavailability Regulations. The Division of Biopharmaceutics recommends that the waiver of an *in vivo* bioavailability be granted. Accordingly, a bioavailability study should not be undertaken.

Donald L. Heald 4-18-84
Donald L. Heald, Ph.D.

FT INITIALED BY H MALINOWSKI, Ph.D.

cc: Orig. NDA 18-238, HFN-110, HFN-525 (Heald), Drug, Chron, Review, and Division.

DLH/cs/dea/3-5-84:0987x

DIVISION DIRECTOR'S REVIEW

MAR 16 1984

NDA #: 18-238/S-011

Applicant: A. H. Robins
Richmond, Virginia 23220

Drug Name: Micro K-10 (potassium chloride, 10 mEq) Tablets

Dosage Form: Microencapsulated KCl, S.R.

Date of Supplement: April 22, 1983

Comments:

This supplement provides for a 750 mg (10 mEq) sized tablet for KCl. The applicant has approval to market currently a 500 mg (8 mEq) sized tablet of the same formulation.

There are several mEq K products currently marketed, i.e., K-Tab by Abbott Laboratories, Klotrix by Mead Johnson and Kaon-Cl-10 by Adria Labs. In view of the fact that there is several years of marketing experience with similar products, I see no safety issue for a 10 mEq Micro K product.

Ray Lipicky
Raymond J. Lipicky, M.D.

cc:
Orig. NDA 18-238/S-011
HFN-110
HFN-110:JKnight
HFN-110:RLipicky:3/1/84
sie:3/13/84:5351c

ORIGINAL

A. H. Robins Company
Research Laboratories
1211 Sherwood Ave.
Richmond, Virginia 23220
Telephone (804) 257-2361

A·H·ROBINS

National Center for Drugs & Biologics
Division of Cardio-Renal Drug
Products, HFN-110
Attention: Document Control Room #16B-30
5600 Fishers Lane
Rockville, MD 20857

April 22, 1983

NDA No. 18-238 SUPP. NO. S011
NDA SUPPL FOR ES

RE: NDA 18-238 (Micro-K Extencaps

Gentlemen:

This supplement to our New Drug Application provides for a new dosage size; namely, Micro-K-10 Extencaps which contain 750 mg of potassium chloride (10 mEg K).

Included with this supplement are the following:

Part 4	Immediate container labels for bottles of 100, 500, and blister units, carton copy for blister units of 4s and 100; package outsert
Part 6	List of components
Part 7	Composition
Part 8d	Raw Material Specifications
8h	Manufacturing
8i	Packaging Specifications
8n	Product Specifications
8p	Stability

Samples are available on request, and market packages will be furnished when available.

Sincerely,

Frances Aaroe

Frances Aaroe

sc

Enclosures

RECEIVED
APR 25 1983
HFD-110
BUREAU OF DRUGS