LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

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February 9, 2001

OVERNIGHT COURIER 2/09/01

Dockets Management Branch
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Citizen Petition

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act and in accordance with 21 CFR 10.30 on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug product Potassium Chloride Extended Release Tablets, 15 mEq, is suitable for consideration in an abbreviated new drug application (ANDA).

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration make a determination that Potassium Chloride Extended Release Tablets, 15 mEq is suitable for submission as an ANDA. The listed reference drug product upon which this petition is based is K-Dur® Extended Release Tablets 10 mEq and 20 mEq, (See Attachment I, Page 3-276 of the Approved Drug Products with Therapeutic Equivalence Evaluations, 20th Edition, "The Orange Book"). Therefore, the petitioner seeks a change in strength (from 10 mEq and 20 mEq tablets to include a 15 mEq tablet) from that of the listed drug product.

B. Statement of Grounds

The Federal Food, Drug and Cosmetic Act provides for the submission of an Abbreviated New Drug Application for a new drug that differs in strength from a listed drug provided the FDA has approved a petition that proposed the filing of such an application. This petition involves a change in strength for the proposed drug from that of the listed drug. The reference-listed drug (RLD) on which this petition is based is

01P-0108 CP1

K-Dur® Tablets manufactured by Key Pharmaceuticals. The proposed drug product differs only in strength from the reference-listed drug. The RLD is marketed as a tablet dosage form containing 10 mEq or 20 mEq of Potassium Chloride. The proposed drug product represents the same dosage form and route of administration as the RLD.

K-Dur is currently approved for marketing as 10 mEq and 20 mEq tablets. The proposed 15 mEq drug product offers an alternate strength of Potassium Chloride Extended Release Tablets for use in the treatment of potassium depletion or prevention of hypokalemia. The approved labeling for K-Dur states that the dose for prevention of hypokalemia is typically in the range of 20 mEq per day, and doses of 40-100 mEq per day or more are used for the treatment of potassium depletion. The inclusion of a 10 mEq tablet is clearly to be used for patients requiring less than 20 mEq per day, or as an aid to adjust dosage to an individual patient's needs. The inclusion of a 15 mEq strength will provide the prescribing physician with a greater degree of flexibility in achieving proper dosing for a specific patient's needs.

The strength of the proposed tablet, an intermediate strength between those currently approved, is, therefore, contemplated in the approved labeling of the listed drug product. The proposed tablet strength will enable patients to use multiples of the new strength tablet to achieve optimal dosing or they can be used in addition to the currently approved 10 mEq and 20 mEq tablets, to adjust dosage levels as necessary. In addition, this will provide the prescribing physician greater flexibility in titrating the patient.

Therefore, the petitioner's request for the Commissioner to find that a change in strength for K-Dur Potassium Chloride Extended Release Tablets, from 20 mEq and 10 mEq to include 15 mEq tablets, should not raise questions of safety or effectiveness, and the Agency should approve the petition.

A copy of the reference-listed drug labeling is included in Attachment 2. Draft labeling for the proposed drug product is included in Attachment 3. The proposed drug product represents the same uses, dosage, and indications as those for K-Dur Tablets, the reference-listed drug.

C. Environmental Impact

An environmental assessment on the action requested in this petition qualifies for a categorical exclusion under 21 CFR 25.31.

D. Economic Impact

Pursuant to 21 CFR 10.30 (b), economic impact information is to be submitted only when requested by the Commissioner. Lachman Consultant Services, Inc. (LCS) will promptly provide such information if so requested.

E. Certification

Lachman Consultant Services, Inc. certifies that, to its best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

Robert W. Pollock
Vice President

Lachman Consultant Services, Inc.
1600 Stewart Avenue, Suite 604
Westbury, NY 11590

RP/cc

Attachments: *Page 3-276, Approved Drug Products with Therapeutic Equivalence Evaluations, 20th Edition*
K-DUR (Potassium Chloride) Extended Release Tablets Insert Labeling
Draft Insert Labeling for Proposed Drug Product

cc: G. Davis (OGD), L. Lachman

84p1040

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 1

POTASSIUM CHLORIDE

INJECTABLE; INJECTION

POTASSIUM CHLORIDE 10MEQ IN PLASTIC CONTAINER

+	BAXTER HLTHCARE	14.9MG/ML	N19904 001 DEC 26, 1989	

POTASSIUM CHLORIDE 20MEQ IN PLASTIC CONTAINER

AP	+ ABBOTT	**29.8MG/ML**	**N20161 006** AUG 11, 1998	
AP	+ BAXTER HLTHCARE	**29.8MG/ML**	**N19904 002** DEC 26, 1989	
	+	1.49GM/100ML	N19904 006 DEC 17, 1990	

POTASSIUM CHLORIDE 30MEQ IN PLASTIC CONTAINER

AP	+ ABBOTT	**2.24GM/100ML**	**N20161 003** AUG 11, 1998	
AP	+ BAXTER HLTHCARE	**2.24GM/100ML**	**N19904 003** DEC 26, 1989	

POTASSIUM CHLORIDE 40MEQ IN PLASTIC CONTAINER

AP	+ ABBOTT	**2.98GM/100ML**	**N20161 004** AUG 11, 1998	
AP	+ BAXTER HLTHCARE	**2.98GM/100ML**	**N19904 004** DEC 26, 1989	

POTASSIUM CHLORIDE IN PLASTIC CONTAINER

AP	AM PHARM PARTNERS	**2MEQ/ML**	**N88901 001** JAN 25, 1985	
AP		**2MEQ/ML**	**N88908 001** JAN 25, 1985	

TABLET, EXTENDED RELEASE; ORAL

K+10

BC	ALRA	10MEQ	N70999 001 OCT 22, 1987	

K+8

AB	ALRA	**8MEQ**	**N70998 001** JAN 25, 1993	

K-DUR 10

BC	+ KEY PHARMS	10MEQ	N19439 002 JUN 13, 1986	

K-DUR 20

AB	+ KEY PHARMS	**20MEQ**	**N19439 001** JUN 13, 1986	

K-TAB

BC	ABBOTT	10MEQ	N18279 001	

KLOR-CON

AB	UPSHER SMITH	**8MEQ**	**N19123 001** APR 17, 1986	
BC		10MEQ	N19123 002 APR 17, 1986	

POTASSIUM CHLORIDE

TABLET, EXTENDED RELEASE; ORAL

KLOR-CON M20

AB	UPSHER SMITH	**20MEQ**	**N74726 001** NOV 20, 1998

KLOTRIX

BC	APOTHECON	10MEQ	N17850 001

POTASSIUM CHLORIDE

BC	ABBOTT	8MEQ	N18279 002 AUG 01, 1988
AB	COPLEY PHARM	**8MEQ**	**N70618 001** SEP 09, 1987

SLOW-K

AB	+ NOVARTIS	**8MEQ**	**N17476 002**

POTASSIUM CHLORIDE; *MULTIPLE*

SEE AMINO ACIDS; CALCIUM ACETATE; GLYCERIN; MAGNESIUM ACETATE; PHOSPHORIC ACID; POTASSIUM CHLORIDE; SODIUM ACETATE; SODIUM CHLORIDE

SEE AMINO ACIDS; CALCIUM CHLORIDE; DEXTROSE; MAGNESIUM CHLORIDE; POTASSIUM CHLORIDE; POTASSIUM PHOSPHATE, DIBASIC; SODIUM CHLORIDE

SEE AMINO ACIDS; DEXTROSE; MAGNESIUM CHLORIDE; POTASSIUM CHLORIDE; SODIUM CHLORIDE; SODIUM PHOSPHATE, DIBASIC

SEE AMINO ACIDS; MAGNESIUM ACETATE; PHOSPHORIC ACID; POTASSIUM ACETATE; POTASSIUM CHLORIDE; SODIUM ACETATE

SEE AMINO ACIDS; MAGNESIUM ACETATE; PHOSPHORIC ACID; POTASSIUM CHLORIDE; SODIUM ACETATE; SODIUM CHLORIDE

SEE AMINO ACIDS; MAGNESIUM CHLORIDE; POTASSIUM CHLORIDE; POTASSIUM PHOSPHATE, DIBASIC; SODIUM CHLORIDE

SEE CALCIUM CHLORIDE; DEXTROSE; GLUTATHIONE DISULFIDE; MAGNESIUM CHLORIDE; POTASSIUM CHLORIDE; SODIUM BICARBONATE; SODIUM CHLORIDE; SODIUM PHOSPHATE

SEE CALCIUM CHLORIDE; DEXTROSE; MAGNESIUM CHLORIDE; POTASSIUM CHLORIDE; SODIUM ACETATE; SODIUM CHLORIDE

SEE CALCIUM CHLORIDE; DEXTROSE; MAGNESIUM CHLORIDE; POTASSIUM CHLORIDE; SODIUM ACETATE; SODIUM CHLORIDE; SODIUM CITRATE

SEE CALCIUM CHLORIDE; DEXTROSE; MAGNESIUM CHLORIDE; POTASSIUM CHLORIDE; SODIUM ACETATE; SODIUM CHLORIDE; SODIUM LACTATE

SEE CALCIUM CHLORIDE; DEXTROSE; MAGNESIUM SULFATE; POTASSIUM CHLORIDE; SODIUM BICARBONATE; SODIUM CHLORIDE; SODIUM PHOSPHATE, DIBASIC

SEE CALCIUM CHLORIDE; DEXTROSE; POTASSIUM CHLORIDE; SODIUM ACETATE; SODIUM CHLORIDE

SEE CALCIUM CHLORIDE; DEXTROSE; POTASSIUM CHLORIDE; SODIUM CHLORIDE

SEE CALCIUM CHLORIDE; DEXTROSE; POTASSIUM CHLORIDE; SODIUM CHLORIDE; SODIUM LACTATE

LACHMAN CONSULTANT SERVICES, INC.
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ATTACHMENT 2

K-Dur Microburst Release System ER Tablets

DESCRIPTION

K-DUR® 20 is an immediately dispersing extended release oral dosage form of potassium chloride containing 1500 mg of microencapsulated potassium chloride USP equivalent to 20 mEq of potassium in a tablet.
K-DUR® 10 is an immediately dispersing extended release oral dosage form of potassium chloride containing 750 mg of microencapsulated potassium chloride USP equivalent to 10 mEq of potassium in a tablet.
These formulations are intended to slow the release of potassium so that the likelihood of a high localized concentration of potassium chloride within the gastrointestinal tract is reduced.
K-DUR 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.
K-DUR is a tablet formulation (not enteric coated or wax matrix) containing individually microencapsulated potassium chloride crystals which disperse upon tablet disintegration. In simulated gastric fluid at 37°C and in the absence of outside agitation, K-DUR begins disintegrating into microencapsulated crystals within seconds and completely disintegrates within one minute. The microencapsulated crystals are formulated to provide an extended release of potassium chloride.
Inactive Ingredients: Crospovidone, Ethylcellulose, Hydroxypropyl Cellulose, Magnesium Stearate, and Microcrystalline Cellulose.

CLINICAL PHARMACOLOGY

The potassium ion is the principal intracellular cation of most body tissues. Potassium ions participate in a number of essential physiological processes including the maintenance of intracellular tonicity, the transmission of nerve impulses, the contraction of cardiac, skeletal and smooth muscle and the maintenance of normal renal function.
The intracellular concentration of potassium is approximately 150 to 160 mEq per liter. The normal adult plasma concentration is 3.5 to 5 mEq per liter. An active ion transport system maintains this gradient across the plasma membrane.
Potassium is a normal dietary constituent and under steady state conditions the amount of potassium absorbed from the gastrointestinal tract is equal to the amount excreted in the urine. The usual dietary intake of potassium is 50 to 100 mEq per day.
Potassium depletion will occur whenever the rate of potassium loss through renal excretion and/or loss from the gastrointestinal tract exceeds the rate of potassium intake. Such depletion usually develops as a consequence of therapy with diuretics, primary or secondary hyperaldosteronism, diabetic ketoacidosis, or inadequate replacement of potassium in patients on prolonged parenteral nutrition. Depletion can develop rapidly with severe diarrhea, especially if associated with vomiting. Potassium depletion due to these causes is usually accompanied by a concomitant loss of chloride and is manifested by hypokalemia and metabolic alkalosis. Potassium depletion may produce weakness, fatigue, disturbances of cardiac rhythm (primarily ectopic beats), prominent U-waves in the electrocardiogram, and in advanced cases, flaccid paralysis and/or impaired ability to concentrate urine.
If potassium depletion associated with metabolic alkalosis cannot be managed by correcting the fundamental cause of the deficiency, e.g., where the patient requires long term diuretic therapy, supplemental potassium in the form of high potassium food or potassium chloride may be able to restore normal potassium levels.
In rare circumstances (e.g., patients with renal tubular acidosis) potassium depletion may be associated with metabolic acidosis and hyperchloremia. In such patients potassium replacement should be accomplished with potassium salts other than the chloride, such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

INDICATIONS AND USAGE

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

1. For the treatment of patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis. If hypokalemia is the result of diuretic therapy, consideration should be given to the use of a lower dose of diuretic, which may be sufficient without leading to hypokalemia.
2. For the prevention of hypokalemia in patients who would be at particular risk if hypokalemia were to develop, e.g., digitalized patients or patients with significant cardiac arrhythmias.

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

CONTRAINDICATIONS

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

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

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

WARNINGS

Hyperkalemia (see **OVERDOSAGE**)--In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics --Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone, triamterene or amiloride) since the simultaneous administration of these agents can produce severe hyperkalemia.

Interaction with Angiotensin Converting Enzyme Inhibitors --Angiotensin converting enzyme (ACE) inhibitors (e.g., captopril, enalapril) will produce some potassium retention by inhibiting aldosterone production. Potassium supplements should be given to patients receiving ACE inhibitors only with close monitoring.

Gastrointestinal Lesions --Solid oral dosage forms of potassium chloride can produce ulcerative and/or stenotic lesions of the gastrointestinal tract. Based on spontaneous adverse reaction reports, enteric coated preparations of potassium chloride are associated with an increased frequency of small bowel lesions (40-50 per 100,000 patient years) compared to 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. K-DUR is a tablet formulated to provide a controlled rate of release of microencapsulated potassium chloride and thus to minimize the possibility of a high local concentration of potassium near the gastrointestinal wall.

Prospective trials have been conducted in normal human volunteers in which the upper gastrointestinal tract was evaluated by endoscopic inspection before and after one week of solid oral potassium chloride therapy. The ability of this model to predict events occurring in usual clinical practice is unknown. Trials which approximated usual clinical practice did not reveal any clear differences between the wax matrix and microencapsulated dosage forms. In contrast, there was a higher incidence of gastric and duodenal lesions in subjects receiving a high dose of a wax matrix 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. K-DUR should be discontinued immediately and the possibility of ulceration, 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 hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.
Information for Patients: Physicians should consider reminding the patient of the following:
To take each dose with meals and with a full glass of water or other liquid.
To take each dose without crushing, chewing, or sucking the tablets. If those patients are having difficulty swallowing whole tablets, they may try one of the following alternate methods of administration:

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

Aqueous suspension of K-DUR tablets that is not taken immediately should be discarded. The use of other liquids for suspending K-DUR tablets is not recommended.
To take this medicine following the frequency and amount prescribed by the physician. This is especially important if the patient is also taking diuretics and/or digitalis preparations.
To check with the physician at once if tarry stools or other evidence of gastrointestional bleeding is noticed.
Laboratory Tests: When blood is drawn for analysis of plasma potassium it is important to recognize that artifactual elevations can occur after improper venipuncture technique or as a result of in-vitro hemolysis of the sample.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity, mutagenicity and fertility studies in animals have not been performed. Potassium is a normal dietary constituent.
Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. 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). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see CONTRAINDICATIONS and WARNINGS).
The most common adverse reactions to oral potassium salts are nausea, vomiting, flatulence, abdominal pain/discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals or reducing the amount taken at one time.

OVERDOSAGE

The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see CONTRAINDICATIONS and WARNINGS). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration (6.5-8.0 mEq/L) and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest. (9-12 mEq/L).
Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of any agents with potassium-sparing properties.
2. Intravenous administration of 300 to 500 mL/hr of 10% dextrose 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 intake of potassium by the average adult is 50 to 100 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store.
Dosage must be adjusted to the individual needs of each patient. The dose for the prevention of hypokalemia is typically in the range of 20 mEq per day. Doses of 40-100 mEq per day or more are used for the treatment of potassium depletion. Dosage should be divided if more than 20 mEq per day is given such that no more than 20 mEq is given in a single dose.
Each K-DUR 20 tablet provides 20 mEq of potassium chloride.
Each K-DUR 10 tablet provides 10 mEq of potassium chloride.
K-DUR tablets should be taken with meals and with a glass of water or other liquid. This product should not be taken on an empty stomach because of its potential for gastric irritation (see WARNINGS).
Patients having difficulty swallowing whole tablets may try one of the following alternate methods of administration:

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

Aqueous suspension of K-DUR tablets that is not taken immediately should be discarded. The use of other liquids for suspending K-DUR tablets is not recommended.

HOW SUPPLIED

K-DUR 20 mEq Extended Release Tablets are available in bottles of 100 (NDC 0085-0787-01); bottles of 500 (NDC 0085-0787-06); bottles of 1000 (NDC 0085-0787-10) and boxes of 100 for unit dose dispensing (NDC 0085-0787-81). K-DUR 20 mEq tablets are white, oblong, imprinted K-DUR 20 and scored for flexibility of dosing. K-DUR 10 mEq Extended Release Tablets are available in bottles of 100 (NDC 0085-0263-01) and boxes of 100 for unit dose dispensing (NDC 0085-0263-81). K-DUR 10 mEq tablets are white, oblong, imprinted K-DUR 10.

STORAGE CONDITIONS

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

CAUTION

Federal law prohibits dispensing without prescription.
Rev. 4/90 14274766

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 3

Potassium Chloride Extended Release Tablets USP

DESCRIPTION

POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS, USP 20 mEq is an immediately dispersing extended release oral dosage form of potassium chloride containing 1500 mg of microencapsulated potassium chloride USP equivalent to 20 mEq of potassium in a tablet.
POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS, USP 15 mEq is an immediately dispersing extended release oral dosage form of potassium chloride containing 1125 mg of microencapsulated potassium chloride USP equivalent to 15 mEq of potassium in a tablet.
POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS, USP 10mEq is an immediately dispersing extended release oral dosage form of potassium chloride containing 750 mg of microencapsulated potassium chloride USP equivalent to 10 mEq of potassium in a tablet.
These formulations are intended to slow the release of potassium so that the likelihood of a high localized concentration of potassium chloride within the gastrointestinal tract is reduced.
POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS 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.
POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS is a tablet formulation (not enteric coated or wax matrix) containing individually microencapsulated potassium chloride crystals which disperse upon tablet disintegration. In simulated gastric fluid at 37°C and in the absence of outside agitation, POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS begin disintegrating into microencapsulated crystals within seconds and completely disintegrates within one minute. The microencapsulated crystals are formulated to provide an extended release of potassium chloride.
Inactive Ingredients: To be listed.

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 CONTROLLED RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For the treatment of patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis. If hypokalemia is the result of diuretic therapy, consideration should be given to the use of a lower dose of diuretic, which may be sufficient without leading to hypokalemia.
2. For the prevention of hypokalemia in patients who would be at particular risk if hypokalemia were to develop, e.g., digitalized patients or patients with significant cardiac arrhythmias.

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

CONTRAINDICATIONS

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

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

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

WARNINGS

Hyperkalemia (see **OVERDOSAGE**)--In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics --Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone, triamterene or amiloride) since the simultaneous administration of these agents can produce severe hyperkalemia.

Interaction with Angiotensin Converting Enzyme Inhibitors --Angiotensin converting enzyme (ACE) inhibitors (e.g., captopril, enalapril) will produce some potassium retention by inhibiting aldosterone production. Potassium supplements should be given to patients receiving ACE inhibitors only with close monitoring.

Gastrointestinal Lesions --Solid oral dosage forms of potassium chloride can produce ulcerative and/or stenotic lesions of the gastrointestinal tract. Based on spontaneous adverse reaction reports, enteric coated preparations of potassium chloride are associated with an increased frequency of small bowel lesions (40-50 per 100,000 patient years) compared to 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. POTASSIUM CHLORIDE EXTENDED RELEASE

TABLETS are formulated to provide a controlled rate of release of microencapsulated potassium chloride and thus to minimize the possibility of a high local concentration of potassium near the gastrointestinal wall.
Prospective trials have been conducted in normal human volunteers in which the upper gastrointestinal tract was evaluated by endoscopic inspection before and after one week of solid oral potassium chloride therapy. The ability of this model to predict events occurring in usual clinical practice is unknown. Trials which approximated usual clinical practice did not reveal any clear differences between the wax matrix and microencapsulated dosage forms. In contrast, there was a higher incidence of gastric and duodenal lesions in subjects receiving a high dose of a wax matrix 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. POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS should be discontinued immediately and the possibility of ulceration, 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 hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.
Information for Patients: Physicians should consider reminding the patient of the following:
To take each dose with meals and with a full glass of water or other liquid.
To take each dose without crushing, chewing, or sucking the tablets. If those patients are having difficulty swallowing whole tablets, they may try one of the following alternate methods of administration:

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

Aqueous suspension of POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS that is not taken immediately should be discarded. The use of other liquids for suspending POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS is not recommended.
To take this medicine following the frequency and amount prescribed by the physician. This is especially important if the patient is also taking diuretics and/or digitalis preparations.
To check with the physician at once if tarry stools or other evidence of gastrointestional bleeding is noticed.
Laboratory Tests: When blood is drawn for analysis of plasma potassium it is important to recognize that artifactual elevations can occur after improper venipuncture technique or as a result of in-vitro hemolysis of the sample.

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

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

Pregnancy Category C: Animal reproduction studies have not been conducted with POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS. 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). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see CONTRAINDICATIONS and WARNINGS).
The most common adverse reactions to oral potassium salts are nausea, vomiting, flatulence, abdominal pain/discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals or reducing the amount taken at one time.

OVERDOSAGE

The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see CONTRAINDICATIONS and WARNINGS). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration (6.5-8.0 mEq/L) and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest. (9-12 mEq/L).
Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of any agents with potassium-sparing properties.
2. Intravenous administration of 300 to 500 mL/hr of 10% dextrose 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 intake of potassium by the average adult is 50 to 100 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store.
Dosage must be adjusted to the individual needs of each patient. The dose for the prevention of hypokalemia is typically in the range of 20 mEq per day. Doses of 40-100 mEq per day or more are used for the treatment of potassium depletion. Dosage should be divided if more than 20 mEq per day is given such that no more than 20 mEq is given in a single dose.
Each POTASSIUM CHLORIDE EXTENDED RELEASE TABLET USP 20 mEq provides 20 mEq of potassium chloride.
Each POTASSIUM CHLORIDE EXTENDED RELEASE TABLET USP 15 mEq provides 15 mEq of potassium chloride.
Each POTASSIUM CHLORIDE EXTENDED RELEASE TABLET USP 10 mEq provides 10 mEq of potassium chloride.

POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS USP should be taken with meals and with a glass of water or other liquid. This product should not be taken on an empty stomach because of its potential for gastric irritation (see **WARNINGS**).
Patients having difficulty swallowing whole tablets may try one of the following alternate methods of administration:

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

Aqueous suspension of POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS that is not taken immediately should be discarded. The use of other liquids for suspending POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS is not recommended.

HOW SUPPLIED

POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS 20 mEq are available in bottles of 100; bottles of 500; bottles of 1000, and boxes of 100 for unit dose dispensing. POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS 20 mEq are white, oblong, imprinted XXX and scored for flexibility of dosing.
POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS 15 mEq are available in bottles of 100, bottles of 500; bottles of 1000, and boxes of 100 for unit dose dispensing. POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS 15 mEq are white, oblong, imprinted XXX and scored for flexibility of dosing.
POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS 10 mEq are available in bottles of 100 and boxes of 100 for unit dose dispensing. POTASSIUM CHLORIDE EXTENDED RELEASE TABLETS 10 mEq are white, oblong, imprinted XXX.

STORAGE CONDITIONS

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

Rx only.

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