DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-439/S-022

Schering Corporation
Attention: Deborah Urquhart, Ph.D.
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Urquhart:

Please refer to your supplemental new drug application dated August 28, 2001, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for K-Dur® (potassium chloride) extended-release 10 and 20 mEq Tablets.

We also refer to your submission of September 29, 2006 and February 1, 2008. Your submission of February 1, 2008 constituted a complete response to our October 29, 2002 action letter.

This supplemental new drug application provides for the following revisions to the **WARNINGS**/**Gastrointestinal Lesion** subsection, **PRECAUTIONS**/**Information for Patients** and **Geriatric** subsections, and **OVERDOSAGE** section of the package insert.

1. Under **WARNINGS**, the following subsection has been deleted:

   Interaction with Non-Steroidal Anti-Inflammatory Drugs (NSAIDS): NSAIDS may produce potassium retention by reducing renal synthesis of prostaglandin E and impairing the renin-angiotensin system. Potassium supplementation should be extremely cautious in elderly patients receiving NSAIDS and diuretics, with close monitoring of plasma potassium.

2. Under **WARNINGS**/**Gastrointestinal Lesion**, the phrase "particularly in the elderly who may have reduced esophageal and gastrointestinal motility" has been omitted and replaced with:

   Solid oral dosage forms of potassium chloride can produce ulcerative and/or stenotic lesions of the gastrointestinal tract.

3. Under **PRECAUTIONS**/**Information for Patients**, the phrase "Physicians should consider reminding the patient, particularly an elderly patient, of the following" has been revised to read as follows:

   Physicians should consider reminding the patient of the following:

4. Under **PRECAUTIONS**, the following proposed language has been deleted:

   Geriatric Use: Clinical studies of K-DUR Tablets and spontaneous safety surveillance data did not provide sufficient information to determine whether subjects 65 years and older respond

differently from younger subjects. Additional clinical data from published literature indicate that the elderly may be at greater risk for esophageal irritation and stricture because of age-related decline in amplitude of esophageal contractions slowing passage of solid dosage forms. The use of potassium chloride in the elderly has been associated with hyposalivation, which may affect oral health. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range. Serum potassium should be closely monitored, reflecting the greater frequency of decreased renal or cardiac function, and of concomitant disease or other drug therapy, which may lead to hyperkalemia.

The following text has been inserted:

PRECAUTIONS/Geriatric Use:
Clinical studies of K-DUR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection; and it may be useful to monitor renal function.

5. Under the **OVERDOSAGE** section the following changes have been noted:

   - The sentence "Consultation with a poison center should be considered." has been deleted.

   - The deletion of the following text:

     The extended release feature means that absorption and toxic effects may be delayed for hours. Consider standard measures to remove any unabsorbed drug. Due to the extended release feature of K-DUR Tablets, whole bowel irrigation with isosmotic polyethylene glycol solution may be useful to promote elimination of the tablets.

     A serious electrocardiogram change or a true potassium level greater than 7.5 mEq/L mandate immediate therapy usually consisting of administration of one or more of the following: β-receptor agonist, calcium chloride, sodium bicarbonate or glucose and insulin. Typical doses include albuterol 5-10 mg by nebulizer, calcium chloride 5 ml of a 10% solution every 5 minutes until the patient improves, sodium bicarbonate 1-2 mEq/kg or more by intravenous push or the administration of D50 (25 g) followed by 10 units of regular insulin intravenously. In severe cases, these temporizing measures may be followed by dialysis, which will decrease the serum potassium level quickly.

     Sodium polystyrene sulfonate (Kayexalate) increases gastrointestinal excretion of potassium. Its onset of action is 2-12 hours and is not of use for emergency therapy. Precise indications for its use have not been developed.

   - The above text has been replaced with the following:

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. Patients should be closely monitored for arrythmias and electrolyte changes.

2. Elimination of foods and medications containing potassium and of any agents with potassium-sparing properties such as potassium-sparing diuretics, ARBS, ACE inhibitors, NSAIDS, certain nutritional supplements and many others.

3. Intravenous calcium gluconate if the patient is at no risk or low risk of developing digitalis toxicity.
4. Intravenous administration of 300 to 500 mL/hr of 10% dextrose solution containing 10-20 units of crystalline insulin per 1,000 mL.
5. Correction of acidosis, if present, with intravenous sodium bicarbonate.
6. 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.

- The addition of the following text at the end of the **OVERDOSAGE** section:

  The extended release feature means that absorption and toxic effects may be delayed for hours. Consider standard measures to remove any unabsorbed drug.

6. In the second sentence under **HOW SUPPLIED**, the 20 mEq tablet description was changed from:

   K-DUR 20 mEq tablets are white, oblong, imprinted “K-DUR 20” and scored for flexibility of dosing.

   To:

   Potassium Chloride Extended Release Tablets, USP 20 mEq are white, to off-white capsule-shaped tablets imprinted “W-1714”and scored on the other side.

7. In the second paragraph under the **HOW SUPPLIED** section, the 10mEq tablet description was changed from:

   K-DUR 10 mEq tablets are white, oblong, imprinted “K-DUR 10”.

   To:

Potassium Chloride Extended Release Tablets, USP 10 mEq are white, to off-white capsule-shaped tablets imprinted “W-1715” on one side and plain on the other side.

8. Under **HOW SUPPLIED/Storage Conditions**, the second sentence has been changed from:

   Store at controlled room temperature 15º - 30 ºC (59 º - 86 ºF).

   To:

   Store at 25 ºC (77 ºF); excursions permitted to 15º - 30ºC (59º - 89ºF) [see USP Controlled Room Temperature].

9. The copyright and revised dates have been updated under the **HOW SUPPLIED** section.

10. The product name has been revised throughout the label as Potassium Chloride Extended Release Tablets 10 mEq and 20mEq. The product will no longer be marketed under the name, K-Dur Extended Release Tablets 10 mEq and 20mEq.

We have completed our review of this application and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. The final printed labeling (FPL) must be identical to the electronic draft labeling package insert submitted on February 1, 2008.

Within 14 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the submitted electronic draft labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission “SPL for approved supplement NDA 19-439/S-022.” Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Russell Fortney
Regulatory Project Manager
(301) 796-1068

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Stockbridge

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