CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206814Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	12-11-2014
From	Kasturi Srinivasachar, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	206814
Applicant	Pharma-Med, Inc.
Date of Submission	Feb 27, 2014
PDUFA Goal Date	Dec 27, 2014
Proprietary Name / Established (USAN) names	Potassium Chloride Oral Solution
Dosage forms / Strength	Oral solution, 20 mEq/15 mL and 40 mEq/15 mL
Proposed Indication(s)	1. Treatment of patients with hypokalemia, with or without metabolic alkalosis; (b) (4) . 2. (b) (4)
Recommended:	**Approval with PMC**

This secondary review is based on the primary reviews of:

- **CMC (Mohan Sapru), 10-27-2014 and 12-09-2014**
- **Quality Biopharmaceutics (Sandra (Suarez), 10-16-2014**
- **Microbiology (Denise Miller), 10-24-2014**
- **Clinical Phamacology (Sreedharan Sabarinath), 10-09-2014**
- **DMEPA (Janine Stewart), 10-24-2014 and 11-19-2014**

1. Introduction

This is a 505(b)(2) NDA for potassium chloride oral solution, 20 mEq/15mL and 40 mEq/15 mL. Although potassium chloride has been previously approved in other dosage forms – injection and extended release tablets or capsules, the oral solution is a new dosage form which has been marketed but never approved. This filing is based upon the reference listed drug (RLD), K-DUR, potassium chloride extended release tablets, NDA 19439 approved in 1986.

2. Background

The current application relies on the Agency's determination of safety and efficacy for the RLD and supporting relevant published literature and consequently there are no pre-clinical or clinical sections. The regulatory decision will be primarily based on the recommendations in the CMC, Quality Microbiology, Biopharmaceutics, Clinical Pharmacology and the Division of Medication Error Prevention and Analysis (DMEPA) reviews of this application.

3. CMC

The reviewer recommends approval from a CMC perspective.
Drug Substance: The Applicant referenced DMF (b) (4) for complete information on the drug substance, potassium chloride. The reviewer states that the original DMF has been reviewed and found to be adequate.
Drug Product: The product will be marketed in two strengths, 20 mEq/15 mL and 40 mEq/15mL. The excipients in the formulation include glycerin, propylene glycol, methylparaben, propylparaben, sucralose, citric acid, natural and artificial orange flavor, FD&C Yellow #6 and purified water.. The drug product is packaged in (b) (4) mL white HDPE bottles with (b) (4). The specification has been revised to include a test for pH with limits between 3.0 and 6.5 based on the reviewer's recommendation. An expiration dating period of 24 months has been requested by the Applicant and is granted for both strengths based on the stability data provided.
Facilities review/inspection: The drug substance and drug product manufacturing sites were submitted for inspection and the current overall Office of Compliance recommendation is "Acceptable".

4. Biopharmaceutics

The reviewer recommended approval from the Biopharmaceutics perspective. It was concluded that the provided formulation and PK information support the bridging of the proposed product and the products used in the published pharmacokinetic literature and therefore a biowaiver for the proposed product could be granted.

5. Product Quality Microbiology

The reviewer recommended approval from a quality microbiology perspective but requested that the antimicrobial preservative effectiveness testing be also performed, post approval, on the second formulation. The Applicant has committed to conduct this testing.

6. Clinical Pharmacology

The reviewer recommended approval based on the results of studies that showed that the bioavailability of potassium chloride, as measured by the cumulative urinary excretion of K^+ over a 24 hour post dose period, is comparable across the liquid formulation and various types of modified release products. It was also concluded from these studies that the overall gastrointestinal tolerance to potassium chloride can be considered to be at least similar for the liquid and modified release products.

7. Non-Clinical Pharmacology/Toxicology

N/A

8. Clinical/Statistical- Efficacy

N/A

9. Safety

N/A

10. Advisory Committee Meeting

N/A

11. Pediatrics

PeRC review pending.

12. Other Relevant Regulatory Issues

N/A

13. Labeling

The DMEPA reviewer recommended revisions to the proposed Prescribing Information (PI) and container labels and concluded that both can be improved to increase clarity, readability, and the prominence of important information to promote safe use of this product. The Applicant submitted revised container labels which the reviewer concluded were adequate from the medication error perspective. The PI revisions recommended will be evaluated by the Division along with other changes contemplated for the Indications which, although identical to other approved potassium chloride products, are considered to be outdated. At this stage, the final labeling is still pending but this is not expected to impact Approvability of the NDA.

14. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

All primary reviews of this application recommended approval and I concur with the reviewers. Potassium Chloride Oral Solution, 20mEq/15mL and 40mEq/15mL may be approved with an expiration dating period of 24 months when stored at room temperature. The Approval letter should include appropriate language for the Post Marketing Commitment agreed to by the Applicant for antimicrobial preservative effectiveness testing of the 40mEq/15mL formulation.

- Risk Benefit Assessment

This is a 505(b)(2) application for potassium chloride oral solution which relies on the safety and efficacy established for the marketed products, potassium chloride extended release tablets, 20 mEq. Consequently, the risk/benefit of this product is expected to be the same.

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/s/

KASTURI SRINIVASACHAR
12/12/2014