CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209478Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	August 3, 2017
From	Aliza Thompson
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 209478
Applicant	CMP Pharma, Inc
Date of Submission	October 4, 2016
PDUFA Goal Date	August 4, 2017
Proprietary Name / Established (USAN) names	CaroSpir / Spironolactone
Dosage forms / Strength	Oral Suspension / 25 mg/5 mL
Proposed Indication(s)	(b) (4)
Recommended:	*Approval for the indications delineated in Section 12 of this memo*

Material Reviewed/Consulted	
Quality Assessment (6/30/17)	Haripada Sarker, Thomas Wong, Peter Guierri, Jason God, Cassandra Abellard, Kaushal Dave, Dahlia Walters, Quallyna Porte, Wendy Wilson-Lee (Application Technical Lead)
Pharmacology-Toxicology Review (5/4/17)	Thomas Papoian
Clinical Pharmacology Review (6/5/17)	Xiaolei Pan, Martina Sahre, Sudharshan Hariharan
Clinical Review (7/28/17)	Melanie Blank
Division of Medication Error Prevention and Analysis Review (12/12 and 12/30/16)	Ashleigh Lowery, Chi-Ming (Alice) Tu
Division of Epidemiology II Review (6/22/17)	Marie Bradley, Margie Goulding, Lockwood Taylor
Maternal Health Review (7/19/17)	Christos Mastroyannis, Tamara Johnson, Lynne Yao
Division of New Drug Bioequivalence Evaluation Reviews (2/13, 6/13 and 7/7/17)	Shila Nkah (2/13/17) Li-Hong Yeh, Amanda Lewin, Arindam Dasgupta (6/13/17) Srinivas Chennamaneni, Charles Bonapace (7/7/17)
Office of Prescription Drug Promotion Review (7/25/17)	Zarna Patel, James Dvorsky

1. Introduction

On October 4, 2016, CMP Pharma, Inc. submitted a New Drug Application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for CaroSpir (spironolactone) oral suspension for the following proposed indications:

- Severe Heart Failure (NYHA Class III – IV): to increase survival, and to reduce the need for hospitalization for heart failure (b) (4)
- Essential Hypertension

(b) (4)

The application relies on the Agency's previous finding of safety and effectiveness for the reference listed drug, Aldactone® (NDA 012151).

2. Background

Spironolactone is an antagonist of aldosterone, acting primarily through competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule. The reference listed drug, Aldactone tablets, (b) (4) . At present, there is no FDA-approved ready-made oral suspension of spironolactone.

3. CMC

OPQ recommends approval of the application from a quality perspective. There are no unresolved issues at this time and no phase 4 commitments are needed.

Drug substance: Spironolactone is a synthetic, white or cream-colored powder that is practically insoluble in water, soluble in 96% ethanol, and slightly soluble in ether. There are different polymorphic forms; (b) (4)

Drug Product: The drug product is a white to off-white, opaque, banana-flavored, immediate release oral suspension. Each 5 mL of the oral suspension contains 25 mg of spironolactone. The product is supplied in 4-ounce (118 mL) and 16-ounce (473 mL) bottles. Inactive ingredients include: xanthan gum, simethicone emulsion, sorbic acid, potassium sorbate, sodium saccharin, citric acid anhydrous, sodium citrate dihydrate, Magnasweet 110, glycerin, banana flavor (b) (4), and purified water.

Expiration Date and Storage Conditions: According to the Quality Assessment, the available stability data support the proposed expiry dating of 18 months for the 4-ounce bottle and 24 months for the 16-ounce bottle. The oral suspension is stored at 20°C to 25°C (68°F to 77°F), with excursions permitted to 15 °C to 30°C (59°F to 86°F).

Facilities review/inspection: The manufacturing facilities were found to be acceptable based on profile or district file review.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted as part of the application. The label for Aldactone states that spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (b) (4). Dr. Tom Papoian reviewed the data in the label and published literature to determine whether, in light of current labeling practices, such a warning is warranted.

As discussed in Dr. Papoian's review, the Aldactone label includes information on tumor findings in rats treated with spironolactone and also rats treated with potassium canrenoate, a structurally related aldosterone receptor antagonist, "apparently based on the fact that both drugs share a common pharmacologically active metabolite canrenone." Although both drugs produced some similar proliferative changes and tumors in rats, as shown below, differences were also observed, such as the development of myelocytic leukemia in rats treated with potassium canrenoate but not spironolactone.

> - Spironolactone: liver, thyroid and Leydig cell tumors, and benign uterine endometrial stromal polyps in females. (Data from Lumb, 1978, did not find increased liver tumors.)
>
> - Potassium canrenoate: hepatic, thyroid, testicular, and mammary tumors; and myelocytic leukemia.

Source: Dr. Papaion's Review, page 10

In his review, Dr. Papoian notes that published metabolism studies with potassium canrenoate showed production of mutagenic epoxide metabolites that were not seen with spironolactone, raising questions about the relevance of the findings in animals treated with potassium canrenoate for spironolactone. Dr. Papoian also indicates that the rat tumor findings seen with spironolactone

are common tumors in long-term rodent studies and that the NOAEL dose for rat tumors with spironolactone was somewhat higher than the human recommended daily dose of 200 mg/day (5X, when based on body surface area). Given these considerations, Dr. Papoian recommends (b) (4) making revisions to the Carcinogenicity Section of the label.

Dr. Papoian also recommended that "the known risk of gynecomastia in human males and possible risk of such endocrine effects in females for development of breast cancer justifies continued inclusion of rat tumor findings in the spironolactone label, (b) (4) …"

In light of Dr. Papoian's recommendations, the Division of Epidemiology (DEP) II was asked to conduct a review of published epidemiologic studies examining the association between spironolactone and cancer risk. As discussed in their review, DEP II agrees with Dr. Papoian's recommendation to (b) (4) citing the following findings:

> *"Across the five studies examining spironolactone only (not in combination with other agents) there was no indication that spironolactone increased the risk of any of the cancers examined. Indeed one of the largest studies, conducted in the UK Clinical Practice Research Database (CPRD, examining 36 cancers (1), suggested spironolactone might actually be associated with a reduced risk of prostate cancer. Among the three case control studies examining spironolactone grouped with diuretics in a similar class there were some suggestions of an increased risk of breast cancer (2, 3) and squamous cell carcinoma (SCC) (4) although limitations including recall bias (2, 3) and missing information on important lifestyle factors reduces the credibility and validity of these findings. The increased cancer risks found may also be attributable to the other drugs and not just spironolactone.*
>
> *Overall there is little evidence that spironolactone is associated with an increased risk of any cancer …"*

5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology (OCP) recommends approval of the application from a clinical pharmacology perspective. In support of the application, the applicant submitted the results of two relative bioavailability studies-- one comparing the 100-mg suspension to 100-mg Aldactone tablets (Study 064-15) and the other comparing the 25-mg suspension to 25-mg Aldactone tablets (Study 063-15), and a food effect study (Study 084-15).

As discussed in the OCP review, the relative bioavailability studies indicate that the bioavailability of spironolactone suspension is 15% and 37% higher than the reference listed drug (RLD) at the 25-mg and 100-mg tablet strengths, respectively. The food effect study indicates that food has a significant impact on the bioavailability of spironolactone suspension, as is also true for the RLD. After administration of 100 mg of the spironolactone suspension with a high-fat and high-calorie meal, the Cmax decreased by 22% and AUC increased by 90% and Tmax was delayed from 0.9 ± 0.3 hours to 2.4 ± 1.0 hours in the fasted and fed state, respectively.

Given the findings in the relative bioavailability studies (i.e., the different relative bioavailability estimates obtained in the comparison against the 25- and 100 mg tablet strengths) and the lack of information on dose proportionality for Aldactone tablets, the review team could not exclude the

possibility that doses of the suspension greater than 100 mg could result in spironolactone concentrations higher than expected relative to the RLD. In the absence of information on dose proportionality across the clinically relevant dose range (25 to (b) (4) mg) and relative bioavailability for all dose strengths, OCP recommends (b) (4) The review team is also recommending a 25% dose reduction to adjust for the higher exposure to spironolactone from the suspension between the dose range of 25 and 100 mg.[1] These recommendations were conveyed to the applicant during the course of the review, and agreement has been reached with the applicant on revisions to the label to address these issues.

Facility Inspections: The Office of Study Integrity and Surveillance (OSIS) conducted a surveillance inspection of the analytical portion of in vivo bioequivalence studies 064-15 conducted by (b) (4); other studies not yet submitted to the FDA were also audited for surveillance purposes. No significant deficiencies were observed; hence, OSIS recommends accepting the data for review.

OSIS also arranged an inspection of Studies 063-15 and 064-15, conducted at ClinSync Clinical Research Pvt. Ltd., Hyderabad, Telangana, India. Form FDA 483 was issued; however, the final inspection classification was Voluntary Action Indicated (VAI). According to the OSIS review, although objectionable findings were observed during the inspection, the findings did not impact the reliability of the data from the audited studies. Hence, OSIS recommends accepting the data for review. The clinical pharmacology review team has also reviewed the findings and agrees that they do not raise concerns about the reliability of the clinical study data.

6. Clinical/Statistical- Efficacy

As discussed under Clinical Pharmacology, two relative bioavailability studies provide the bridge to the reference listed drug, Aldactone.

7. Safety

The application relies on the Agency's previous determination of safety for the reference listed product. As discussed in Dr. Blank's review, the applicant also conducted a broad search of the published literature to address the postmarketing safety experience with the product, and Dr. Ana Szarfman performed an analysis of spontaneous adverse event reports submitted to FAERS. For the most part, these searches confirmed the known/labeled risks of spironolactone and did not raise new safety concerns. Specific findings with implications for labeling are discussed under "Labeling".

[1] The review team acknowledges that there is no labelled dose reduction for the RLD for an increase in exposure of almost 100% with food; their recommendation is based on concern about the combined effect of an increase in exposure due to food and the higher bioavailability with the suspension.

8. Advisory Committee Meeting

The application does not raise significant issues regarding the safety or effectiveness of the drug; hence, no Advisory Committee Meeting was held.

9. Pediatrics

Because it is a new dosage form, the product triggers PREA. As agreed with the PeRC, pediatric studies for the treatment of hypertension and severe heart failure will be waived, and deferred studies will be conducted for the treatment of edematous conditions.[2] Pediatric studies for the treatment of hypertension will be waived based on safety considerations. Hypertension requires chronic treatment and there are safety concerns in pediatric patients related to spironolactone's antiandrogenic, progestogenic, and estrogenic properties, particularly given existing therapies for hypertension that do not possess such significant risks. Pediatric studies for the treatment of heart failure will be waived because the causes and mechanisms of heart failure are different in children and adults. Heart failure in children is most commonly caused by congenital heart malformations and cardiomyopathy whereas the primary etiology of adult heart failure is ischemic heart disease due to atherosclerotic coronary artery disease. The form of heart failure seen in adults is rare in children; hence conducting a trial is highly impractical.

10. Other Relevant Regulatory Issues

None.

11. Labeling

The approved label for the reference listed drug is not in the Physician Labeling Rule (PLR) format and substantial edits were made to convert the CaroSpir (spironolactone) oral suspension label to PLR format and update the label to reflect the current state of knowledge. The label was also revised to address the Pregnancy and Lactation Labeling Rule (PLLR). I thank the members of the review team and, in particular, Michael Monteleone, Associate Director for Labeling, for their work on the label.

Key aspects of labeling/conclusions include the following:

- *Dosage and Administration:* Based on the findings in the submitted relative bioavailability studies, the Dosage and Administration of the CaroSpir label will state that CaroSpir is not therapeutically equivalent to Aldactone, that doses of the suspension greater than 100 mg may result in spironolactone concentrations higher than expected and that another formulation should be used in patients requiring a dose greater than 100 mg. Doses in this section will also reflect a 25% dose reduction relative to Aldactone.

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2 [redacted] (b) (4)

- (b) (4)

- *Drug Interaction:* The label for Aldactone states that spironolactone has been shown to increase the half-life of digoxin and that it may be necessary to reduce the digoxin dose when spironolactone is administered. As discussed in Dr. Blank's review, at this time, it is unclear whether a PK interaction exists since the reported effect on digoxin PK may reflect assay interference (i.e., an effect of spironolactone and its metabolites on the accuracy of the radioimmunoassay historically used to measure digoxin levels). Pending completion of a postmarketing requirement to address the potential for a drug interaction between digoxin and spironolactone, the label will state that spironolactone and its metabolites interfere with radioimmunoassays for digoxin and increase the apparent exposure to digoxin and that it is unknown to what extent, if any, spironolactone may increase actual digoxin exposure; the label will also advise use of a digoxin assay that does not interact with spironolactone.

- *Pregnancy and Lactation Labeling Rule:* The Division of Pediatric and Maternal Health (DPMH) has provided input on the pregnancy and lactation subsections of the label. In her clinical review, Dr. Blank recommends revising the text proposed by DMPH to (1) include information about a male fetus with ambiguous external genitalia who was exposed to spironolactone until week 5 in utero and (2) remove the following statement: "Limited available data from published case reports and case series did not demonstrate an association of major malformations or other adverse pregnancy outcomes with spironolactone." My sense is that the current text in labeling, which reads as follows, is sufficient to convey the risk to the fetus and is a reasonable representation of the data, as described in the DPMH review.

  "Based on mechanism of action and findings in animal studies, spironolactone may affect sex differentiation of the male during embryogenesis…. Rat embryofetal studies report feminization of male fetuses and endocrine dysfunction in females exposed to spironolactone in utero. Limited available data from published case reports and case series did not demonstrate an association of major malformations or other adverse pregnancy outcomes with spironolactone…. Because of the potential risk to the male fetus due to anti-androgenic properties of spironolactone and animal data, avoid spironolactone in pregnant women or advise a pregnant woman of the potential risk to a male fetus."

Reviewer's comment: Some of the aforementioned issues have bearing on labeling for the reference listed drug, Aldactone, and digoxin. Mary Ross Southworth, Deputy Director for Safety, and Mike Monteleone are aware of these issues and will follow up as needed.

Proprietary name: According to DMEPA, the proposed proprietary name, CaroSpir, is acceptable.

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
Approval for the following indications:

- Heart Failure: CaroSpir is indicated for treatment of NYHA Class III-IV heart failure and reduced ejection fraction to increase survival, manage edema, and to reduce the need for hospitalization for heart failure.
- Hypertension: CaroSpir is indicated as add-on therapy for the treatment of hypertension, to lower blood pressure in adult patients who are not adequately controlled on other agents.
- Edema caused by Cirrhosis: CaroSpir is indicated for the management of edema in adult cirrhotic patients when edema is not responsive to fluid and sodium restriction.

(b) (4)

Risk Benefit Assessment
The application relies on the Agency's previous finding of safety and effectiveness for the reference listed drug, Aldactone tablets. Studies conducted in healthy subjects provide the needed bridge to the reference listed drug and agreement has been reached on labeling. From a CMC, non-clinical pharmacology-toxicology, clinical pharmacology and clinical safety and efficacy perspective, the application can be approved for the indications listed above.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
None.

Recommendation for other Postmarketing Requirements (PMR) and Commitments
The applicant has agreed to the following deferred pediatric studies under PREA:

- a single-dose pharmacokinetic study in pediatric patients 0 to < 17 years of age with edematous condition.
- a multiple- dose pharmacokinetic, pharmacodynamic, and safety study in pediatric patients 0 to < 17 years of age with edematous conditions

The applicant has also agreed to the following FDAAA PMR for safety:

- a clinical drug-drug interaction study to evaluate a potential interaction between digoxin and spironolactone using a validated analytical method to quantify plasma digoxin levels

Recommended Comments to Applicant
None at this time.

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/s/

ALIZA M THOMPSON
08/03/2017

NORMAN L STOCKBRIDGE
08/03/2017
I concur in all respects with Dr. Thompson's review and conclusions.