

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209478Orig1s000

OTHER REVIEW(S)

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA/BLA/Supplement # NDA 209478

PMR/PMC Set (####-#) 3256-2

Product Name: CaroSpir[®] (Spironolactone Oral Suspension, 25 mg/5 mL) Oral Suspension

Applicant Name: CMP Pharma, Inc

ODE/Division: Division of Cardiovascular and Renal Products

SECTION B: PMR/PMC Information

1. PMR/PMC Description

A multiple- dose pharmacokinetic, pharmacodynamics, and safety study in pediatric patients 0 to < 17 years of age with edematous conditions.

1) PMR/PMC Schedule Milestones^{2, 3}

Final Protocol Submission: 01 /2022

Study/Trial Completion: 01 /2026

Final Report Submission: 01 /2027

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² Final protocol, study/trial completion, and final report submissions are required milestones. Draft protocol submissions and interim milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

This study is a multiple-dose PK-PD study in patients with edematous conditions. The objectives of this study are (1) to determine the exposure-response relationship for spironolactone oral solution in the target population following multiple doses and (2) to identify a safe and effective treatment regimen.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☒ PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to* approval.]

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal of serious risk related to the use of the drug
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

- e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either “Yes” or “No” and provide the appropriate responses.]

☐ Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

☐ No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

- f. ☐ Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study
- ☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☒ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- ☐ Yes
- ☒ No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- ☐ For *non-PREA* pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. **The PMR/PMC is clear, feasible, and appropriate⁹ because:** *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ **(If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.
- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☐ **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.**

Insert electronic signature (usually the Deputy Director for Safety)

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

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/s/

Lori A WACHTER
08/04/2017

MARY R SOUTHWORTH
08/04/2017

505(b)(2) ASSESSMENT

Application Information		
NDA # 209478	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: CaroSpir® Established/Proper Name: Spironolactone Dosage Form: Oral Suspension Strengths: 25 mg/5 mL		
Applicant: CMP Pharma Inc.		
Date of Receipt: October 4, 2016		
PDUFA Goal Date: August 4, 2017		Action Goal Date (if different):
RPM: Brian Proctor		
Proposed Indication(s): (b) (4)		
(b) (4) essential hypertension; (b) (4) severe heart failure		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 12151 for Aldactone oral tablets	FDA's previous finding of safety and effectiveness (clinical and nonclinical)
Published literature	PLLR sections

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The applicant conducted two relative bioavailability studies, comparing spironolactone oral suspension to the listed drug (LD) Aldactone® (NDA 12,151). One of these studies was conducted comparing a 25 mg Aldactone® tablet to spironolactone oral suspension, and another comparing 100 mg tablets to spironolactone oral suspension. In addition, a food-effect study was conducted on spironolactone oral suspension at 100 mg. The results show that the bioavailability of spironolactone suspension is 15% and 37% higher than the LD at 25 mg and 100 mg tablet strengths, respectively. To address the higher exposures, of the Agency proposed a dose adjustment between 25 mg and 100 mg, to which the applicant agreed. Due to lack of information about proportional similarity of dose strengths and dose proportionality in the label or the published literature, doses of spironolactone suspension will be limited to between 25 and 100 mg until the applicant can generate information to show that the 25% dose adjustment can adjust for increased exposures at higher doses as well. Administration of 100 mg spironolactone suspension with a high-fat and high-calorie meal caused an AUC increase by 90%, similar to the extent described in the Aldactone® label.

Division of Pediatric and Maternal Health (DPMH) provided input for labeling of the pregnancy and lactation subsections of CaroSpir (Spironolactone) Oral Suspension labeling and to ensure compliance with the Pregnancy and Lactation Labeling Rule requirements. A review of published literature was conducted to evaluate the use of spironolactone in pregnant women and no reports were found to establish a link between spironolactone and human congenital anomalies. There is reliance on a case report discussed in published literature related to the presence of the active metabolite of spironolactone, canrenone, in breast milk. The information available in the scientific literature is scientifically relevant to the proposed product because the active ingredient, spironolactone, is the same as that in the proposed drug product. See DPMH's review for additional information.

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

If “NO,” proceed to question #5.

If “YES,” list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Aldactone oral tablets	NDA 12151	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES ☐ NO ☒

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

If “**YES**”, please list which drug(s) and answer question d) i. below.

If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application provides for a change in dosage form, from oral tablets to liquid suspension.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

If “**NO**” to (a) proceed to question #11.
If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

If this application relies only on non product-specific published literature, answer “N/A”

If “YES” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “NO” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES ☒ NO ☐

If “NO”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

If this application relies only on non product-specific published literature, answer “N/A”

If “YES” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “NO” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): Yes

PATENT CERTIFICATION/STATEMENTS
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- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

- ☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- ☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- ☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- ☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- ☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- ☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

BRIAN L PROCTOR
08/03/2017

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA/BLA/Supplement # **NDA 209478**

PMR/PMC Set (####-#) **3256-1**

Product Name: CaroSpir[®] (Spironolactone Oral Suspension, 25 mg/5 mL) Oral Suspension

Applicant Name: **CMP Pharma, Inc**

ODE/Division: **Division of Cardiovascular and Renal Products**

SECTION B: PMR/PMC Information

1. PMR/PMC Description

A single-dose pharmacokinetic study in pediatric patients 0 to < 17 years of age with edematous conditions.

1) PMR/PMC Schedule Milestones^{2, 3}

Final Protocol Submission: **08 /2018**

Study/Trial Completion: **08 /2020**

Final Report Submission: **01 /2021**

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² Final protocol, study/trial completion, and final report submissions are required milestones. Draft protocol submissions and interim milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

The objective of this study is to determine the relevant PK parameters of Spironolactone Oral Suspension in pediatric patients with edematous conditions. The results of this study would be used to derive the doses that will be evaluated in an efficacy and safety trial.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☒ PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to approval*.]

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal of serious risk related to the use of the drug
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

- e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either “Yes” or “No” and provide the appropriate responses.]

☐ Yes, a study is sufficient [Explain your answer in the textbox and then go to Q.5]

[Explain why a study is sufficient]

☐ No, a study is not sufficient [Select all explanations that apply then go to Q.4.f]

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

- f. ☐ Because a study is not sufficient, a clinical trial is required. [Go to Q.5]

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study
- ☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☐ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☒ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- ☐ Yes
- ☒ No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. **The PMR/PMC is clear, feasible, and appropriate⁹ because:** *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ **(If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.
- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.**

Insert electronic signature (usually the Deputy Director for Safety)

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

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

/s/

Lori A WACHTER
08/02/2017

MARY R SOUTHWORTH
08/02/2017

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do **not** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA/BLA/Supplement # 209478

PMR/PMC Set (####-#) 3256-3

Product Name: CaroSpir[®] (Spironolactone Oral Suspension, 25 mg/5 mL) Oral Suspension

Applicant Name: CMP Pharma, Inc. [REDACTED]

ODE/Division: ODE I/ Division of Cardiovascular and Renal Products

SECTION B: PMR/PMC Information

1. PMR/PMC Description

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

2. PMR/PMC Schedule Milestones^{2, 3}

Final Protocol Submission: 03/2018

Study/Trial Completion: 09/2018

Final Report Submission: 03/2019

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² Final protocol, study/trial completion, and final report submissions are required milestones. Draft protocol submissions and interim milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

- Digoxin and spironolactone are often coprescribed and it has long been thought that spironolactone increases digoxin levels. However, the study that reported this interaction used a radioimmuno assay (RIA) to measure serum digoxin levels. This study was done prior to other studies that showed that spironolactone and metabolites interferes with the digoxin RIA. It is not clear if when using more modern digoxin assays whether spironolactone would increase digoxin levels. As it now stands, it is not clear if a clinician should lower the digoxin dose if digoxin levels become elevated while the patient is also on spironolactone (i.e., is it a real drug interaction or just a false positive?)
- The PMR study would clarify if spironolactone increases digoxin levels using more modern digoxin assays and inform labeling.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

(Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- ☐ PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☒ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected “other reason,” expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to approval*.]

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- ☐ Assess a known serious risk related to the use of the drug
- ☒ Assess a signal of serious risk related to the use of the drug
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel’s postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☒ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either “Yes” or “No” and provide the appropriate responses.]

☐ Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

☐ No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

f. ☐ Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- ☐ Drug interaction or bioavailability studies (nonclinical only)
- ☐ Epidemiologic (observational) study related to safe drug use
- ☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Immunogenicity study (nonclinical)
- ☐ Meta-analysis or pooled analysis of previous observational studies
- ☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- ☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- ☐ Pharmacogenetic or pharmacogenomic study
- ☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- ☐ Quality CMC study (e.g., manufacturing, studies on impurities)
- ☐ Quality stability study
- ☐ Registry-based observational study
- ☐ Other (describe) _____

TYPE OF CLINICAL TRIAL

- ☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- ☐ Dose-response clinical trial
- ☐ Dosing trial (e.g., alternative dosing schedule)
- ☒ Drug interaction or bioavailability clinical trial (clinical only)
- ☐ Immunogenicity trial (clinical)
- ☐ Meta-analysis or pooled analysis of previous clinical trials
- ☐ Pharmacogenetic or pharmacogenomic clinical trial
- ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- ☐ Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- ☐ Safety outcomes trial (SOT)**
- ☐ Thorough Q-T clinical trial
- ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- ☐ Yes
- ☒ No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- ☐ For non-PREA pediatric studies/trials only: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. **The PMR/PMC is clear, feasible, and appropriate⁹ because:** *[Select all that apply]*

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ **(If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.
- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.**

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

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/s/

Lori A WACHTER
08/02/2017

MARY R SOUTHWORTH
08/02/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: July 25, 2017

To: Brian Proctor
Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Zarna Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: James Dvorsky, PharmD
Team Leader
OPDP

Subject: **Spironolactone Oral Suspension (25mg/5 mL) oral suspension**
NDA: 209478
Comments on draft product labeling

OPDP has reviewed the proposed Package Insert (PI) submitted for consult on October 31, 2016, for Spironolactone Oral Suspension (25mg/5 mL) oral suspension. OPDP's comments are provided directly on the attached copy of the proposed labeling emailed to us on July 19, 2017.

OPDP has also reviewed the attached Carton and Container Labeling submitted by the sponsor on October 3, 2016. We have no comments on the proposed Carton and Container labeling at this time.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

ZARNA PATEL
07/25/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: July 18, 2017 **Date Consulted:** January 23, 2017

From: Christos Mastroyannis, M.D.,
Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS,
Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health (DPMH)

To: Division of Cardiovascular and Renal Products

Drug: CaroSpir (Spironolactone) Oral Suspension,

Class: Anti-Hypertensive Agents/Aldosterone Antagonists

NDA: 209478

Applicant: The Carolina Medical Products (CMP) Pharma, Inc.

Subject: Labeling review of an initial NDA application to be compliant with PLLR

Indications:

(b) (4)

- Essential hypertension

(b) (4)

- Severe heart failure

Materials Reviewed:

- DPMH consult request dated January 23, 2017, DARRTS Reference ID 4044850
- Applicant's response to IR of February 17, 2017
- Applicant's submission of October 4, 2016

Consult Question:

The Division of Cardiovascular and Renal Products (DCRP) is seeking recommendations on Pregnancy and Lactation labeling as per PLLR. The applicant did not submit initially labeling in PLLR format.

INTRODUCTION

DCRP consulted the Division of Pediatric and Maternal Health (DPMH) on June 20, 2016, to provide input for appropriate labeling of the pregnancy and lactation subsections of CaroSpir (Spironolactone) Oral Suspension labeling and to ensure compliance with the Pregnancy and Lactation Labeling Rule formatting requirements.

REGULATORY HISTORY

This NDA submission for CaroSpir (Spironolactone) Oral Suspension is an original 505(b)(2) application that differs from the reference listed drug (RLD), ALDACTONE tablets NDA 12151, with respect to new dosage form, a liquid dosage form for patients who have difficulty swallowing tablets (b) (4)

In addition, the two preparations use different inactive ingredients in their composition.

CMP (the Applicant) filed a Citizens' Petition (Docket No. 86P-0055/CP) on February 3, 1986, requesting permission to file an ANDA for Spironolactone Suspension (25 mg/5 mL) and FDA subsequently determined that the above referenced product was suitable for an ANDA submission. (b) (4)

The CaroSpir (Spironolactone) Oral Suspension proposed indications (b) (4)

- Essential hypertension (b) (4)

- Severe heart failure

Off-label use is reported in females for:

- Acne, [Acne Vulgaris (AV)],
- Androgen-excess syndromes, including hirsutism,

- Androgenic Alopecia.

BACKGROUND

Drug Characteristics¹

Spirolactone is a diuretic and renal tubule inhibitor which is a specific pharmacologic antagonist of aldosterone, acting primarily through competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule. Spirolactone causes increased amounts of sodium and water to be excreted, while potassium is retained. Due to this mechanism of action, it acts both as a diuretic and as an antihypertensive drug. It may be given alone or with other diuretic agents that act more proximally in the renal tubule.

In both men and women, spironolactone decreases the rate of testosterone production, increases testosterone's metabolic clearance and diminishes the effects of peripheral androgens on target end organs.^{2,5} Spirolactone also inhibits sebaceous gland activity leading to reduced formation of acne lesions,^{2,3} a common sequelae of androgen excess. The ability of spironolactone to inhibit androgens at different physiological levels has led to its use in women with androgenic alopecia, hirsutism, and excess sebum production.^{4,5}

Peak plasma concentration is reached 0.5 to 1.5 hours after dosing. The bioavailability of spironolactone is greater following administration of CaroSpir than with the tablet (15% higher than the RLD at 25mg).⁶ The plasma half-life of spironolactone itself is short (1.3 hours) but the half-lives of the active metabolites are longer (ranging from 2.8 to 11.2 hours). Spirolactone is metabolized to canrenone and 7- α -(thiomethyl) spironolactone (TMS). Spirolactone and its metabolites bind to plasma proteins by more than 90%. The molecular weight is 416.59. The configuration of the molecule corresponds to the configuration of the skeleton of the natural hormone testosterone molecule.⁷

Spirolactone crosses the placenta.⁸ Canrenone is present in human milk.

Pregnancy and Lactation Labeling Rule (PLLR)

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and*

¹ Currently approved Aldactonelabeling. Drugs@FDA, October 22, 2014

² Kim GK, Del Rosso JQ. Oral Spirolactone in Post-teenage Female Patients with Acne Vulgaris Practical Considerations for the Clinician Based on Current Data and Clinical Experience. *Clinical Aesthetic*, 2012; 5(31):37-50

³ Luderschmidt C, Bidlingmaier F, Plewig G. Inhibition of sebaceous gland activity by spironolactone in Syrian hamster. *J Invest Dermatol*. 1982;78:253–255.

⁴ Burke BM, Cunliffe WJ. Oral spironolactone therapy for female patients with acne, hirsutism or androgenic alopecia. *Br J Dermatol*. 1985;112:124–125.

⁵ Cumming DC. Use of spironolactone in treatment of hirsutism. *Cleve Clin J Med*. 1990;57(3):285-7

⁶ Clinical Pharmacology Review by Xiaolei Pan, Ph.D. June 5, 2017 in DARTS. Reference ID 4107586

⁷ Currently approved Aldactonelabeling. Drugs@FDA, October 22, 2014

⁸ Kamoun M, Mnif MF, Charfi N, Kacem FH, Naceur BB, Mnif F, Dammak M, Rekik N & Abid M. Adrenal diseases during pregnancy: pathophysiology, diagnosis and management strategies. *American Journal of Medical Sciences* 2014 347 64–73.

*Biological Products; Requirements for Pregnancy and Lactation Labeling*⁹ also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule¹⁰ format to include information about the risks and benefits of using these products during pregnancy and lactation.

Current labeling for Aldactone (RLD) approved October 22, 2014, states:

Pregnancy:

Teratogenic effects. Pregnancy Category C.

Studies with ALDACTONE have been carried out in mice and rabbits at doses of up to 20 mg/kg/day. On a body surface area basis, this dose in the mouse is substantially below the maximum recommended human dose and, in the rabbit, approximates the maximum recommended human dose. No teratogenic or other embryotoxic effects were observed in mice, but the 20 mg/kg dose caused an increased rate of resorption and a lower number of live fetuses in rabbits. Because of its antiandrogenic activity and the requirement of testosterone for male morphogenesis, ALDACTONE may have the potential for adversely affecting sex differentiation of the male during embryogenesis. When administered to rats at 200 mg/kg/day between gestation days 13 and 21 (late embryogenesis and fetal development), feminization of male fetuses was observed. Offspring exposed during late pregnancy to 50 and 100 mg/kg/day doses of ALDACTONE exhibited changes in the reproductive tract including dose-dependent decreases in weights of the ventral prostate and seminal vesicle in males, ovaries and uteri that were enlarged in females, and other indications of endocrine dysfunction, that persisted into adulthood. There are no adequate and well-controlled studies with ALDACTONE in pregnant women. ALDACTONE has known endocrine effects in animals including progestational and antiandrogenic effects. The antiandrogenic effects can result in apparent estrogenic side effects in humans, such as gynecomastia. Therefore, the use of ALDACTONE in pregnant women requires that the anticipated benefit be weighed against the possible hazards to the fetus.

Nursing mothers:

Canrenone, a major (and active) metabolite of ALDACTONE, appears in human breast milk. Because ALDACTONE has been found to be tumorigenic in rats, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother. If use of the drug is deemed essential, an alternative method of infant feeding should be instituted.

⁹ Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

¹⁰ Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006).

REVIEW

SPIRONOLACTONE AND PREGNANCY

Nonclinical experience

The Applicant did not submit any new nonclinical data but is relying on literature and the nonclinical data from the RLD, the currently marketed product, as per Pharm Tox reviewer, Papoian T, Ph.D., in DARRTS, October 11, 2016, Reference ID: 3997142. Therefore, the animal data remains the same as it appears in the existing labeling. Because of its antiandrogenic activity and the requirement of testosterone for male morphogenesis, spironolactone may have the potential for adversely affecting sex differentiation of the male during embryogenesis.

Neither Aldactone nor potassium canrenoate produced mutagenic effects in tests using bacteria or yeast. Studies with Aldactone have been carried out in mice and rabbits at doses of up to 20 mg/kg/day.

Briggs states that studies in mice using exposures far below the maximum recommended human dose (MRHD) with correction for body surface area revealed no embryotoxicity or adverse effects on the fetus. In rabbits dosed at approximately the MRHD, an increase in fetal resorption and a decrease in the number of viable fetuses were noted. In male rats exposed to spironolactone during late embryogenesis and fetal development, using a daily dosage 10-fold higher than with the mice or rabbits, feminization of male rat fetuses was documented. Another study showed permanent alterations in the reproductive tracts of both male and female rats exposed in utero to 50–100mg/kg/day of spironolactone during late gestation.²⁰

Review of Clinical Literature

No registries of spironolactone use during pregnancy exist.

ALDACTONE labeling carries the “Pregnancy category C” classification because of the animal observed findings and the potential adverse reactions for adversely affecting sex differentiation of the male during embryogenesis.

Based on exposure and reproduction studies in animals, as stated earlier, there are concerns regarding spironolactone causing hypospadias, feminization of a male fetus, and other possible adverse effects. See also a review of hormonal concepts and therapy by Thiboutot D (2004)¹¹ discussing the antiandrogenic effects of spironolactone. Rathnayake D and Sinclair R (2010) concluded that spironolactone should be avoided in pregnancy due to the theoretical risk of teratogenicity, especially in a male fetus. It should also be avoided in men due to the risk of impotence, gynecomastia, and loss of libido. However, the risk of masculinization of the male fetus occurs approximately six weeks post-conception, and if inadvertent administration is discontinued at an early stage, the potential risk to the male fetus should be negligible.¹² Reprotox states:

Based on experimental animal studies, spironolactone is not expected to increase the risk of congenital anomalies. An antiandrogenic effect in rat

¹¹ Thiboutot D. Acne: hormonal concepts and therapy. *Clin Dermatol*. 2004;22:419–428.

¹² Rathnayake D, Sinclair R. Use of spironolactone in dermatology. *Skinmed*. 2010; 8:328–332.

offspring raised concern about possible adverse effects on male genital development; however, there has been no confirmation in humans of this possible adverse effect.

The Applicant performed a literature search using the terms: “spironolactone, pregnancy”, “spironolactone, lactation”, “spironolactone, pregnancy, lactation”, and “spironolactone, pregnancy, lactation, milk”. Many publications were identified. A review of published literature in PubMed and MicroMedex was also conducted by DPMH to evaluate the use of spironolactone in pregnant women.

Currently, there are no reports linking spironolactone with human congenital anomalies, and there are no well-controlled, prospective studies evaluating spironolactone exposures in pregnant women.¹³ Based on known antiandrogenic effects in humans and the feminization observed in male rat fetuses, Messina *et al.* (1979) commented that spironolactone may be contraindicated during pregnancy.¹⁴ In other publications, the authors consider diuretics in general to be contraindicated in pregnancy, because they have no effect on pre-eclampsia/ eclampsia (they do not alter the course of pre-eclampsia/eclampsia) and may decrease placental perfusion, while in hypertensive disease of pregnancy, they may cause maternal hypovolemia.^{15,16}

In a surveillance study in Michigan Medicaid recipients conducted between 1985 and 1992, and involving 229,101 completed pregnancies, 31 newborns had been exposed to spironolactone during the first trimester of pregnancy. Two major congenital anomalies were noted; one expected and the other an oral cleft defect. No other anomalies were noted among these 31 newborns; including hypospadias, cardiovascular anomalies, spina bifida, polydactyly, and limb reduction anomalies.²⁰

There is at least one case report of two appropriately developed, healthy males after exposure to high-dose treatment with spironolactone (200-400 mg daily) and potassium supplementation for maternal Bartter's syndrome.¹⁷

- A case report describes a woman who at age 20 years was diagnosed with Bartter's syndrome. She experienced symptomatic hypokalemia with paresthesias and weakness; her symptoms improved when the serum potassium level was raised with the use of spironolactone 200 mg/day plus potassium supplementation. She continued to use spironolactone throughout three separate, otherwise normal, uneventful pregnancies. During the pregnancies, the dose of spironolactone may have been as high as 400 mg/day. Pregnancy outcomes were the delivery of two healthy male infants and one healthy female infant.¹⁸ There was no evidence of inadequate androgen effect in the

¹³ Briggs GG, Freeman RK, Yaffe S. In: *Drugs in Pregnancy and Lactation*, 7th ed. Philadelphia: Lippincott-Williams & Wilkins; 1480–1481.

¹⁴ Messina M, Biffignandi P, Ghiga E *et al.* Possible contraindication of spironolactone during pregnancy. *J Endocrinol Invest*: 1979;2:222

¹⁵ Lindheimer MD, Katz AL. Sodium and diuretics in pregnancy. *N Engl J Med* 1973;288:891-4

¹⁶ Christianson R, Page EW. Diuretic drugs and pregnancy. *Obstet Gynecol* 1976;48:647-52

¹⁷ Groves TD, Corenblum B. Spironolactone therapy during human pregnancy. *Am J Obstet Gynecol*. 1995;172(5):1655–1656.

¹⁸ Groves TD, Corenblum B. Spironolactone therapy during human pregnancy. *Am J Obstet Gynecol* 1995;172:1655-6.

boys, the oldest who was 13 at the time of the report, and there were no abnormalities in the children attributed to the drug exposure.

- Other case reports, reviewed in by Riester A and Reincke M, (2015) also showed no evidence of anti-androgenic effects in male or female newborns.¹⁹
- One case report, available only as a meeting abstract (Endocrine Society 93rd Annual Meeting in Boston, MA), described ambiguous genitalia in a newborn with spironolactone exposure through the fifth week of gestation; the mother was being treated for polycystic ovary syndrome.²⁰ The author concluded: “We should use caution in treating females of child-bearing age with spironolactone as the anti-androgen effects of this medication could have impact on sexual differentiation of the infant”.

The Applicant reports several publications that describe the birth of healthy newborns exposed to spironolactone in utero (all are case reports). Overall, the literature does not appear to provide any published clinical trials of women administered spironolactone during pregnancy which reported fetal outcome. No well-controlled studies on spironolactone in pregnancy were identified in the literature review by the Applicant or by this reviewer. The reader is referred to the Applicant’s response to information request, dated February 17, 2017 for a table of available case reports and pregnancy outcomes, Table 1, pp 11-18.

Summary

Although there are theoretical concerns due to antiandrogenic properties of spironolactone and animal data suggesting of effects on sex differentiation of the male during embryogenesis, the available data from limited published literature failed to demonstrate an association of adverse developmental outcomes and spironolactone use. These data suggest that spironolactone administered during pregnancy is not teratogenic. Spironolactone is indicated for heart failure, edema caused by heart failure or cirrhosis and for hypertension. Therefore, there are clinical considerations to be included in the labeling referring to these diseases-associated maternal and/or embryo/fetal risk. Clinical considerations should state:

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Pregnant women with congestive heart failure are at increased risk for preterm birth. Stroke volume and heart rate increase during pregnancy, increasing cardiac output, especially during the first trimester. Clinical classification of heart disease may worsen with pregnancy and lead to maternal death. Closely monitor pregnant patients for destabilization of their heart failure.

Pregnant women with symptomatic cirrhosis generally have poor outcomes including hepatic failure, variceal hemorrhage, preterm delivery, fetal growth restriction and maternal death. Outcomes are worse with coexisting esophageal varices. Pregnant women with cirrhosis of the liver should be carefully monitored and managed accordingly.

¹⁹ Riester A, Reincke M. 2015. Mineralocorticoid receptor antagonists and management of primary aldosteronism in pregnancy. Eur J Endocrinol 172: R23-R30

²⁰ Shah A. 2011. Ambiguous genitalia in a newborn with spironolactone exposure. 93rd Annual Meeting of the Endocrine Society, abstract, Vol 4, P3-227

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

SPIROLACTONE AND LACTATION

Nonclinical Experience

No animal literature about the presence of spironolactone or its metabolites in the animal milk is reported.

Human Experience

It is unknown whether the parent compound, spironolactone, is present in human breast milk; however, the active and predominant metabolite, canrenone, is present in human breast milk.^{20,21} A publication by Phelps and Karim (1977)²² and referenced by the applicant and in Hale's Medications and Mothers' milk,²³ reports on a lactating woman receiving 25 mg spironolactone four times daily (100 mg/d). While breastfeeding, the infant's serum electrolytes were monitored. Seventeen days after birth, the mother's blood and expressed breast milk specimens were taken in the morning, 14.5 hr after her last 25 mg dose (the dosage by that time had been increased to 25 mg four times a day). The mother took her first dose of the day, and 2 hr later (after nursing) the maternal blood and expressed milk specimens were again obtained. After 2 hours of ingestion of spironolactone (25 mg), the serum and milk concentration of canrenone (average $\pm$ SD) were 144 ± 8 and 104 ± 4 ng/mL during two determinations respectively. At 14.5 hr, the corresponding values were 92 ± 4 and 47 ± 3 ng/mL, respectively. The milk to serum concentration ratios at early and late periods were 0.72 and 0.51, respectively. This declined rate was similar to that in the serum. It was estimated that the maximum quantity of canrenone ingested daily by a human infant *via* its mother's milk would be approximately 0.2% of the daily dose of spironolactone given to the mother. Briggs *et al.* in "Drugs in Pregnancy and Lactation" consider that the effects on the infant from this amount are unknown but they appear to be clinically insignificant. The American Academy of Pediatrics and the WHO Working Group classify spironolactone as compatible with breastfeeding, and state that consideration should be given to the tumorigenic potential of spironolactone in rats.^{22,24,25} Toxnet²⁶ states that spironolactone

²¹ Beermann B, Groschinsky-Grind M. Clinical pharmacokinetics of diuretics. *Clin Pharmacokinet.* 1980;5:221–245

²² Phelps DL and Karim A. Spironolactone: relationship between concentrations of dethioacetylated metabolite in human serum and milk. *J Pharm Sci.* 1977; 66: 1203

²³ Hale, Thomas (2012) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing

²⁴ Committee on Drugs. American Academy of Pediatrics. The transfer of drugs and other chemicals in human breast milk. *Pediatrics.* 2001;108:776–789.

²⁵ Truven Health Analytics information, <http://www.micromedexsolutions.com/Reprotox>

²⁶ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels,

appears acceptable to use during breastfeeding and would not be expected to cause any adverse effects in breastfed infants. Intense diuresis may suppress lactation.^{27,28} However, it is unlikely that spironolactone alone is sufficiently potent to cause this effect. Spironolactone can also cause gynecomastia.²⁹

No additional reports of clinical lactation studies or case reports of spironolactone use in lactating women were found in published literature.

Reviewer's comment

Because the clinical importance of the finding (very low exposure of the breastfed infant to spironolactone) is not known, breastfeeding should not be discouraged.

Summary

It is not known if spironolactone is present in the breastmilk. Its major metabolite, canrenone, is present in the breastmilk. Because only limited lactation information for spironolactone exists, the following statement should be included in the risk summary of the labeling: "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for spironolactone and any potential adverse effects on the breastfed child from spironolactone or from the underlying maternal condition."

SPIRONOLACTONE AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Aldactone labeling states:

In a three-litter reproduction study in which female rats received dietary doses of 15 and 50 mg ALDACTONE/kg/day, there were no effects on mating and fertility, but there was a small increase in incidence of stillborn pups at 50 mg/kg/day. When injected into female rats (100 mg/kg/day for 7 days, intraperitoneally (i.p.)), Aldactone was found to increase the length of the estrous cycle by prolonging diestrus during treatment and inducing constant diestrus during a two-week post-treatment observation period. These effects were associated with retarded ovarian follicle development and a reduction in circulating estrogen levels, which would be expected to impair mating, fertility, and fecundity. Aldactone (100 mg/kg/day), administered intraperitoneally to female mice during a two-week cohabitation period with untreated males, decreased the number of mated mice that conceived (effect shown to be caused by an inhibition of ovulation) and decreased the number of implanted embryos in those that became pregnant (effect shown to be caused by an inhibition of implantation), and at 200 mg/kg, also increased the latency period to mating.

any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

²⁷ Healy M. Suppressing lactation with oral diuretics. Lancet. 1961;1:1353-4.

²⁸ Cominos DC, Van Der Walt A, Van Rooyen AJ. Suppression of postpartum lactation with furosemide. S Afr Med J. 1976;50:251-2.

²⁹ Bowman JD, Kim H, Bustamante JJ. Drug-induced gynecomastia. Pharmacotherapy. 2012;32:1123-40.

Administration of spironolactone can delay sexual maturation in female rats and mice and decreased fertility and implantation in rats and mice.³⁰

Interstitial (Leydig cell) adenomas of the testis were observed in the 78 week study in Charles River (Sprague Dawley derived) rats at doses of 150 and 500 mg/kg/day because of sustained stimulation of Leydig cells with elevated LH. Potassium canrenoate behaves as a very weak genotoxic chemical in liver and also in thyroid and bone marrow and in greater degree in testes and ovaries of rats treated with single oral doses ranging from 1/8 to 1/2 of the corresponding LD50. For more extensive discussion, the reader is referred to the Pharm Tox review by Papoian T, Ph.D in DARRTS.³¹

Reviewer comment

From animal studies, it appears that spironolactone may cause interstitial (Leydig cell) adenomas in rats, and its metabolite, canrenoate, appears to be genotoxic in some organs including testes and ovaries. Spironolactone, because of its mode of action, may feminize male fetuses and alter the reproductive tracts of male and female rats when exposed in utero during late pregnancy.

Clinical Experience

In clinical studies using spironolactone, the most common reproductive adverse reactions included menstrual irregularities in women and gynecomastia in men.^{32,33}

Summary

There are no human data available on the effect of spironolactone on fertility to inform a potential clinical risk. The use of spironolactone over the years has failed to produce any reports of Leydig cell tumors or any effects on fertility. In addition spironolactone does not cause an increase to major congenital anomalies and miscarriage in humans; therefore, there are no recommendations for contraception and need for pregnancy testing. Section 8.3, Females and Males of Reproductive Potential, will not be included in spironolactone labeling.

SAFETY OF LONG USE OF SPIRONOLACTONE

Long-term use of spironolactone appears to be safe overall. In 1975 concerns raised about the potential link between breast cancer and spironolactone use. Since then, no definitive data demonstrating a correlation has been found. In one long-term study by Shaw *et al.* (2002) with patients who received spironolactone for up to eight years for the treatment of AV³³, the most common adverse reactions were diuretic effects (29%), menstrual irregularities (22%), and breast tenderness (17%). There were no cases of breast carcinoma in this long-term study.

³⁰ Nagi S, Virgo BB: The effects of spironolactone on reproductive functions in female rats and mice. *Toxicol Appl Pharmacol* 66:221-8, 1982

³¹ Papoian T, Ph.D. Pharmacology Toxicology Review in DARRTS, May 4, 2017. Reference ID: 4093507

³² de Gasparo M, Whitebread SE, Preiswerk G, Jeunemaitre X, Corvol P, Menard J. Antialdosterones: incidence and prevention of sexual side effects. *J Steroid Biochem* 32:223-7, 1989

³³ Shaw JC, White LE. Long-term safety of spironolactone in acne: results of an 8 year follow-up study. *J Cut Med and Surg.* 2002;12:541–545

It is recommended that spironolactone be avoided in women with an increased risk for breast cancer or estrogen-related tumors (either through personal or family history).^{34,35,36,37, 38}

CONCLUSION

The Pregnancy and Lactation, sections of spironolactone labeling were structured to be consistent with the PLLR as follows:

- Pregnancy, Section 8.1
 - The “Pregnancy” section of spironolactone labeling was formatted in the PLLR format to include: “Risk Summary”, and “Data” sections.
- Lactation, Section 8.2
 - The “Lactation” section of spironolactone labeling was formatted in the PLLR format to include the “Risk Summary” and “Data” sections.
- Females and Males of Reproductive Potential, Section 8.3
 - Females and Males of Reproductive Potential, Section 8.3 is omitted.
- Patient Counseling Information, Section 17
 - The “Patient Counseling Information” section of labeling was updated to correspond with sections 8.1 and, 8.2 of labeling.

³⁴ Danielson DAN, Jick H, Hunter JR, et al. Nonestrogenic drugs and breast cancer. *Am J Epidemiol.* 1982;116: 329–332.

³⁵ Brest AN. Spironolactone in the treatment of hypertension: a review. *Clin Ther.* 1986;8:585–586.

³⁶ Loube SD, Quirk RA. Breast cancer associated with administration of spironolactone [Letter]. *Lancet.* 1975;1:1428–1429.

³⁷ Friedman GD, Ury HK. Initial screening for carcinogenicity of commonly used drugs *J Natl Cancer Inst.* 1980;65:723–733.

³⁸ Barker DJP. The epidemiological evidence relating to spironolactone and malignant disease in man. *J Drug Dev.* 1978;1 (Suppl 1. 2):22–25.

DPMH LABELING RECOMMENDATIONS

DPMH Proposed Spironolactone Pregnancy Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----

- **Pregnancy:** Based on animal data, spironolactone may affect sex differentiation of the male during embryogenesis (8.1)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on mechanism of action and findings in animal studies, spironolactone may affect sex differentiation of the male during embryogenesis [see *Clinical Pharmacology* (12.1)]. 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. (b) (4)

Rat embryofetal studies report feminization of male fetuses and endocrine dysfunction in females exposed to spironolactone in utero. Advise a pregnant woman of the potential risk to a male fetus.

The estimated background risk of major congenital anomalies and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major congenital anomalies and miscarriage in the clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Pregnant women with congestive heart failure are at increased risk for preterm birth. Stroke volume and heart rate increase during pregnancy, increasing cardiac output, especially during the first trimester. Clinical classification of heart disease may worsen with pregnancy and lead to maternal death. Closely monitor pregnant patients for destabilization of their heart failure.

Pregnant women with symptomatic cirrhosis generally have poor outcomes including hepatic failure, variceal hemorrhage, preterm delivery, fetal growth restriction and maternal death. Outcomes are worse with coexisting esophageal varices. Pregnant women with cirrhosis of the liver should be carefully monitored and managed accordingly.

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. (b) (4)

Data

Animal Data

Teratology studies with spironolactone have been carried out in mice and rabbits at doses of up to 20 mg/kg/day. On a body surface area basis, this dose in the mouse is substantially below the maximum recommended human dose and, in the rabbit, approximates the maximum recommended human dose. No teratogenic or other embryotoxic effects were observed in mice, but the 20 mg/kg dose caused an increased rate of resorption and a lower number of live fetuses in rabbits. Because of its antiandrogenic activity and the requirement of testosterone for male morphogenesis, CAROSPIR may have the potential for adversely affecting sex differentiation of the male during embryogenesis. When administered to rats at 200 mg/kg/day, a dose 10-times the human dose of 200 mg/day, when based on body surface area, between gestation days 13 and 21 (late embryogenesis and fetal development), feminization of male fetuses was observed. Offspring exposed during late pregnancy to 50 and 100 mg/kg/day doses of spironolactone exhibited changes in the reproductive tract including dose-dependent decreases in weights of the ventral prostate and seminal vesicle in males, ovaries and uteri that were enlarged in females, and other indications of endocrine dysfunction, that persisted into adulthood. Spironolactone (CAROSPIR) has known endocrine effects in animals including progestational and antiandrogenic effects.

8.2 Lactation

Risk Summary

Spironolactone is not present in breastmilk; however, limited data from a lactating woman at 17 (b) (4) postpartum reports the presence of the active metabolite, canrenone, in human breast milk in low amounts that are expected to be clinically remarkable. In this case, there were no adverse effects reported for the breastfed infant after short term exposure to spironolactone; however, long term effects on a breastfed infant are unknown. There are no data on spironolactone effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for spironolactone and any potential adverse effects on the breastfed child from spironolactone or from the underlying maternal condition

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise a pregnant woman of the potential risk to a fetus. Advise females of reproductive potential to inform their prescriber of a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

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/s/

CHRISTOS MASTROYANNIS
07/18/2017

TAMARA N JOHNSON
07/19/2017

LYNNE P YAO
07/19/2017

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: July 7, 2017

TO: Norman Stockbridge, M.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Office of New Drugs

FROM: Srinivas R. Chennamaneni, Ph.D.
Staff Fellow
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences

SUBJECT: Surveillance inspection of ClinSync Clinical Research
Pvt. Ltd., Hyderabad, Telangana, India

Inspection Summary:

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of clinical studies 063-15 and 064-15 (NDA 209478) conducted at ClinSync Clinical Research Pvt. Ltd., Hyderabad, Telangana, India.

Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

Although objectionable findings were observed during this inspection, the findings did not impact the reliability of the data from the audited studies. Thus, I recommend that the data from studies 063-15, 064-15 and other studies of similar design conducted at ClinSync, India be accepted for further Agency review.

Inspected Studies:

NDA 209478

Study Number #1: 063-15 (Pilot Study)

Study Title: "An open label, randomized, two treatment, two period, two sequence, crossover, single dose, oral pharmacokinetic and comparative bioavailability study of Spironolactone suspension 25 mg/5 mL of CMP Pharma, USA with Aldactone® Spironolactone tablets 25 mg of G.D. Searle LLC, Division of Pfizer Inc. USA, in healthy, human subjects under fasting condition"

Dates of conduct: March 04 - 14, 2016

Study Number #2: 064-15 (Pivotal Study)

Study Title: "An open label, randomized, two treatment, two period, two sequence, crossover, single dose, oral pharmacokinetic and comparative bioavailability study of Spironolactone suspension 100 mg (20 mL of 25 mg/5 mL) of CMP Pharma, USA with Aldactone® (spironolactone) tablets USP, 100 mg of G.D. Searle LLC, Division of Pfizer Inc. USA, in healthy, human adult subjects under fasting condition"

Dates of conduct: June 09 - 19, 2016

Clinicals Site: ClinSync Clinical Research Pvt. Ltd.
#4-1-1, Hayathnagar
Hyderabad 501505
Telangana, India

ORA investigator Jennifer C. Adams (FDA, India Office) inspected ClinSync Clinical Research Pvt. Ltd., Hyderabad, Telangana, India from April 17-21, 2017.

The inspection included a thorough examination of study records (paper-based), subject records, informed consent, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, case report forms, employee training, viewing of audio-visual recordings of subject screening, enrollment and interviews, and discussions with the firm's management and staff.

At the conclusion of the inspection, investigator Adams observed objectionable findings and Form FDA 483 was issued to the clinical site. The Form FDA 483 observation(s) (**Attachment 1**), the firm's response dated 05/06/2017 (**Attachment 2**), and my evaluation are presented below.

OBSERVATION 1:

Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Specifically, source records for study 64-15 show conflicting time-frames for study procedures, including informed consent, screening procedures, and check-in to the clinic on 9-Jun-2016. For example:

- The Independent Ethics Committee (IEC) approved addenda to the Informed Consent Form (ICF) informing subjects of a change in Principal Investigator (PI) on 9-Jun-2016 at 4:48pm (English version) and 5:11pm (Telugu version).
- Audio-Visual (AV) recordings show that the one-on-one informed consent sessions occurred on 9-Jun-2016 between approximately 5:31pm and 7:53pm. The consent recordings show subjects wearing street clothing and reviewing and signing the ICF addenda. This further indicates that informed consent took place after 5:00pm (after receipt of the approved addenda). The AV recordings also show subjects in street clothes in the consenting rooms as late as 10:10pm.
- You stated that your firm obtained informed consent prior to screening or checking subjects in to the clinic. Screening included an alcohol breath test, urine drug screen, obtaining vital signs, and medical exam. At check-in, subjects change from street clothing into a uniform before entering the clinic.
- Source records and Case Report Forms (CRFs) show conflicting time-frames to those listed above. For example:
 - o Subject (b) (6)
 - ICF Distributed 12:40pm / Presentation 1:35-2:56pm
 - Urine Drug Screen 3:26pm / Vitals 3:40pm
 - Check-In 4:00PM
 - o Subject (b) (6)
 - ICF Distributed 12:49PM / Presentation 1:35-2:56pm
 - Urine Drug Screen 3:41PM / Vitals 4:04PM

- Che -In 4:20PM
- o Subject (b) (6)
 - ICF Distributed 12:50PM / Presentation 1:35-2:56pm
 - Urine Drug Screen 3:43PM / Vitals 4:08PM
 - Che -In 4:25PM
- o Subject (b) (6)
 - ICF Distributed 12:58PM / Presentation 1:35-2:56pm
 - Urine Drug Screen 4:00PM / Vitals 4:32PM
 - Che -In 4:50PM
- o Subject (b) (6)
 - ICF Distributed 1:06PM / Presentation 1:35-2:56pm
 - Urine Drug Screen 4:17PM / Vitals 4:29PM
 - Che -In 5:10PM
- o Subject (b) (6)
 - ICF Distributed 1:12PM / Presentation 1:35-2:56pm
 - Urine Drug Screen 4:23PM / Vitals 4:40PM
 - Check-In 5:22PM

Firm's Response:

The firm acknowledged the observation and stated that the paper copy of approval from (b) (4) Independent Ethics Committee (IEC) for a change of principal investigator was received on June 09, 2016, before the informed consent process took place, which was evident from the audio visual (AV) recordings. The same IEC approval was then received by email the same day. This was clarified to the investigator during the inspection.

(b) (6) informed consent process for subjects (b) (6) (b) (6) was started at 3:20 pm and completed by 3:42 pm IST for Study 064-15. The firm stated that all the times in the CRFs were recorded from a synchronized clock and the conflicting times in the AV recordings appear to be due to an error in the software or computer system. The individual consent for the last volunteer was completed by 8:10 pm and the subjects were served dinner between 9:00 pm and 9:22 pm. The protocol required 10 hours fasting before dosing. In response to the observation, the firm conducted an investigation and did not find any assignable cause for the observed discrepancy in the AV recordings. The same discrepancy was not seen in Study 063-15.

OSIS Evaluation:

The firm notified the IEC about the change of PI and initiated the informed consent process only after receiving the IEC approval. Although there was a discrepancy noted in the times between the AV recordings and the CRFs, the site followed the protocol for subject enrollment in the study. In addition, the information in the CRFs matched the Volunteer Reporting Record for Study and the Meals Log, which show that the requirement for 10h of fasting before dosing was met. The corrective actions taken by the firm appear to be adequate. This observation has no impact on subject safety or the study outcome.

OBSERVATION 2:

An adequate final report was not provided to the sponsor shortly after completion of the investigators participation in the investigation.

Specifically, on 9 June 2016, Dr. Satya Siva Varaprasad Marrey handed over the responsibilities of Principal Investigator for Study 64-15 to Dr. Nama Netaji. Dr. Netaji had overall responsibility for the conduct and reporting of Period 1 of the investigation, beginning on 9 June 2016. Your firm failed to inform the sponsor of the change in PI. The clinical study report identifies only Dr. Satya Siva Varaprasad Marrey as the PI for this study.

Firm's Response:

In response to this observation, the firm stated that (b) (4) IEC was notified of the change in PI before commencement of the study, but they didn't inform the sponsor because they assumed this was a temporary arrangement due to an emergency situation to the assigned PI (Dr. Satya Siva Varaprasad Marrey). The PI responsibilities were transferred to another qualified PI (Dr. Netaji) before period-I for Study 064-15. The assigned PI resumed his responsibilities during period-II. Information concerning the change in PI was specified in a protocol amendment and later the same was included in the Period-I update to the sponsor. The information about the change of PI was not included in the study report because the firm assumed that it was sufficient to include it in the study protocol. As a corrective action, the firm revised their SOP on the procedure to handle PI responsibilities and retrained the staff.

OSIS Evaluation:

Although the firm did not notify the sponsor immediately after the change of PI, the information was provided to them in the Period-I update. The temporary PI (Dr. Netaji) was a qualified physician and he was trained by the original PI, Dr. Satya. The information of a temporary PI was also included in the ICF and his participation in the study was cleared by IEC. The subjects were also made aware of this. The corrective and preventive actions taken by the firm are adequate and should prevent recurrence of this observation during the conduct of future studies. This observation has no impact on subject safety or study outcome.

OBSERVATION 3:

Investigational records were not retained for a period of two years following approval of a drug's marketing application and discontinuance of the investigation and notification of FDA.

Specifically, your firm failed to retain ICFs for the following screening procedures used to qualify subjects for study 64-15:

- Subject (b) (6) Chest X-Ray dated 16-Dec-15
- Subject (b) (6) Chest X-Ray dated 22-Jan-16
- Subject (b) (6) Chest X-Ray dated 9-May-16
- Subject (b) (6) Chest X-Ray dated 30-Jan-16

and for study 63-15:

- Subject (b) (6) Chest X-Ray dated 13-Jan-16
- Subject (b) (6) Chest X-Ray dated 27-Jan-16
- Subject (b) (6) Chest X-Ray dated 24-Nov-15

Firm's Response:

The firm acknowledged the observation and stated that they did not retain the ICFs of the screening volunteers who did not participate in studies within 28 days of initial screening. The source data for screening consent, laboratory investigations, X-rays, ECG recordings, and destruction of ICFs for the subjects listed in (b) (6) observation were available for review. The ICFs of subjects (b) (6) were found during firm's verification and submitted with the response. As a corrective action, the firm updated their SOP on volunteer screening process for retaining the screening ICFs for all study subjects with the source documents like X-rays for 15 years. The firm will implement the SOP for current and future studies.

OSIS Evaluation:

The tests performed at the time of the screening informed consent are routine laboratory tests to verify the health status of study subjects before enrollment into a study. The missing screening ICFs listed in the observation were not specific to Studies 63-15 and 64-15, but were general screening ICFs to obtain consent for routine laboratory tests. The X-rays and the study specific screening ICFs for the listed subjects were available during the inspection.

There are no incidences of underreporting of adverse events or intentional manipulation of the data. The corrective action taken by the firm appears to be adequate and will prevent recurrence of similar observations in future studies. This observation has no impact on subject safety or the integrity of the study data.

OBSERVATION 4:

An investigation was not conducted in accordance with the investigational plan.

Specifically,

- Study Drug Storage. The protocols for study 63-15 and 64-15 read, "The investigational products will be stored as per the storage condition supplied along with the investigational products in the pharmacy." The test product label specifies storage conditions 20 - 25°C and the reference product label specifies storage below 25°C. On 19-Feb-2016, the sponsor shipped test and reference products to your firm for study 63-15 and 64-15. Your firm received the products on 25-Feb-2016. Your firm has no documentation of the temperature of the investigational products from their departure on 19-Feb-2016 to their arrival on 25-Feb-2016. Your firm did not obtain approval from the sponsor to use these products for studies 63-15 and 64-15.

Plasma Sample Storage. The protocol for study 64-15 reads, "plasma samples will be then stored upright in a box containing dry ice or in a freezer at a temperature of $-20 \pm 5^{\circ}\text{C}$ for interim storage (pre-dose and post dose up to 4.00 hours) and the $70 \pm 15^{\circ}\text{C}$ at the clinical site (b) (4) ."

The temperature in the ultra-low temperature freezer ($-70 \pm 15^{\circ}\text{C}$) was out of range while plasma samples were in storage prior to analysis. For example:

- o 6/14/2016 from 11:18 – 11:48am (up to -47.88°C) and 4:03-5:48pm (up to -36.69°C)
- o 6/21/2016 from 10:17am – 2:02pm (up to -43.06°C)
- o 6/22/2016 from 2:17-6:47pm (up to -25.88°C)

The study report reads, "All plasma samples were stored in a freezer at a temperature of $-20 \pm 5^{\circ}\text{C}$ up to 3.00 hours and then were transferred to $-70 \pm 15^{\circ}\text{C}$ at the clinical site."

Your firm's Standard Operating Procedure (SOP) CP-022-03 reads, "If the temperature is out of the set range for continuously for about 5 hours or more it will be recorded as deviation as per the scenario." The provision for 5 or more hours of out-of-range temperature is not consistent with the study protocol or report.

- Plasma Sample Storage. The protocols for study 63-15 and 64-15 read, "After collecting the blood samples from all the subjects at each sampling time point, samples will be centrifuged for all pharmacokinetic samples. The collected blood samples will be kept on ice-packs until centrifugation." There is no documentation of sample storage in ice-baths prior to centrifugation. The time between sample collection and centrifugation ranged, including for example:

- o 34 minutes for Subject (b) (6) at time-point 0.00h (64-15 Period 1) – 7:00 – 7:34 am
- o 40 minutes for Subject (b) (6) at time-point 1.00h (64-15 Period 1) – 9:00 – 9:40 am
- o 23 minutes for Subject (b) (6) at time-point 3.00h (64-15 Period 2) – 11:10 – 11: am
- o 38 minutes for Subject (b) (6) at time-point 0.50h (64-15 Period 1) – 8:34 – 9:12am
- o 30 minutes for Subject (b) (6) at time-point 0.50h (63-15 Period 1) – 7:30– 8:00am
- o 30 minutes for Subject (b) (6) at time-point 0.00h (63-15 Period 2) – 6:04 – 6:34am
- o 30 minutes for Subject (b) (6) at time-point 1.50h (63-15 Period 1) – 8:34 – 9:04
- o 20 minutes for Subject (b) (6) at time-point 1.25h (63-15 Period 2) – 8:25 – 8:45am

Firm's Response:

The firm stated that the investigational products were stored at appropriate temperatures per study protocol during shipment and upon arrival. The temperature data was retrieved from the data logger with Sponsor's intervention and verified for temperature excursions during shipment. No issues were identified, which is evident from the temperature data during shipment (February 19-25, 2016; **Attachment 3**). Regarding study sample storage, the firm acknowledged that temperature excursions were identified on 06/14/2016, 06/21/2016, and 06/22/2016 in one of the deep freezers due to improper closing of the freezer door during scheduled plasma sample sorting activities. The firm did not report the temperature deviations for the above three days per their SOP because the duration was less than five hours.

(b) (4)

OSIS Evaluation:

The retrieved data logger recordings confirm that there were no temperature excursions during shipment. Further, the stability data support that spironolactone is stable in plasma at room temperature (~25 °C) for 15 hours (**Attachment 4**), which exceeds the duration of the temperature excursion during storage in the deep freezer. This observation does not impact the integrity of the study data.

Conclusion:

Some objectionable findings were observed during this inspection and Form FDA 483 was issued. The final inspection classification is Voluntary Action Indicated (VAI).

After reviewing the inspectional findings and the firm's response to Form FDA 483, the objectionable findings did not impact the reliability of the data from the audited studies. In addition, the overall performance of the site was adequate and is unlikely to impact the integrity of the data from other studies of similar design.

I recommend that the data from studies 063-15 and 064-15 (NDA 209478) be accepted for further Agency review. In addition, studies of similar design conducted between the last inspection (03/2015) and the end of the current Surveillance Interval

should also be accepted for review by the Agency without an inspection.

Srinivas R. Chennamaneni, Ph.D.
Staff Fellow

Final Classification:

VAI- ClinSync Clinical Research Pvt. Ltd.
Hyderabad, Telangana, India
FEI#: 3003706125

CC:
OTS/OSIS/Kassim/Choe/Taylor/Kadavil/Turner-Rinehardt/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Chennamaneni
OTS/OSIS/DGDBE/Cho/Haidar/Choi/Skelly/Au
OND/ODEI/DCaRP/Proctor/Stockbridge
ORA/OIP-India/Adams/Chasey

Draft: SRC 6/29/2017; 7/6/2017
Edit: GB 7/2/2017; CB 7/7/2017

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/ClinSync Clinical Research Pvt. Ltd., Hyderabad, Telangana, India/NDA 209478_Spironolactone oral suspension, 25 mg/5 mL

OSIS File #: 7327
FACTS: 11706067

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/s/

SRINIVAS RAO N CHENNAMANENI
07/07/2017

CHARLES R BONAPACE
07/07/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Epidemiology: Comparison of Multiple Studies or Literature Review

Date:	06/22/2017
Reviewer:	Marie Bradley PhD, MPH, MPharm Division of Epidemiology II
Team Leader	Margie Goulding PhD Division of Epidemiology II
Deputy Division Director	Lockwood Taylor PhD, MPH Division of Epidemiology II
Subject	Spironolactone and cancer risk
Drug Name(s):	Spironolactone
Application Type/Number:	NDA 209478, supplement for an oral suspension formulation
OSE RCM #:	RCM# 2017-594

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EXECUTIVE SUMMARY

The Division of Cardio Renal Products (DCRP) has a new drug application (NDA) under review for spironolactone (under 505 (b)2 NDA 209478 (CaroSpir®) oral suspension (25 mg/5 ml). [REDACTED] (b) (4)

[REDACTED] DCRP [REDACTED] (b) (4)
[REDACTED] requested that DEPI conduct a review of published epidemiologic studies that examines the association between spironolactone and cancer risk to inform their decision.

Literature searches were conducted by a DEPI reviewer in Pubmed and Embase for epidemiologic studies examining spironolactone use and cancer risk. These searches yielded 10 studies (six case-control and four cohort) for review. Some studies examined spironolactone exclusively and some examined spironolactone as part of a group of other diuretics such as aldosterone antagonists and potassium sparing diuretics.

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 and may actually be associated with a reduced risk of prostate cancer although further studies are required to confirm this finding. DEPI agrees with the recommendation of the DCRP non-clinical review [REDACTED] (b) (4)

1 INTRODUCTION

DCRP has an application under review for spironolactone (under 505 (b)2 NDA 209478 (CaroSpir®) oral suspension (25 mg/5 ml) indicated for treatment of (b) (4)

(b) (4). During the application review process DCRP will be modernizing the product's label and converting it to Physician Labelling Review (PLR) language. (b) (4)

(b) (4) s. DCRP (b) (4)

(b) (4) requested that DEPI conduct a review of published epidemiologic studies that examine the association between spironolactone and cancer risk to inform their decision.

1.1 BACKGROUND

Spironolactone, an aldosterone antagonist potassium sparing diuretic, was first approved by the FDA in 1960, (Aldactone®; NDA 012151) for primary hyperaldosteronism, edematous conditions for patients with congestive heart failure, cirrhosis of the liver, nephrotic syndrome and essential hypertension, hypokalemia and severe heart failure (NYHA class III – IV). It acts primarily through competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule causing increased amounts of sodium and water to be excreted, while potassium is retained. It acts both as a diuretic and as an antihypertensive drug by this mechanism and it may be given alone or with other diuretic agents that act more proximally in the renal tubule. There are multiple generic versions of spironolactone now available as well as products that combine it with hydrochlorothiazide.

Spironolactone available in the US has a warning on the label since 1977 detailing findings of tumors in rats treated with potassium canrenoate, a structurally related aldosterone receptor antagonist, apparently based on the fact that both drugs share a common metabolite, canrenone. Both drugs produced somewhat similar, yet distinct, proliferative changes. In rats given potassium canrenoate tumors manifested in the endocrine organs, the liver, thyroid, testes, mammary glands and as myelocytic leukemia and in those given spironolactone thyroid and testicular tumors were seen.

(b) (4) DCRP (b) (4) requested that DEPI conduct a review of published epidemiologic studies that examine the association of spironolactone and cancer risk to inform their decision.

A 5/4/17 non-clinical labeling review conducted by DCRP made the following recommendation:

Given that: (1) metabolism studies with potassium canrenoate showed production of mutagenic epoxide metabolites not seen with spironolactone, (2) the rat tumor findings seen with spironolactone were common tumors seen in long-term rodent studies, (3) and the NOAEL dose for rat tumors was somewhat higher than the human dose (5X, when based on surface area), the box warning (b) (4) does not represent findings of sufficient concern from rats treated with spironolactone to justify its inclusion. The “Carcinogenesis” section of the label should be modified (b) (4) a statement should be added to show the multiples of the human dose described.

1.2 REGULATORY HISTORY FOR CARO SPIR

Date	Event
10/04/2016	CaroSpir new NDA submitted
11/08/2016	Labeling SPL Draft filed
03/23/2017	Consult requested that OSE conduct literature review to inform labelling
05/04/2017	Non-clinical labeling review filed

2 REVIEW METHODS AND MATERIALS

Literature search strategy

Step 1: The following combination of search terms were applied in both Pubmed (National Library of Medicine, Bethesda, MD) and Embase (Reed Elsevier PLC, Amsterdam, the Netherlands) on 04/26/17 to identify articles related to spironolactone and cancer risk. The search encompassed all studies published from database inception to April 26th 2017. The restrictions of English language and human only studies were applied.

1. **“Spironolactone”** and **“Cancer”**
PubMed 570 results, Embase 1599 results
2. **“Spironolactone”** and **“Cancer Risk”**
PubMed 67 results, Embase 369 results
3. **“Diuretics”** and **“Cancer Risk”** (Only those which clearly identify spironolactone or potassium sparing diuretics will be considered)

PubMed 383 results, Embase 617 results

4. **“Aldosterone antagonists”** and **“Cancer Risk”** (limited to studies examining spironolactone)

PubMed 10 results, Embase 91 results

5. **“Potassium sparing diuretics”** and **“Cancer Risk”** (limited to studies examining spironolactone)

PubMed 13 results, Embase 122 results

Step 2: Article titles and abstracts were screened (by inclusion criteria below) to assess relevancy for full text examination by DEPI’s reviewer.

Step 3: For the publications identified in Step 2, review of their reference lists resulted in identification of 1 additional article for inclusion in the literature summary.

Inclusion Criteria

The following inclusion criteria were applied to select appropriate studies:

- Population: adults aged 18 years and older
- Exposure: exposure to spironolactone individually or exposure to aldosterone antagonists or potassium sparing diuretics as a group.
- Comparator: non exposed or exposed to another diuretic
- Outcome: Incident cancer of any type
- Study type: Observational studies including: cohort, case control, cross sectional

Data Extraction

Data was extracted from those articles included for full text examination on study author, country, year, design, exposure, outcomes, methodologic considerations, RR (95%CI) and other important information and are displayed in table 1.

3. REVIEW RESULTS

Forty two articles were screened as potentially eligible for full text examination, and thirty two of these were excluded based on relevance to this review. The key characteristics of the ten articles selected for review are presented in table 1, and a synopsis of each study is provided below.

Studies examining Spironolactone only (3 case-control studies and 3 cohort studies)

Case-control studies

1. **Chuang et al. (2017)** conducted a large nationwide population based retrospective case-control study using data from the Taiwanese National Health Insurance program. They examined the association between the use of renin-angiotensin-aldosterone system inhibitors including spironolactone and urinary tract cancer (UTC) among 32,167 cases of UTC and 32,167 controls. A slightly lower risk of UTC was reported (OR 0.91 95% CI 0.87-0.96) among spironolactone users compared to non-users. However, it was not clear exactly how exposure was classified in this study. Compared to non-use of spironolactone it appeared that neither use of high dose spironolactone ($> 180\text{DDD}$) (OR 0.93 95% CI 0.81-1.08) or lower doses ($< 15\text{DDD}$) (OR 0.93 95% CI 0.87-0.99) was associated with an increased risk of UTC. Despite its large size, this study was limited by the lack of information on important covariates such as BMI and smoking, the poorly described exposure information and use of other drugs in the claims database used. (5)
2. **Busby et al. (2017)** conducted a nested case control study using routine healthcare data in Scotland to investigate the effect of medications which cause inflammation of the gastroesophageal tract on cancer risk. They used data from the Scottish primary care clinical information unit research database and included 1979 cases of oesophageal cancer and 1119 cases of gastric cancer. Users of spironolactone were defined as those with at least one prescription during the exposure period defined as between January 1st 1996 until the year prior to the index date (diagnosis date of the case in each matched group). No association was seen between spironolactone and combined gastro-oesophageal (G-O) cancer (OR 1.04 95% CI 0.73-1.49), between spironolactone and oesophageal (OR 1.04 95% CI 0.68-1.61) or gastric cancer (OR 1.05 95% CI 0.55-2.00) individually. Higher usage (11+ prescriptions) was not associated with higher risk of G-O cancer (OR 0.71 95% CI 0.27-1.87) compared to lower use (1-10). Sensitivity analyses changing the definition of a user to patients with at least three prescriptions (instead of one) did not change the results. Although this study appeared more robust than the study by Chuang et al. there were some limitations. Misclassification of cancer site in this study may have occurred as the data source was general practitioner (GP) records instead of a cancer registry. There was also missing data on important confounders such as smoking and alcohol use although multiple imputation was used in an attempt to account for these. (6)
3. **Jensen et al. (2008)** conducted a population based case control study in Jutland County, Denmark examining the risk of skin cancer among those using photosensitizing diuretics. They included 5964 cases and 23,856 controls. The incidence rate ratio (IRR) for basal cell carcinoma (BCC) was 1.06 (95% CI 0.87-1.28) among ever users of spironolactone and 1.20 (95% CI 0.86-1.68) for > 5 years of use. For squamous cell carcinoma (SCC) the IRR was 1.11 (95% CI 0.75-1.65) among ever users and 0.90 (95% CI 0.44-1.84) for > 5 years of use. As

in the previous studies, the use of registers meant that this study lacked important information on lifestyle factors and about skin phenotypes (such as skin sensitivity to sun exposure).(7) A major strength of this study was the use of information from the Danish cancer registry to confirm primary diagnoses of cancer and the reliable comprehensive prescription data available from the prescription database in North Jutland County which covers the entire population of ambulatory patients. Data on chronic medical conditions that could have been confounders was also obtained from the Danish national registry of patients which includes 99.4% of all discharge records from Danish Hospitals and also covers outpatient and emergency room visits.

Cohort studies

1. **Mackenzie et al. (2017)** conducted a large retrospective matched cohort study examining spironolactone use and incident cancer in the UK Clinical Practice Research Datalink (CPRD). They identified 74,272 spironolactone users of which 52,671 were incident users and 21,601 were prevalent users and investigated risk of 36 different cancers. The median follow-up time for incident users was 11.3 years and 11.5 years in the non-exposed cohort. There was no association between spironolactone use and any cancer risk except for prostate cancer where it was associated with a significantly lower risk (HR 0.69, 95% CI 0.60-0.80). This was a methodologically robust study which adjusted for a wide number of relevant covariates, used propensity score matching with comparator cohorts and applied a 180 day lag after the last prescription to appropriately classify exposure before diagnosis.(1)
2. Another large cohort study was conducted by **Biggar et al. (2013)** among 2.3 million women (with 28.5 million person years of exposure) in a Danish prescription drug registry. The registry was linked to a cancer registry to examine the risk of breast and gynecologic cancers among spironolactone users. **Breast Cancer:** Spironolactone use was associated with an increased risk of breast cancer among current users (IRR 1.19, 95% CI 1.12-1.27) and former users (IRR 1.13, 95% CI 1.04-1.22). However, a more detailed examination of first year use showed first exposure became increasingly common in the months just before breast cancer diagnosis which could indicate reverse causation. In women with ≥ 3 years of exposure the IRR for breast cancer was 1.25, 95% CI 1.06-1.47. **Uterine Cancer:** Among women using spironolactone for ≥ 1 year the risk of uterine cancer was not significantly increased. **Ovarian Cancer** Current spironolactone users had an increased risk of ovarian cancer (IRR 2.12, 95% CI 1.86-2.42) whereas in former users no increased risk was seen (IRR 0.85, 95% CI 0.66-1.09). The high risk in current users was driven by the high risk associated with <1 year of use (IRR 5.89, 95% CI 5.02-6.90) again, most likely resulting from reverse causation due to use for edema in the early stages of cancer. Use for more than one year had an IRR of 0.69 (95% CI 0.46-1.02) and risk was not associated with prolonged use. There were no significant relationships seen

between cervix cancer and spironolactone use. Most of the increased cancer risk observed was driven by exposures in the months immediately preceding a cancer diagnosis as a result of the care of women presenting with symptoms of cancer. However, no information was available on indication for use. As a prescription registry was used, this study was limited in that it did not have information on all covariates required and models were adjusted merely for age and calendar year.(8)

3. **Mackenzie et al. (2012)** conducted another retrospective matched cohort study in the UK CPRD among 1,290,625 female patients older than 55 years with no history of breast cancer. The exposed cohort (29,032 patients) and the control cohort (55,961 patients) had unadjusted incidence rates of 0.39% and 0.38% per year over a mean follow up time of 4.1 years. Spironolactone use (defined as at least two prescriptions) was not associated with breast cancer risk (RR 0.9, 95% CI 0.87-1.1). This study may have been limited by the accuracy of coding for the exposure, outcome and covariates. Linkage to the national cancer registry to verify cancer diagnoses was not performed. There was also some missing data. Important covariates for breast cancer such as family history, genetic abnormalities, information on breast feeding and parity, age of menarche and menopause, and use of complementary and recreational medications were either unavailable or poorly recorded in CPRD.(9)

Four studies (three case control and one cohort) examining spironolactone as part of a group with other diuretics (other aldosterone antagonists or potassium sparing diuretics)

Case Control studies

1. **Coogan et al. (2009)** conducted a case control study investigating use of diuretics and risk of breast cancer using data collected from patients admitted to collaborating hospitals in Boston, New York, Philadelphia and Baltimore from 1976 through 2007. Cases included 5989 women aged 22-79 years old. Diuretic use was grouped according to type, but no separate estimate for spironolactone was reported. Regular diuretic use was classified as use for at least four times a week for at least 3 continuous months. There was some suggestion of an increased risk of breast cancer with regular use of potassium sparing diuretics (OR: 1.22, 95% CI 0.61-2.46) although statistical significance was not achieved. This study is limited in that it obtained data on diuretic use from nurse-administered standard questionnaires, thus recall bias may have been an issue.(3)
2. **Schmidt et al. (2015)** conducted a case control study in Northern Denmark using various registries associated with the Danish welfare system. The study included

2,282 cases of squamous cell carcinoma (SCC) and 17,242 cases of basal cell carcinoma (BCC) and 3,660 cases of malignant melanoma (MM) skin cancer. Aldosterone antagonists including spironolactone (triamterene, eplerenone and canrenone) were included but no separate estimate was reported for spironolactone. Use of aldosterone antagonists appeared to be associated with an increased risk of squamous cell carcinoma (OR SCC 1.48, 95% CI 1.16-1.90) but not BCC (OR 1.00, 0.88-1.13) or MM (OR 0.88, 95% CI 0.62-1.24). There may have been some misclassification of the outcome as the investigators state that BCCs and SCCs are notoriously under reported. There was also no adjustment for important lifestyle factors which could affect cancer risk in this study such as smoking, BMI, and sun exposure.(4)

3. **Li et al. (2003)** conducted a population based case-control study of women ages 65-79 years living in Seattle including 975 breast cancer cases and 1007 controls. Data on drug use and covariates was collected from in-person interviews. They included estimates for potassium sparing diuretics which included spironolactone. Ever use of potassium sparing diuretics was associated with an increased risk of breast cancer (OR 1.6, 95% CI 1.2-2.1). This increased risk persisted with 5 or more years of use (OR 1.4, 95% CI 1.0-2.1). However, certain limitations inherent in this study may have biased the results. Only 80.6% of cases and 73.8% of controls were interviewed. Recall bias when interviewing participants may have been an issue as well as the limited age range of the women studied. Multiple comparisons were performed which may have led to some of the positive associations shown that were likely just due to chance (2).

Cohort study

1. **Ruiter et al (2010)** conducted a cohort study among 10,692 participants over 20 years as part of the Rotterdam study, a large population-based follow-up study examining the association of diuretics and BCC in the Netherlands. In this study, a new user design was used and BCC cases were identified from general practitioners records and by linkage with a national registry of histopathology in the Netherlands. As in the previous studies, estimates were given for potassium sparing diuretics which included spironolactone. The relative risk (RR) for basal cell carcinoma with <152 days of use of potassium sparing diuretics was 0.73 (95% CI 0.32-1.63) and the RR for > 923 days was 0.92 (95% CI 0.41-2.08). While this study included long-term follow-up, its failure to adjust for UV light exposure, a major BCC risk factor, is an important limitation. There may also have been some recall bias as participants were interviewed at home by trained interviewers (10).

3 DISCUSSION

Summary of findings

This review identified six studies (3 case control and 3 cohort), which examined spironolactone use exclusively and risk of various cancers. A further four studies (3 case control and one cohort) presented results for diuretic groups combined and examined cancer risk for spironolactone in combination with other aldosterone antagonists and potassium sparing agents.

Studies examining spironolactone use only

Overall, there was no indication that spironolactone increased the risk of any cancer in the six studies examining spironolactone only (not in combination with other agents). Indeed, one of the largest well-conducted studies, which used data from the UK CPRD to examine 36 cancers (1) suggested spironolactone might actually be associated with a reduced risk of prostate cancer. A second cohort study (5) conducted in Taiwan suggested a slightly reduced risk of UTC among spironolactone users. However, this study was limited by a lack of information on important covariates (e.g. BMI, smoking and other medications used) and failed to describe details of spironolactone exposure classification. Failure to account for these factors might have led to a spurious protective association between spironolactone and UTC given that spironolactone users were more likely to be smokers and have a higher BMI.

Studies examining spironolactone grouped with other diuretics

There were some suggestions of an increased risk of breast cancer (2, 3) and SCC (Schmidt) among the three case control studies examining spironolactone grouped with other diuretics in a similar class. However, limitations including recall bias (2, 3) and missing information on important lifestyle factors may affect the interpretation of these findings and may explain some of the observed increased risk. Often cancer cases, as a result of their diagnosis, may recall information on exposure and other factors differently than non-cases (differential bias). Equally the findings may be attributed to other agents in the group and not just spironolactone and so are less useful in addressing our study question than those from studies that examined spironolactone only.

Limitations of included studies

As the incidence of most specific cancer types are rare, special requirements and diligence are required in the choice of study design and data source when conducting epidemiologic studies to examine drug-cancer associations. Large observational studies with long-term follow-up are generally needed. Many of the studies in this review did not have long enough follow-up to sufficiently ascertain malignancy. Some of the case-control studies included examined drug-cancer associations using interviews or surveys (2, 3) and this self-reported information can result in differential bias (e.g., recall bias) and misclassification of medication exposure. These studies reported increased risks of breast cancer among spironolactone users but such associations may have been

influenced by differential misclassification of exposure in cases. The majority of studies were conducted using large healthcare databases, either from healthcare insurers or providers or from national databases and registries, such as those in the UK, (CPRD), Denmark, and Taiwan. While large healthcare databases linkable to cancer registries generally provide high quality data on prescription drugs and enable studies of rare exposures and outcomes (such as drug–cancer associations), these databases typically do not contain information on non-prescription drugs or on lifestyle factors (e.g., smoking and BMI), introducing potential residual/unmeasured confounding. However, given that most studies found no association between spironolactone use and cancer risk and the fact that spironolactone users were more likely to smoke and have a higher BMI, both of which are known to increase cancer risk, we can be somewhat assured even of these biased results. Few of the studies in this review used cancer registries to verify cancer outcomes. Cancer registries are considered the gold standard for information on cancer diagnoses, although the time period covered, data collected, and quality control procedures vary by registry program.

Some study findings in this review were very likely influenced by an early sign or symptom of undiagnosed cancer, such as the case with spironolactone, use to treat edema, an early symptom of ovarian cancer, in the study by Biggar et al. This reverse causation, also called protopathic bias, can lead to spurious drug–cancer association results as seen in that study (8).

This review is limited in that the available studies in the literature did not include all cancer types and many were limited to one or two types of cancer. However, the large study conducted in CPRD (1) evaluated 36 different types of cancer and found no association between spironolactone use and any of these cancers.

4. CONCLUSION

Based on the findings of this review of epidemiologic studies, it appears there is little evidence that spironolactone is associated with an increased risk of any cancer and may actually be associated with a reduced risk of prostate cancer, although further studies are required to confirm this finding.

5. RECOMMENDATION

Based on the current findings from the observational studies included in this review there is little evidence to support (b) (4). DEPI agrees with the recommendation of the non-clinical review (b) (4).

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Appendix 1

Table 1: Characteristics of included studies

Study, Author, Country/countries, Year	Study design and Number of participants	Exposure Definition	Methodologic considerations	Outcome	Risk Measure	Adjustments	Discussion points
Spironolactone use and risk of incident cancers: a retrospective matched cohort study. Mackenzie et al. UK, 2017.	Propensity score matched cohort study. 74,272 patients exposed to spironolactone.	At least two prescriptions for spironolactone . Index date was date of second script. Mean dose and proportion of days examined.	Used a 180 day lag after last prescription in which users were considered exposed to allow for lag in diagnosis of new cases.	First incidence of cancer during follow-up period. Did not link to cancer registry-used READ code lists only.	No evidence of an increased risk of any cancer associated with spironolactone use except for prostate cancer where it was associated with a significantly lower risk (HR 0.69 95% CI 0.60-0.80 P<0.001).	Sex, age, history of drug use, medical history, BMI, smoking, alcohol use. Age, history of exposure and history of disease were examined as time dependent covariates.	Spironolactone prescribing from secondary care was excluded.
Spironolactone and the risk of urinary tract cancer in patients with	Retrospective case control study matched 1:1. 64,334	No description of exposure classification in the	Excluded those with previous cancer.	Urinary Tract cancer based on ICD 9 codes from the RCIPD- a dataset containing	OR 0.91(95% CI= 0.87-0.96) for UTC risk OR 0.88 (95% CI 0.82-0.94) for	Unclear from the methods section which variables were included in the models	Low quality study. No information on BMI smoking or drug

hypertension: a nationwide population based retrospective case control study. Chuang YW et al., Taiwan 2017.	(32167 cases and 32167 controls).	methods. Appears to be any use.		health claims data on catastrophic illness treatment. Results for prostate and bladder cancer in females are presented in the results but are not mentioned in the methods section.	prostate cancer OR 0.81 (95% CI 0.72-0.92) for bladder cancer in females.	although in the discussion they list age, sex, diabetes, COPD, stroke, coronary arterial disease and related comorbidities such as benign prostatic hyperplasia, CKD, urinary stones and urinary tract infection.	exposure history from the claims database. No information on dose or duration. Included cases aged 20 years or older population likely to be a little young to be seeing UTC and spironolactone use.
The effect of medications which cause inflammation of the gastro-oesophageal tract on cancer risk: a nested case-control study of routine	Nested case control study in the primary care clinical information unit Research database in the UK. Medical records from around 15% of the Scottish	Bisphosphonates tetracycline and spironolactone prescriptions were identified from electronic prescription records. Patients were defined as	Sensitivity analyses examined follow-up censored at date of last contact (rather than last data collection date) and outcomes identified from	First time oesophageal or gastric cancer diagnosis after January 1, 1999 and before April 30, 2011. Those with prior cancer were excluded.	Gastro-oesophageal cancer and spironolactone OR 1.04 95% CI 0.73-1.49 Oesophageal 1.04 (95% CI 0.68-1.61) Gastric	Age, gender, general practice, year of diagnosis, statin use yes/no, aspirin use and presence of each comorbidity.	No information on OTC aspirin use. May have been some misclassification of cancer site as used GP records instead of cancer registry. Histological data not

Scottish data. Busby J et al Scotland 2017	general practice. population. 3908 cases of gastro-oesophageal cancer (1979 oesophageal and 1119 gastric cancer)	users if they had one prescription during the exposure period. Total number of prescriptions in exposure period were stratified into less than medium and more than medium.	hospital episodes statistics (HES) as well as CPRD.		1.05 (95%CI 0.55-2.00)		available to allow separate analysis of squamous cell carcinoma and adenocarcinoma.
Spironolactone use and the risk of breast and gynecologic cancers. Biggar RJ et al. Denmark 2013.	Cohort study in a Danish prescription drug registry linked to cancer registry for cancer outcomes. 2.3 million women followed for 28.8 million person-years.	Women classed as prevalent users if they had a prescription in the first 6 months of registry initiation and incident users if their first prescription was after the first six months of registry	Propensity score matching with comparator cohort.	Incidence of breast, uterus, ovary and cervix cancers. Incident cancers since 1995 through 2010 were included and those with prior cancers were excluded.	Breast cancer IRR 1.19 95% CI 1.12-1.27 current users and 1.13 1.04-1.22 former users. >1 year of use IRR 1.09 0.97-1.22 and risk increased with duration of exposure p=0.06. >3 years of exposure IRR	Age and calendar year only.	Significantly increased risks appeared to be driven by exposures in the months immediately preceding cancer diagnosis probably due to use for abdominal swelling or ascites. Authors conclude that

		initiation. Subjects assumed to have continued the drug for 6 months after last prescription and were considered former users after that. If they later obtained another prescription they were considered restarters. In duration analyses prevalent users were excluded as duration is unknown and including restarters only to the point they first stopped use.			1.25 (1.06-1.47). Uterine Cancer IRR first year 1.48 (1.13-1.95. More than one year risk not significantly increased. Overall risk increased slightly with duration of use beyond first year p trend =0.12. Ovarian cancer Current users IRR 2.12 (1.86-2.42 driven by <1 year use IRR 5.89(5.02-6.90) former users 0.85 (0.66-1.09). > 1 year IRR 0.69 (0.46-1.02) and risk was not associated with prolonged use P trend 0.95.		breast and gynecologic cancer risk is not increased with spironolactone use.
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					Cervical Cancer Not much use among younger women. IRR >1year 1.05 (0.63-1.75). Prolonged use not statistically significant (p=0.84).		
Spironolactone and risk of incident breast cancer in women older than 55 years: retrospective matched cohort study Mackenzie IS et al UK 2012	Retrospective matched cohort study. 1, 290,625 females. 2, 8032 exposed.	Women with at least two prescriptions for spironolactone after age 55 years, followed from the first prescription date (index date) Controls who were subsequently exposed to spironolactone were eligible		READ codes for confirmed diagnoses of breast cancer including breast cancer in situ after the index date. In situ cases excluded in a sensitivity analysis.	Breast cancer RR 0.99 (95% CI 0.87-1.12) Breast cancer recurrence RR 0.88 (95% CI 0.64-1.21) Sensitivity analysis RR close to 1.	Age, calendar year of entry to study, Townsend score (socioeconomic status), use of combined oral contraceptive pill or hormone replacement therapy, history of benign breast disease, alcohol intake, body mass index, family history of breast cancer, use of drugs that may	

		for inclusion in the control cohort before this exposure.				protect against breast cancer (aspirin, metformin), (digoxin, finasteride, cimetidine, nifedipine) and history of hypertension, heart failure, or diabetes mellitus.	
High ceiling diuretics are associated with an increased risk of basal cell carcinoma in a population based follow-up study. Netherlands, 2010 Ruiter et al	Cohort study 10692 participants from the Rotterdam study a large population based follow-up study.	Data on drugs provided by 7 pharmacies that dispense outpatient prescriptions for all participants from January 1 st 1991. Cumulative time of use and average DDD of diuretic dispensations were calculated over the period 1st	No information on type of exposure available or how exposure was defined.	Cancer diagnoses obtained through GP and linkage to the nationwide registry of histology and cytopathology in the Netherlands (PALGA) from January 1 st 1986 to 31 st December 2007. Two research physicians independently assessed the first date and diagnosis of BCC.	BCC RR for <152 days of K+ sparing agents 0.73 (0.32-1.63). >923 days 0.92 (0.41-2.08).	Gender, age, smoking status (current smoker, former smoker or never smoked), self-reported tendency to sunburn (high or low), outdoor work (>4 h daily for >25 years), history of living in a country with a high sun exposure (>1 year), ethnicity, natural hair color during childhood (blond, brown, red or	20 years of follow up

		April 1991 through 31st December 2007. Each participant could contribute cumulative exposure time to one or more of three categories, high ceiling diuretics, potassium sparing agents, and thiazides.				black), natural hair color when adult, eye color and cohort (Rotterdam Study I or Rotterdam Study II). Furthermore, concomitant use of other diuretics and/or other photosensitizing drugs was considered as potential confounder and/or effect modifier. amiodarone, quinidine, calcium antagonists, sulfonylurea derivatives used in diabetes mellitus (tolbutamide, glibenclamide, gliclazide, glimepiride), (piroxicam, flurbiprofen, ibuprofen, ketoprofen, naproxen, celecoxib and	
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						diclofenac), antipsychotics (chlorpromazine, haloperidol, phenothiazines), antibiotics (tetracyclines, fluoroquinolones, sulfonamides) and antimalarial drugs (aminoquinoline and methanolquinoline s).	
Diuretic use and risk of breast cancer Coogan et al 2009	Case control study using data collected from patients admitted to collaborating hospitals in Boston, new York, Philadelphia and Baltimore. Cases comprised 5989 Women aged 22-79 years.	Potassium sparing diuretics only not spironolactone alone. Classified regular diuretic use a use for at least four times a week for at least 3 continuous months. All	Exposure based on questionnaire data not very reliable. Hospital based controls. Recall bias.	Diagnosis of invasive breast cancer in the year prior to hospitalization with no prior or concurrent cancers other than non-melanoma cancer of the skin.	Breast Cancer OR 1.22 (0.61-2.46) for regular use of potassium sparing diuretics. <5 year 1.50 (0.57-3.96) 5+ 1.05 (0.38-2.88)	Race, years of education, menopausal status, parity, body mass index, use of female hormones, use of oral contraceptives and alcohol use. Adjustment for age at first birth, age at menarche, age at menopause and family history of breast cancer did not change the estimates.	

	Controls frequency matched on age, interview year, and study center.	other use classified as sporadic.					
Use of antihypertensive drugs and risk of skin cancer. Schmidt et al, Denmark, 2015	Case control study. 2282 SCC cases 17242 BCC cases 3660MM cases and 231743 population controls from Danish prescription and cancer registries.	Identified all prescriptions from the Aarhus university prescription database redeemed by study subjects before their index date. Non users < 2 scripts. Ever users > 2 prescriptions before index date. Duration of use Short term < 5 years. Long term > 5 years. Intensity of use number of		All cases aged 20 years or older of non-lip SCC, BCC or MM recorded in the Danish Cancer registry. Excluded previous cancers, HIV organ transplantation (high risk for skin cancer).	Potassium sparing diuretics OR SCC 1.40 (1.09-1.80) OR BCC 1.02 (0.91-1.15) OR MM 0.96 (0.69-1.33) Aldosterone antagonists OR SCC 1.48 (1.16-1.90) OR BCC 1.00 (0.88-1.13) OR MM 0.88 (0.62-1.24)	Charlson Comorbidity Index (CCI) (obesity, atrial fibrillation/flutter, angina pectoris, myocardial infarction, congestive heart failure, oesophageal varices, tremor, anxiety, thyrotoxicosis, chronic obstructive pulmonary disease, migraines, stroke, chronic kidney disease or hypertension systemic glucocorticoids, aspirin, non-aspirin NSAIDs and statins.	

		days of prescription coverage/ duration of use in days. <50% >50%					
Relation between use of antihypertensive medications and risk of breast carcinoma among women ages 65-79 years Christopher Li et al,2003 Washington state, US	Case control study (population based) 975 cases and 1007 controls from women living in three-county Seattle Puget sound metropolitan area aged 65-79 with no history of	Potassium sparing diuretics (amiloride and spironolactone) Never users- no use. Users women who had used the specified medication for 6 months or longer. Former users were ever users who had stopped taking the medication more than 6 months prior to their	Recall bias Generalizability as conducted in older women.	Cancers identified via the Cancer surveillance system of the Seattle-Puget tumor registry which participates in SEER. Women received social security (used to identify controls).	Breast cancer and Potassium sparing diuretics Ever use OR 1.6 (1.2-2.1) 6mos to 5 years 1.8 ((1.1-2.8) 5+ years 1.4 ((1.0-2.1) Former use 1.6 (0.9-2.9) Current use 1.6 (1.2-2.2)	Race, income, marital status, education, age at menarche, parity, age at first birth, type of menopause, age at menopause, duration of oral contraceptive use, ever use of HRT, first degree family history of breast carcinoma, smoking status, average daily alcohol intake and body mass index.	

		reference date. Current users were ever users who had used the medication within 6 months of their reference date. Users of antihypertensive medications for less than 6 months were excluded.					
Use of photosensitizing diuretics and risk of skin cancer: a population-based case-control study Jensen et al 2008 Denmark	Case control study 5964 cases and 23856 controls in North Jutland County in Denmark.	Data on diuretic prescriptions were obtained from the prescription database in North Jutland County. Ever use, total amount of prescribed drug before the index date by multiplying package size,	NMSC is rarely fatal and so is often under reported in the Danish Cancer registry and so potential under ascertainment could have led to a substantial underestimation of the overall effect of diuretics.	Used Danish Cancer registry to identify all patients registered with a first primary diagnosis of BCC, SCC or MM in North Jutland County from 1989 to 2003.	Spirolactone IRR for BCC 1.06 (0.87-1.28) Prescriptions > 1 year before diagnosis IRR 1.10 (0.89-1.37) Prescriptions > 5 years before diagnosis IRR 1.20 (0.86-1.68)	Six chronic disease categories, prior prescription of a glucocorticoid and prescriptions for other photosensitizing diuretics.	Well conducted case-control study. Used multiple imputations for variables for which some data was missing such as smoking and alcohol consumption. Sensitivity analyses of

		the number of pills in each package and the amount of drug in each pill-continuous variable.					excluding scripts in the two years prior to the index date (as opposed to one in main analysis) and defining medication users as patients with at least three prescriptions (as opposed to one in main).
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/s/

MARIE N BRADLEY
06/22/2017

MARGIE R GOULDING
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LOCKWOOD G TAYLOR
06/22/2017

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 13, 2017

TO: Norman Stockbridge, M.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Office of New Drugs

FROM: Li-Hong Yeh, Ph.D.
Chemical Engineer
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

Amanda Lewin, Ph.D.
Pharmacologist
DNDBE, OSIS

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE, OSIS

SUBJECT: [REDACTED] of [REDACTED] (b) (4)

Inspection Summary:

The Office of Study Integrity and Surveillance (OSIS) conducted a surveillance inspection of the analytical portion of bioequivalence studies **064-15 (NDA 209478)**, [REDACTED] (b) (4)
(not yet submitted to FDA) conducted by [REDACTED] (b) (4)
[REDACTED] (b) (4)

No significant deficiencies were observed and Form FDA 483 was not issued at the inspection. [REDACTED] (b) (4) is No Action Indicated (NAI).

After reviewing the inspectional findings, we conclude the data from the analytical portion of studies **064-15, 063-15**, [REDACTED] (b) (4) are reliable. Thus, we recommend that the data from these studies be accepted for further Agency review.

Although we did not fully audit the records from study **063-15 (NDA 209478)**, the analytical data should also be accepted for further Agency review based on the findings from study 064-15 submitted under the same application (NDA 209478).

Inspected studies:

NDA 209478

Study Number #1: 064-15

Study Title: "An open label, randomized, two treatment, two period, two sequence, crossover, single dose, oral pharmacokinetic and comparative bioavailability study of Spironolactone suspension 100 mg (20 mL of 25 mg/ 5 mL) of CMP Pharma, USA with Aldactone® (spironolactone) tablets USP, 100 mg of G.D. Searle LLC, Division of Pfizer Inc. USA, in healthy, human adult subjects under fasting condition."

Dates of

Study Conduct: 06/09/2016 - 06/19/2016

Dates of

Sample Analysis: 07/06/2016 - 08/03/2016

Study Number #2: 063-15

Study Title: "An open label, randomized, two treatment, two period, two sequence, crossover, single dose, oral pharmacokinetic and comparative bioavailability study of Spironolactone suspension 25 mg / 5 mL of CMP Pharma, USA with Aldactone® Spironolactone tablets 25 mg of G.D. Searle LLC, Division of Pfizer Inc. USA, in healthy, human subjects under fasting condition."

Dates of

Study Conduct: 03/04/2016 - 03/14/2016

Dates of

Sample Analysis: 04/04/2016 - 04/11/2016

Other audited studies for surveillance purposes (no available application number and not yet submitted to FDA):

inspection of

(b) (4)

(b) (4)

(b) (4)

OSIS scientists Li-Hong Paul Yeh, Ph.D. and Amanda Le
bioanalytical portion of Studies 064-15,

(b) (4)

(b) (4)

at

(b) (4)

(b) (4)

This was the first FDA BIMO
bioanalytical inspection of the site.

We thoroughly audited the facility, equipment, records for method validation and study sample analysis, correspondence, SOPs, biological sample management and storage, instrument audit trails, as well as interviews and discussions with management and staff.

At the conclusion of the inspection, we did not observe any objectionable findings and did not issue Form FDA 483 to the analytical site.

Conclusion:

After reviewing the inspectional findings, we conclude the analytical data from the audited study **(064-15)** are reliable. Therefore, we recommend that the data from this study be accepted for further review.

We were unable to fully audit the records from study **063-15** submitted in support of NDA 209478 within the allotted inspection

inspection of

(b) (4)

(b) (4)

time. Nevertheless, we believe the bioanalytical data from this study are reliable based on the inspectional findings from study 064-15 (NDA 209478). Therefore, we recommend that the analytical data from this study also be accepted for further review.

We broadened our inspection approach by selecting studies (b) (4) and (b) (4) to better evaluate the firm's bioanalytical operations. Although the studies have not been submitted to the FDA, the audited analytical data are reliable and should be accepted for further review, if the studies are submitted to FDA.

Based on the overall inspectional findings, we also recommend that other bioanalytical studies of similar method conducted at the inspected site between (b) (4) and the current surveillance interval should be accepted for review by the Agency without an inspection.

Li-Hong Yeh, Ph.D.
Chemical Engineer
DNDBE, OSIS

Amanda Lewin, Ph.D.
Pharmacologist
DNDBE, OSIS

Final Classification:

Bioan

NAI-

(b) (4)

(b) (4)

CC:

OTS/OSIS/Kassim/Choe/Kadavil/Turner-Rinehardt/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Lewin/Yeh
OTS/OSIS/DGDBE/Cho/Haidar/Skelly/Choi/Au

Draft: PY 06/03/2017; AL 06/04/2017

Edits: RCA 06/09/2017; 06/12/2017; AD 06/12/2017

ECMS: Cabinets/CDER_OC/OSI/OSIS-Office of Study Integ

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/s/

LI-HONG P YEH
06/13/2017

AMANDA E LEWIN
06/13/2017

RUBEN C AYALA
06/13/2017

ARINDAM DASGUPTA
06/13/2017



Date: May 4, 2017

From: Thomas Papoian, PhD, DABT
Supervisory Pharmacologist

To: NDA 209478 (CaroSpir[®]; Spironolactone oral suspension)

Subject: Labeling Review of Rat Tumor Findings

Background

Spironolactone is a specific pharmacologic antagonist of aldosterone, acting primarily through competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule. By inhibiting aldosterone-mediated sodium reabsorption and potassium secretion in the kidney, the drug causes increased amounts of sodium and water to be excreted, while potassium is retained. It acts both as a diuretic and as an antihypertensive drug by this mechanism. The drug is indicated in the management of several indications, such as primary hyperaldosteronism, edema, congestive heart failure, cirrhosis of the liver accompanied by edema and/or ascites, nephrotic syndrome, essential hypertension, hypokalemia, and severe heart failure (NYHA class III – IV). Recommended doses vary for each indication:

- 25 mg/day for severe heart failure
- 100 mg/day for essential hypertension and hypokalemia
- 200 mg/day for edema (congestive heart failure, hepatic cirrhosis, or nephrotic syndrome)
- 400 mg/day for short-term (3-4 weeks) treatment of hypokalemia, hypertension, and hyperaldosteronism.

Spironolactone was first marketed outside the U.S. in 1953 (Mackenzie et al., 2017), but approved in the U.S. in 1960 (Aldactone[®]; NDA 012151). There are multiple generic versions now available as well as the drug being part of a combination with hydrochlorothiazide. The current NDA 209478 (CaroSpir[®]) is for a spironolactone oral suspension (25 mg/5 ml) and is indicated for treatment of

(b) (4)

(b) (4)

This warning statement regarding rat tumor findings, unusual for commonly used drugs marketed today, began appearing in the U.S. label in 1977, and has been unchanged since then. Further, findings of myelocytic leukemia in rats with a structurally related aldosterone receptor antagonist, potassium canrenoate, currently marketed in Europe, but not in the U.S., began appearing in the “Carcinogenesis” section of the spironolactone labeling in 1985 (discussed further below). According to that 1985 label, canrenone is a major pharmacologically active metabolite of potassium canrenoate, and spironolactone is also metabolized to canrenone. Together, these seemingly worrisome rat tumor findings with two related aldosterone receptor antagonists with common metabolic pathways (b) (4)

This review will examine (b) (4) whether any other changes may be needed in the “Carcinogenesis” section of the current label.

Review of Rat Tumor Findings

The original reports from the 1970’s and 1980’s for the several studies conducted in rats to assess carcinogenic potential of spironolactone and potassium canrenoate are not readily available. However, various sources of information have been reviewed to compile a summary of the original findings.

Spironolactone

The current spironolactone label describes the rat tumor findings with spironolactone as follows:

“Orally administered ALDACTONE has been shown to be a tumorigen in dietary administration studies performed in rats, with its proliferative effects manifested on endocrine organs and the liver. In an 18-month study using doses of about 50, 150, and 500 mg/kg/day, there were statistically significant increases in benign adenomas of the thyroid and testes and, in male rats, a dose-related increase in proliferative changes in the liver (including hepatocytomegaly and hyperplastic nodules). In a 24-month study in which the same strain of rat was administered doses of about 10, 30, 100, and 150 mg ALDACTONE/kg/day, the range of proliferative effects included significant increases in hepatocellular adenomas and testicular interstitial cell tumors in males, and significant increases in thyroid follicular cell adenomas and carcinomas in both sexes. There was also a statistically significant, but not dose-related, increase in benign uterine endometrial stromal

polyps in females.”

As described in the label, and according to Lumb (1978), Sprague-Dawley rats from Charles River were given spironolactone in the diet to assess carcinogenic potential in two long-term studies (Table 1):

- 78 week study at 0, 50, 150, and 500 mg/kg/day
- 104 week study at 0, 10, 30, and 100 mg/kg/day

Table 1
(Table 1 from Lumb, 1978)

TABLE 1. Summary of Animal Studies* with Oral Administration of Spironolactone.

Duration	Strain	Dose Levels	No. of Animals Each Sex	
			Control	Test
RATS				
26 weeks (sacrifices at 5 and 13 weeks)	Charles River C.D.	0, 120, 300, 700 parts/million	25	25
		— (1st 3 weeks)	20	20
		0, 150, 500, 2000 parts/million		
		— (last 23 weeks)		
78 weeks	Charles River (Sprague Dawley derived)	0, 50, 150, 500 mg/kg/day	72	36
104 weeks	Charles River (Sprague Dawley derived)	0, 10, 30, 100 mg/kg/day	30	30

*Aldactone 1960b, 1961, 1971, 1972b, 1976a,b.

Lumb (1978) tabulated the tumor incidences from these two studies as follows:

Table 2
(Table 3 from Lumb, 1978)

TABLE 3. Tumor Incidence in Rats.

		78 Week Study Dose Levels mg/kg/day								104 Week Study Dose Levels mg/kg/day							
		0		50		150		500		0		10		30		100	
Animals at Risk		M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Brain		72	72	36	36	36	36	36	36	30	30	30	30	30	30	30	30
Eye			1				1			1	1			1			2
Pituitary*		15/51	28/56	7/27	7/27	2/25	7/30	7/25	1/31	7/29	22/29	6/27	26/29	10/29	19/28	3/26	12/28
Thyroid*		0/59	1/62	4/33	1/31	15/31	12/34	18/28	13/34	3/30	0/30	5/30	2/30	4/29	4/29	0/27	5/28
Parathyroid*										1/10	0/11	0/18	1/15	0/17	1/13	0/11	0/8
Mammary gland	Hosts		11	1	9	2	6		1		19	1	12		13		8
	Tumors		13	1	14	2	7		1		28	1	13		16		9
Liver						1		2			1			1			
Pancreas		1		3		1		2		2	2				1	4	
Kidney			2			1								1		1	
Adrenal		1	1								3	1	1	5		5	
Testis						5		12				2					
Ovary			1			1		1					1		1		
Uterus											1		1				3
Vagina					1						1		1				
Skin		1		1	3	2		2		2		1		1		2	
Liposarcoma			1						1								
Lipoma		1	1										1		1		
Lymphoma		1	2	1						1	1	1	1	1	2	2	1
Fibroma										1		1	1	1		2	1
Fibrosarcoma														1	1		

*Actual number examined identified.

Isolated single tumors were seen as follows:

Site	Dose mg/kg/day	Sex	Study Duration
Spinal Cord	50	M	78 week
Urinary Bladder	100	F	104 week
Seminal Vesicle	30	M	104 week
Prostate	10	M	104 week
Cervix	30	F	104 week
Small Intestine	0	F	104 week
Leukemia	500	F	78 week
Carcinoma (Unknown origin)	50	M	78 week
Hemangiosarcoma (Thoracic cavity)	150	M	78 week

In the 78 week study, increases of thyroid adenomas in both males and females and of interstitial-cell adenomas in the testis of males were observed at the two higher doses (150 and 500 mg/kg/day).

The incidences of thyroid tumors in controls and in the three drug-treated groups were:

- Males: 0/59, 4/33, 15/31 and 18/28 for 0, 50, 150, and 500 mg/kg/day, respectively.
- Females: 1/62, 1/31, 12/34 and 13/34 for 0, 50, 150, and 500 mg/kg/day, respectively.

Interstitial (Leydig cell) tumors of the testis occurred in 0/72, 0/36, 5/36 and 12/36 males at the same doses, respectively.

No notable increased tumor incidence was seen at these organ sites in the 104-week study at doses up to 100 mg/kg/day. Therefore, the NOAEL from both studies for tumor increases appears to be 100 mg/kg/day. This dose represents about a 5X multiple of the maximum recommended human daily dose (MRHDD) of 200 mg/day for a longer-term indication, such as of edema (congestive heart failure, hepatic cirrhosis, or nephrotic syndrome). This is calculated as follows:

- Human MRHDD = 200 mg/day / 60 kg = 3.3 mg/kg x 37 (km) = 122 mg/m².
- Rat NOAEL = 100 mg/kg x 6 (km) = 600 mg/m² = 5X the MRHDD.

Thyroid tumors

In the thyroid, changes were seen as early as 13 weeks after dosing, and consisted of organ weight increases and follicular hyperplasia that progressed to adenomas, but without malignancy. Similar effects in the thyroid were not seen in dogs or monkeys treated up to 13 weeks and 52 weeks, respectively (Lumb, 1978). Further, according to Lumb (1978) the rat appears to metabolize spironolactone predominantly in the liver, and the majority excreted in the bile, whereas in dogs, monkeys, and humans the drug is metabolized only partially in the liver with 50% excretion by the kidney. Such findings in rats of increased drug metabolism in the liver associated with thyroid follicular hyperplasia and thyroid weight have been considered to be rat-specific resulting from a reduction of thyroxine (TH) by the liver, elevation of thyroid-stimulating hormone (TSH) levels, and thyroid gland hyperfunction and growth (Wu and Farrelly, 2006). Such a mechanism is often considered specific to rats because thyroxine in rodents is metabolized rapidly in the liver, and without thyroid hormone-binding globulin that serves as a reserve, as in humans. Unfortunately, levels of TH or TSH in rats treated with spironolactone were not measured to confirm this association.

Interstitial (Leydig-cell) tumors

Leydig cells of the testes produce virtually all of the testosterone in male mammals (Steinbach et al., 2015). The primary signaling pathway for Leydig cell steroidogenesis is initiated when luteinizing hormone (LH) binds to a G-protein-coupled receptor on Leydig cells. This results in adenylate cyclase activation and cAMP production that then leads to synthesis and production of testosterone.

In male rats, the increase in interstitial Leydig cell tumors of the testis is a common finding in long-term drug studies. It appears to develop as a result from a multitude of hormonally-mediated mechanisms, including a drug-induced increase in liver metabolism of testosterone (Steinbach et al., 2015). This latter pathway leads to reduced testosterone signaling to the hypothalamus and pituitary resulting in a compensatory increase in the production of LH, that then binds to LH receptors on Leydig cells and, when sustained and prolonged, stimulates a hyperplastic response and eventually adenomas in rats.

In humans, there have been conflicting reports on the effects of spironolactone on circulating hormone levels, particularly testosterone and LH. In one report (Rose et al., 1997) six patients with hypertension being treated with spironolactone (200-400 mg/day for 4-13 months) and who had developed gynecomastia participated in the study. Testosterone levels in the spironolactone group that developed gynecomastia were significantly decreased when compared to untreated controls, while LH and estradiol levels in the drug-treated group were significantly greater than controls. The authors stated that these changes (i.e., development of gynecomastia) were primarily due to increased metabolic clearance of testosterone and in the peripheral conversion of testosterone to estradiol.

However, in another report (Huffman et al., 1978), eight normal males were given spironolactone at

200 mg/day for up to 10 months and plasma levels of various hormones (testosterone, estradiol, estriol, luteinizing hormone, follicle stimulating hormone, progesterone, and prolactin) measured. Gynecomastia developed in 62% of the males. However, no changes were seen in the metabolic clearance of testosterone or in circulating levels of any of the hormones measured. They concluded that testosterone synthesis or increased metabolic clearance did not appear to be the cause of spironolactone-induced gynecomastia in man.

Although sustained stimulation of Leydig cells with elevated LH in rats may predispose to Leydig cell adenomas, similar effects in humans treated with spironolactone have been questioned. First, rat Leydig cells have 20,000 LH receptors per cell compared to 1500 LH receptors in human Leydig cells (Rasoulpour et al., 2015). This suggests far greater sensitivity of rat Leydig cells to LH-mediated proliferation when compared to human. Second, the incidence of Leydig cell tumors in the Sprague-Dawley rat strain used in the spironolactone tumor studies is reported to be about 6.5%, whereas in humans testicular cancers account for about 1% of all cancers in men, and only 1% of these are Leydig cell in origin (Steinback et al., 2015). Third, there is genetic defect in humans, termed familial male precocious puberty, where the LH receptor on Leydig cells is mutated resulting in constitutive LH receptor activation and Leydig cell hyperplasia from a young age, even though actual LH levels are undetectable. Although there have been reports of Leydig cell hyperplasia in some of these individuals, apparently there have been no reports of Leydig cell tumors in spite of a lifetime of LH receptor activation. Together, these data suggest somewhat different sensitivities between rats and humans for Leydig cell tumor development resulting from sustained and prolonged LH receptor activation.

Potassium canrenoate

The current label for spironolactone contains the following text in the “Carcinogenesis, mutagenesis, impairment of fertility” section on two long-term studies conducted in rats with potassium canrenoate, an aldosterone receptor antagonist closely-related structurally to spironolactone:

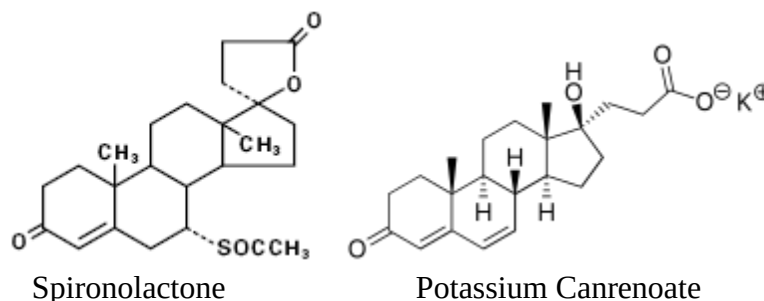
“A dose-related (above 20 mg/kg/day) incidence of myelocytic leukemia was observed in rats fed daily doses of potassium canrenoate (a compound chemically similar to ALDACTONE and whose primary metabolite, canrenone, is also a major product of ALDACTONE in man) for a period of one year. In two-year studies in the rat, oral administration of potassium canrenoate was associated with myelocytic leukemia and hepatic, thyroid, testicular, and mammary tumors.”

Although most of these reported rat tumors appear endocrine in nature (i.e., thyroid, testicular, and mammary tumors), and are somewhat similar to that of spironolactone (thyroid and testicular tumors), the increased incidence of myelocytic leukemia and hepatic tumors with potassium canrenoate presents a new and significant finding. Although it is correct that both spironolactone and potassium canrenoate share the common active metabolite canrenone, other significant differences in the metabolic profiles have been described.

The chemical structural difference between spironolactone and potassium canrenoate is shown below. Spironolactone has a 7 α -thioacetyl group at the 7 position, whereas potassium canrenoate has a 6,7 double bond (Figure 1):

Figure 1

Chemical Structures of Spironolactone and Potassium Canrenoate

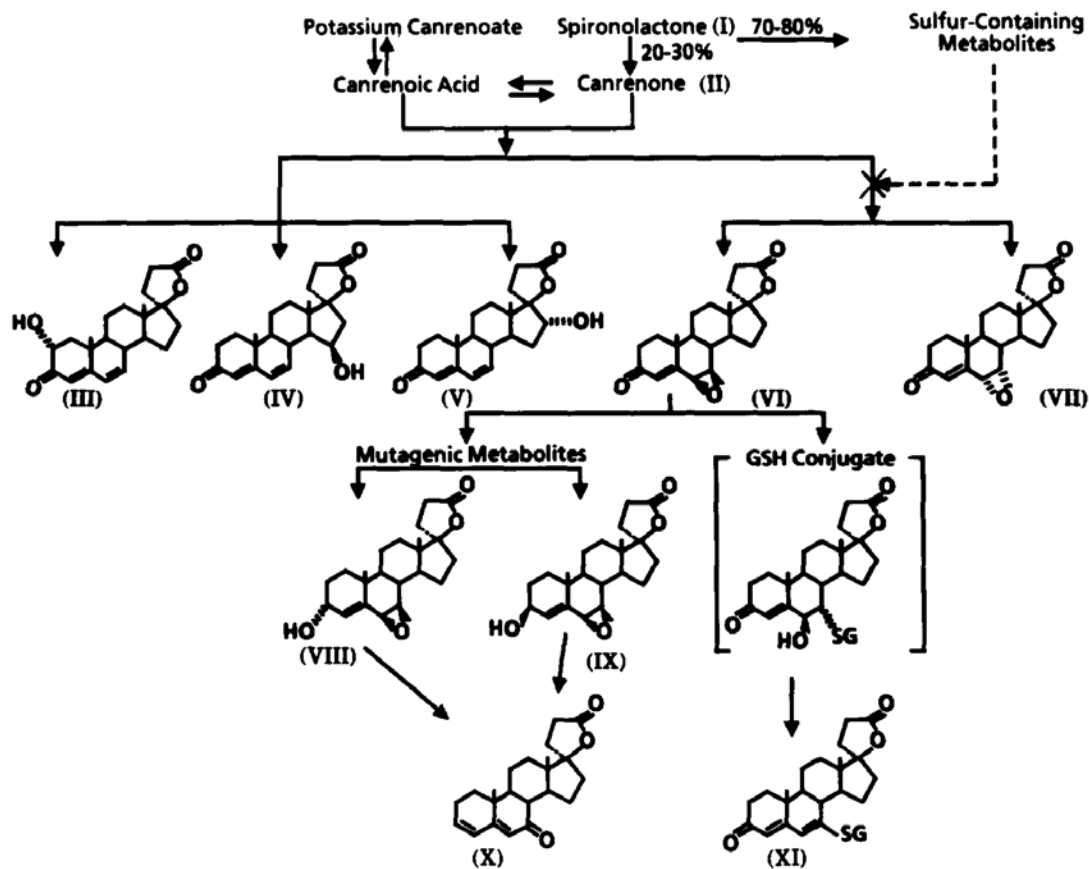


Although both compounds share the common active metabolite canrenone, other possible differences in the metabolism of these two similar, but different, compounds were hypothesized to explain the differences in toxicological responses seen in rat studies, particularly the finding of myelocytic leukemia seen in rats treated with potassium canrenoate, but not spironolactone (Cook et al., 1988). These authors from G.D. Searle & Co. conducted studies in vitro using high performance liquid radiochromatography (HPLRC) and gas chromatography-mass spectrometry (GC-MS) to show that the major route of spironolactone metabolism was through pathways that retain the sulfur moiety in the molecule. In contrast, potassium canrenoate was metabolized by rat hepatic S9 to 6 α , 7 α - and 6 β , 7 β -epoxy-canrenone. The β -epoxide of potassium canrenoate was further metabolized to its 3 α and 3 β -hydroxy derivatives as well as its glutathione (GSH) conjugate. Both 3 α and 3 β -hydroxy-6 β , 7 β -epoxy-canrenoate were shown to be direct acting mutagens in the mouse lymphoma assay, whereas 6 α , 7 β - and 6 β , 7 β -epoxy-canrenone were not. These mutagenic metabolites, their precursor epoxides and their GSH conjugates were not formed from spironolactone under identical conditions.

The authors attributed the differential findings between the two drugs to inhibition of further metabolism of the active metabolite canrenone that is formed from spironolactone by either spironolactone itself and/or its S-containing metabolites. This was because the in vitro metabolism of potassium canrenoate by rat hepatic microsomes was reduced in the presence of spironolactone. They hypothesized that the mechanism(s) for this inhibition was that spironolactone and/or its S-containing metabolites specifically inhibit an isozyme of hepatic cytochrome P-450, or alternatively, spironolactone is a preferred substrate over potassium canrenoate/canrenone for the metabolizing enzymes (Figure 2).

Figure 2

Proposed Metabolic Scheme of Potassium Canrenoate and Spironolactone in the Rat
(Cook et al., 1988)



According to the proposed metabolic scheme, mutagenic metabolites and their precursor epoxides could be formed from the fraction of spironolactone that was metabolized to canrenone/canrenoic acid, but, as mentioned, formation of such metabolites was not detected with spironolactone when incubated under identical conditions. It was suggested that this could be due to inhibition of canrenone/canrenoic acid metabolism by spironolactone and its S-containing metabolites, because the *in vitro* metabolism of potassium canrenoate with hepatic microsomes was substantially reduced in the presence of spironolactone, perhaps through inhibition of an isozyme of hepatic cytochrome P-450 by spironolactone.

The authors concluded that the presence of mutagenic epoxides in potassium canrenoate incubations, but not in those with spironolactone, provided a “logical” explanation why a dose-related increase in myelogenous leukemia was detected in a long-term rat study with potassium canrenoate, but not with spironolactone.

The genotoxic potential of potassium canrenoate was assessed in subsequent studies conducted both

in vitro and in vivo. In the in vitro studies, potassium canrenoate at subtoxic concentrations (10-90 μ M) induced DNA fragmentation in primary cultures of hepatocytes from rat and human donors (Martelli et al., 1999). The response was concentration dependent, as detected by the Comet assay, and also when assessed for DNA repair synthesis, as measured by quantitative autoradiography. DNA fragmentation and micronucleus formation were absent in cultured human lymphocytes. The genotoxic effects appeared to be more marked in rat than in human hepatocytes.

In vivo studies were conducted in rats following intragastric administration of up to one-half the LD₅₀ dose (≤ 325 mg/kg) (Martelli et al., 2002). In this study potassium canrenoate was examined for its ability to induce DNA fragmentation and DNA repair, and of causing formation of micronuclei and of enzyme altered preneoplastic foci in the liver. In addition, the occurrence of potassium canrenoate-induced DNA fragmentation was examined in the thyroid and the bone marrow (i.e., targets of its carcinogenic activity), as well as in organs expressing enzymes involved in the metabolism of steroids (i.e., ovaries and testes). None of the rats died or showed signs of toxicity. Results showed that oral dosing of up to on-half the LD₅₀ dose of potassium canrenoate produced a small, but statistically significant increase of DNA fragmentation in the liver of male, but not of female rats. No increase in micronucleated hepatocytes were seen. For liver cells, the greater genotoxicity seen in vitro vs. that seen in vivo was attributed to either a limited bioavailability or a more efficient detoxification of potassium canrenoate in vivo.

The ability of potassium canrenoate to cause genotoxic effects in other tissues was examined. A statistically significant increased frequency of DNA breaks and/or alkali labile sites was detected in the thyroid and bone marrow of female, but not of male rats, whereas a marginal increase in the frequency of micronucleated polychromatic erythrocytes (i.e., bone marrow) occurred in males, but not in females. These results suggested to the authors that potassium canrenoate behaves as a very weak genotoxic chemical in liver and also in thyroid and bone marrow.

However, the greatest degree of positive genotoxic activity was seen in testes and ovaries of rats treated with single oral doses ranging from 1/8 to 1/2 of the corresponding LD₅₀. This result was interpreted as indicating that potassium canrenoate attains higher concentrations and/or is preferentially activated to reactive species or less efficiently detoxified in these organs.

Whether the marginal degree of positive genotoxic activity seen in the bone marrow may account for the myelocytic leukemia seen in rats treated with potassium canrenoate is uncertain without a similar assessment with spironolactone.

The section for “Mutagenesis” in the current label for spironolactone does not clearly ascribe greater mutagenic activity for one compound over the other (i.e., spironolactone vs. potassium canrenoate):

“Neither ALDACTONE nor potassium canrenoate produced mutagenic effects in tests using bacteria or yeast. In the absence of metabolic activation, neither ALDACTONE nor potassium canrenoate has been shown to be mutagenic in mammalian tests in vitro. In the presence of metabolic activation, ALDACTONE has been reported to be negative in some mammalian mutagenicity tests in vitro and inconclusive (but slightly positive) for mutagenicity in other mammalian tests in vitro. In the presence of metabolic activation, potassium canrenoate has been reported to test positive for mutagenicity in some mammalian

tests in vitro, inconclusive in others, and negative in still others.”

Therefore, based on the available data, the presence of mutagenic epoxides in potassium canrenoate rat hepatic microsome incubations, but not in those with spironolactone, may provide the best evidence why a dose-related increase in myelogenous leukemia was seen in a long-term rat study with potassium canrenoate, but not with spironolactone. Although follow-up publications with potassium canrenoate provided further assessments of the drug’s genotoxic potential both in vitro and in vivo, the absence of similar comparative assessments with spironolactone makes it difficult to ascribe a specific unique mechanism or site of action responsible for the myelogenous leukemia seen in rats treated with potassium canrenoate.

Conclusions

Spironolactone was first approved in the U.S. in 1960, and is still widely used as an aldosterone antagonist to treat a variety of mostly serious indications relating to its activity as a diuretic and antihypertensive agent. The current NDA 209478 (CaroSpir[®]) is for a spironolactone oral suspension (25 mg/5 ml) and is indicated for treatment of (b) (4).

The box warning statement in the current label describing rat tumor findings, unusual for commonly used drugs marketed today, began appearing in the U.S. label in 1977. The label was later modified in 1985 to incorporate tumor findings of 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. Further, both drugs produced somewhat similar, yet distinct, proliferative changes and tumors in rats:

- 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.

However, the unique finding of myelocytic leukemia in rats treated with the related compound potassium canrenoate was somewhat worrisome, (b) (4). The present review examined (b) (4) whether any other changes may be needed in the “Carcinogenesis” section of the current label.

Two tumor types commonly seen during the course of long-term rodent carcinogenicity studies, thyroid and Leydig cell tumors, were discussed. As spironolactone is metabolized predominantly in the liver of rats, increased liver metabolism of thyroid hormone or testosterone may result in a compensatory increase in TSH or LH levels, respectively, resulting in hyperfunction and growth of thyroid glands or Leydig cells, respectively. Further, thyroxine in rodents is metabolized rapidly, without thyroid hormone-binding globulin that serves as a reserve as in humans, and Leydig cell tumors in human males are rare, even in familial male precocious puberty where there is a lifetime of LH receptor activation.

The current label for spironolactone also contains findings on two long-term studies conducted in rats with potassium canrenoate, an aldosterone receptor antagonist closely-related structurally to spironolactone, and in which the two drugs share the common pharmacologically active metabolite canrenone. Tumor findings with potassium canrenoate included not only hepatic, thyroid, testicular, and mammary tumors, but also myelocytic leukemia. Although both spironolactone and potassium canrenoate share the common active metabolite canrenone, other significant differences in the metabolic profiles were identified. In particular, the presence of mutagenic epoxides in potassium canrenoate rat hepatic microsome incubations, but not in those with spironolactone, provided the best evidence why a dose-related increase in myelogenous leukemia was seen in a long-term rat study with potassium canrenoate, but not with spironolactone. Later studies described additional genotoxic activity with potassium canrenoate both in vitro and in vivo, but the absence of similar comparative assessments with spironolactone make it difficult to ascribe a specific unique mechanism or site of action responsible for the myelogenous leukemia seen in rats treated with potassium canrenoate. Regardless, the two drugs, although similar in structure and activity, appear to differ in their metabolic pathways where one (potassium canrenoate) produces mutagenic epoxide metabolites, whereas the other (spironolactone) does not. This may help explain the novel finding of myelogenous leukemia seen with potassium canrenoate. (b) (4)

Recommendations

Many approved drugs on the market today contain rodent tumor findings in their labels. Such findings not only describe the nature of the findings, but also the doses at which they were seen relative to the human therapeutic doses or exposures. However, it is uncommon for rodent tumor findings to appear as a box warning, as such findings normally appear in the Carcinogenesis section of the label. Perhaps in 1985, when the rat tumor findings were first reported, they were considered of sufficient concern to justify a box warning. Since that time, most drugs indicated for long-term use are subject to formal carcinogenicity assessments, and such findings, when present, are not often considered unusual nor worthy of a box warning.

Given that: (1) metabolism studies with potassium canrenoate showed production of mutagenic epoxide metabolites not seen with spironolactone, (2) the rat tumor findings seen with spironolactone were common tumors seen in long-term rodent studies, (3) and the NOAEL dose for rat tumors was somewhat higher than the human dose (5X, when based on surface area), the following recommendations are made to modify the current label:

1. [REDACTED] (b) (4)

[REDACTED] (b) (4)

2. The “Carcinogenesis” section of the label should be modified as follows:

a. Remove the following section on potassium canrenoate, [REDACTED] (b) (4)

[REDACTED] (b) (4)

b. The text for spironolactone should be edited to include multiples of the human dose, when based on surface area, as follows (added text in **BOLD**):

“Orally administered ALDACTONE has been shown to be a tumorigen in dietary administration studies performed in rats, with its proliferative effects manifested on endocrine organs and the liver. In an 18-month study using doses of about 50, 150, and 500 mg/kg/day, there were statistically significant increases in benign adenomas of the thyroid and testes and, in male rats, a dose-related increase in proliferative changes in the liver (including hepatocytomegaly and hyperplastic nodules). In a 24-month study in which the same strain of rat was administered doses of about 10, 30, 100, and 150 mg ALDACTONE/kg/day, the range of proliferative effects included significant increases in hepatocellular adenomas and testicular interstitial cell tumors in males, and significant increases in thyroid follicular cell adenomas and carcinomas in both sexes. There was also a statistically significant, but not dose-related, increase in benign uterine endometrial stromal polyps in females. **No increased tumors were seen at doses of 100 mg/kg/day. This dose represents about 5X the human recommended daily dose of 200 mg/day, when based on body surface area.**”

Finally, 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, [REDACTED] (b) (4) even though a recent epidemiology study in over 70,000 patients found no evidence of an increased cancer risk associated with its use (Mackenzie et al., 2017).

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/s/

THOMAS PAPOIAN
05/04/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 30, 2016
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 209478
Product Name and Strength:	Carospir (spironolactone) oral suspension, 25 mg/ 5 mL
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Carolina Medical Products Co.
Submission Date:	November 8, 2016
OSE RCM #:	2016-2325
DMEPA Primary Reviewer:	Ashleigh Lowery, PharmD, BCCCP
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the proposed Carospir (spironolactone) container labels and prescribing information submitted on November 8, 2016 for risk of medication error.

This NDA proposes a new oral suspension formulation of spironolactone, available in 118 mL and 473 mL bottles.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container labels and PI to identify deficiencies that may lead to medication errors.

Prescribing Information

We noted that the PI does not include the NDC numbers for the products in Section 16 (How Supplied/Storage and Handling). We also note (b) (4) when expressing the quantity contained in each bottle.

Container Labels

We identified that the prominence of the strength can be increased on the 473 mL bottle.

We provide recommendations in Section 4.1 and 4.2 to increase clarity.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed Carospir container labels and PI that can be improved to increase clarity and promote the safe use of this product. We provide recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. *In the Dosage and Administration section*, to provide clarity regarding the route of administration, consider adding the words “taken orally” to the dosage statements.^a
2. *In the How Supplied/Storage and Handling section*,
 - a. As presented, the bottle quantities are expressed using (b) (4) metric units (mL). Revise so that (b) (4) consistent with the container labels.^b
 - b. Add the NDC number for each container size to this section per 21 CFR 201.57(c)(17).

4.2 RECOMMENDATIONS FOR CAROLINA MEDICAL PRODUCTS CO.

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. Increase the font size of the strength or consider displaying on a separate line to make it more prominent on the 473 mL container. The strength should be prominent per 21 CFR 201.15(a)(6).
2. Correct the spacing so that the words “excursions” and “permitted” are separated on the 473 mL container.

^a Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

^b USP General Chapter <659> Packaging and Storage Requirements

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Carospir that Carolina Medical Products submitted on November 8, 2016, and the listed drug (LD).

Table 2. Relevant Product Information for Carospir and the Listed Drug		
Product Name	Carospir	Aldactone
Initial Approval Date	N/A	January 21, 1960
Active Ingredient	Spironolactone	Spironolactone
Indication	(b) (4)	• Primary hyperaldosteronism • Edematous conditions for patients with congestive heart failure, cirrhosis of the liver accompanied by edema and/or ascites, nephrotic syndrome • Essential hypertension • Hypokalemia • Severe heart failure (NYHA class III-IV)
Route of Administration	Oral	Oral
Dosage Form	Oral suspension	Tablet
Strength	25 mg/5 mL	25 mg, 50 mg, 100 mg
Dose and Frequency	(b) (4)	• Hyperaldosteronism: • Long test for evidence: 400 mg daily for 3-4 weeks • Short test for evidence: 400 mg daily for 4 days • Preparation for surgery: 100 mg to 400 mg daily • Long-term maintenance: lowest effective dose for individual patient • Edema: 25 mg to 200 mg daily • Essential hypertension: 50 mg to 100 mg daily • Hypokalemia: 25 mg to

Table 2. Relevant Product Information for Carospir and the Listed Drug		
Product Name	Carospir	Aldactone
	(b) (4)	100 mg daily Severe heart failure: 25 mg daily dose initially
How Supplied	118 mL and 473 mL bottles	Bottles of 100
Storage	Store at 20°C- 25°C (68°F - 77°F). Excursions permitted to 15°C- 30°C (59°F - 86°F).	Store below 77°F (25°C)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 15, 2016, we searched the L:drive and AIMS using the terms, “Carospir” and “spironolactone,” to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous reviews.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On November 16, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, Nursing, Quarterly Action Agenda, Canada Safety Bulletin, Pennsylvania Patient Safety Advisory
Search Strategy and Terms	Match Exact Word or Phrase: Carospir Match Exact Word or Phrase: spironolactone

D.2 Results

There were no ISMP newsletters describing medication errors associated with the label and labeling of spironolactone.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Carospir labels and labeling submitted by Carolina Medical Products Co. on November 8, 2016.

- Container labels
- Prescribing Information

G.2 Label and Labeling Images

A. Container Labels



^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

ASHLEIGH V LOWERY
12/30/2016

CHI-MING TU
12/30/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209478	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: CaroSpir® Established/Proper Name: Spironolactone Dosage Form: Oral Suspension Strengths: 25 mg/5 mL		
Applicant: CMP Pharma Inc.		
Date of Application: October 4, 2016 Date of Receipt: October 4, 2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: August 4, 2016		Action Goal Date (if different):
Filing Date: December 3, 2016		Date of Filing Meeting: November 3, 2016
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☒ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): (b) (4) essential hypertension, (b) (4) and severe heart failure.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

Type of BLA	☐ 351(a) ☐ 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification: The application will be a priority review if: • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 120929				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.	☒	☐		
Are the established/proper and applicant names correct in electronic archive? If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name	☒	☐		

to the supporting IND(s) if not already entered into electronic archive.					
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>		☒	☐	☐	
Application Integrity Policy		YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		☐	☒		
If yes, explain in comment column.					
If affected by AIP, has OC been notified of the submission? If yes, date notified:		☐	☐		
User Fees		YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?		☒	☐		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>		Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov:</i>): ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>		Payment of other user fees: ☒ Not in arrears ☐ In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf		Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ Yes ☐ No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>		☒	☐		

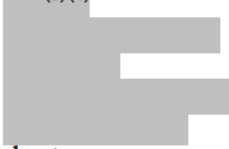
cover letter, and annotated labeling). If yes , answer the bulleted questions below:																					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		☐	☒																		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		☐	☒																		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		☐	☒																		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>																					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm		☐	☒																		
If yes, please list below: <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>						Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration												
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>																					
Exclusivity	YES	NO	NA	Comment																	
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	☐	☒																			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]?	☐	☒	☐																		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>																					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☐	☒	☐																		
If yes, # years requested:																					
Note: An applicant can receive exclusivity without requesting it;																					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☐	☐	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: ☐ legible	☒	☐		

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	☐	☐	☐	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <u>paper</u> forms and certifications with hand-written signatures must be included.</i> Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	☒	☐		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☒	☐	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	☒	☐		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	☒	☐		
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				

Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	☐	☐	☒	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i>	☒	☐		(b) (4)  due to new indications PREA is

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

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Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				triggered.
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)?	☒	☐	☐	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application?	☐	☐	☒	Deferred iPSP
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
BPCA:				
Is this submission a complete response to a pediatric Written Request?	☐	☒		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³)</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	☒	☐	☐	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	☐	☒	☐	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☐ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in Physician Labeling Rule (PLR)	☒	☐		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

format? ⁴				
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	☐	☒	☐	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☐	☒	☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	☐	☐	☒	
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (send WORD version if available)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	☒	☐		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	☒	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☐	☒	☐	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):	☐	☒		
Any Special Protocol Assessments (SPAs)? Date(s):	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 3, 2016

BACKGROUND: On October 4, 2016, CMP Pharma, Inc. submitted a New Drug Application (NDA) for CaroSpir® (Spironolactone Oral Suspension, 25 mg/5 mL) Oral Suspension. In accordance with section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, This NDA relies on IND # 120929, which was originally filed on 10 Oct, 2015.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Brian Proctor	Y
	CPMS/TL:	Edward Fromm	N
Cross-Discipline Team Leader (CDTL)	Aliza Thompson, MD		Y
Division Director/Deputy	Stephen Grant, MD		Y
Office Director/Deputy	Norman Stockbridge		Y
Clinical	Reviewer:	Melanie Blank	Y
	TL:	Aliza Thompson	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Xiaolei Pan	Y
	TL:	Martina Sahre	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:		

	TL:		

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Rama Dwivedi	N
	TL:	Thomas Papoian	N
Statistics (carcinogenicity)	Reviewer:	NA	
	TL:	NA	
Product Quality (CMC) Review Team:	ATL:	Wendy I. Wilson-Lee	Y
	RBPM:	Dahlia Woody	Y
• Drug Substance	Reviewer:	Haripada Sarker	N
• Drug Product	Reviewer:	Thomas Wong	N
• Process	Reviewer:	Peter Guerrieri	N
• Microbiology	Reviewer:	Jason God	N
• Facility	Reviewer:	Cassandra Abellard and Quallyna Porte	N
• Biopharmaceutics	Reviewer:	Kaushalkumar Dave	Y
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Ashleigh Lowery	Y
	TL:	Alice Tu	N
OSE/DRISK (REMS)	Reviewer:	Leah Hart	N
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			
		*For additional lines, right click here and select "insert rows below"	

FILING MEETING DISCUSSION:

GENERAL 505 b)(2) filing issues: - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? - Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):		☐ Not Applicable ☐ YES ☒ NO ☐ YES ☒ NO The 356h specifies reliance on NDA 12151 for Aldactone oral tablets. Per the synopsis for their "pivotal" comparative BA study, they compared their suspension to G.D. Searle's 100 mg oral tablet (which is identified in the OB as the RLD for spironolactone oral tablets). They are relying on our finding of s/e for NDA 12151 for Aldactone oral tablets for approval of their suspension.
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO	
Electronic Submission comments	☐ Not Applicable	

List comments:	☐ No comments
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CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☐ YES ☒ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Norman Stockbridge, MD, PhD Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): NA 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAAs completed: April 2016

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

/s/

BRIAN L PROCTOR
11/30/2016