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RESEARCH**

APPLICATION NUMBER:

022503Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 28, 2015
From	Nikolay Nikolov, M.D. Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Subject	Cross-Discipline Team Leader Review Update
NDA#	NDA 22-503
Supplement#	0
Applicant	CorePharma, LLC
Date of Submission	December 15, 2014
PDUFA Goal Date	June 15, 2015
Proprietary Name / Established (USAN) names	Metaxalone tablet/ metaxalone
Dosage forms / Strength	640 mg tablets
Proposed Indication(s)	1. Adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful, musculoskeletal conditions
Recommended:	<i>Approval, with revisions to proposed labeling</i>

1. Introduction

This is the third cycle for NDA 22,503 for CorePharma's metaxalone 640 mg tablets. The NDA previously received complete response actions on June 11, 2010 and on December 18, 2013 due to manufacturing site inspection deficiencies pertaining to the CorePharma, Middlesex, New Jersey drug product finishing facility. The original application, submitted August 20, 2009, consisted of a single bioavailability study in 48 healthy volunteers comparing metaxalone 640 mg to the listed drug (LD), Skelaxin 800 mg, which provided adequate clinical data to support the approval of metaxalone 640 mg tablets with labeling based on Skelaxin but received a complete response (CR) due to manufacturing inspection deficiencies. Subsequently, the sponsor submitted two CR resubmission extension requests, on June 1, 2011 and May 29, 2012, which were granted. A response to CR was submitted on June 18, 2013, with a cover letter stating that the sponsor considered the deficiencies adequately addressed. However, when FDA attempted to schedule re-inspection for this NDA resubmission, the sponsor stated that they were not ready for re-inspection. Specifically, an inspection at CorePharma, LLC facility by the New Jersey District Office (NWJ-DO) from September 11 to 13, 2013 found that the firm was not ready for pre-approval inspection of NDA 22,503 and demonstrated a lack of capacity to manufacture the drug products (CPGM 7346.832, Part V Item 1). The Office of Compliance determined the need for a follow-up inspection pre-approval. Therefore, the application received another CR action on December 18, 2013. The reader is referred to the first and second cycle cross-discipline team leader (CDTL) reviews for additional details.

In this third cycle submission for NDA 22503, the applicant certified that the inspection deficiencies have been addressed and a pre-approval FDA inspection was conducted by the Division of Inspectional Assessment (DIA). All CorePharma LLC facilities inspected were found to be acceptable, and DIA has recommended an approval action. Thus, the CR deficiencies have been sufficiently addressed.

2. Background

Refer to Section 1, Introduction.

3. CMC

CMC Reviewer: Xiaobin Shen, Ph.D.

CMC Lead: Craig Bertha, Ph.D.

Biopharmaceutics Reviewer: Haritha Mandula, Ph.D., and Kelly Kitchens, Ph.D.

ONDP Branch Chief: Julia Pinto, Ph.D.

The resubmission includes three categories of CMC information. The first is to notify the Agency that the facilities previously not ready for inspection have been inspected and found acceptable as discussed in the next subsection, Facilities review/inspections. The second is to add an additional acceptance limit to the dissolution data; this was found to be justified and acceptable by Dr. Mandula. The third is to update the NDA with additional real time stability data of a total of 6 batches, all completed up to 36 months. The submitted new information is acceptable and supports a product expiry of 36 months.

The labeling review by Dr. Shen identified that registration batch tablets are (b) (4)

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Since the drug product is ready to be approved based on data collected from (b) (4) tablets, the applicant needs to manufacture batches (b) (4) test and submit data to support that the tablets (b) (4) have consistent performance characteristics. Since the data in this application were derived from subjects ingesting the whole tablet and (b) (4) can be done post-approval as a post-marketing commitment (PMC) where the applicant should provide comparative dissolution data (determined by f2 metrics) between the (b) (4) tablets using the approved dissolution method to support the change.

The CMC team recommends approval of this NDA with the abovementioned PMC and I agree.

- **Facilities review/inspection**

OPQ/OPF/DIA Compliance Officer: Linda Ng, Ph.D.

OPQ/OPF/DIA Branch Chief (acting): Mahesh Ramanadham, Pharm.D.

The CorePharma LLC, FEI 3002535019 was found acceptable for the Prompt Release Tablets profile, [REDACTED] (b) (4) was acceptable for the non-sterile active pharmaceutical ingredient (API) by chemical synthesis profile, and three facilities, [REDACTED] (b) (4) were acceptable as control testing laboratories. All facilities are acceptable from the current Good Manufacturing Practice (cGMP) perspective with an overall re-evaluation date of August 12, 2016. Thus, the CR deficiencies have been sufficiently addressed and the Office of Process and Facilities recommends approval of this NDA and I agree.

4. Nonclinical Pharmacology/Toxicology

Primary Pharmacology/Toxicology Reviewer: Asoke Mukherjee, Ph.D.

Pharmacology/Toxicology Supervisor: Timothy Robison, Ph.D.

No new pharmacology/toxicology information was submitted with this application.

5. Clinical Pharmacology/Biopharmaceutics

Primary Clinical Pharmacology Reviewer: Sheetal Agarwal, Ph.D.

Clinical Pharmacology Team Leader: Satjit Brar, Pharm. D., Ph.D.

No new clinical pharmacology information was submitted with this re-submission. Refer to the original submission reviews for details of the clinical pharmacology program supporting the application. To briefly summarize, CorePharma's 640 mg metaxalone tablets were bioequivalent to Skelaxin 800 mg tablets under fasted conditions. CorePharma's metaxalone was not bioequivalent to Skelaxin 800 mg tablets under fed conditions (CorePharma's metaxalone results in approximately 25% lower C_{max} and AUC concentrations). However, the approved Skelaxin label does not contain recommendations or limitations related to food effect, and the efficacy data in support of Skelaxin do not suggest the drug must be taken with food in order to be effective. Further, there are no safety concerns since the metaxalone 640 mg exposure is lower than Skelaxin exposure in the fed state. Therefore, extrapolation of efficacy and safety from Skelaxin 800 mg tablets is justified based on meeting the Agency's standard for bioequivalence in the fasted state. .

6. Clinical Microbiology

Not Applicable.

7. Clinical/Statistical- Efficacy

Primary Clinical Reviewer: Keith Hull, M.D., Ph.D.

No new clinical efficacy information was submitted with this application.

8. Safety

The sponsor has no ongoing clinical program; however in this submission the sponsor has provided a safety update from the published literature. My review of the updated safety information has not identified new safety concerns and concludes that it is consistent with information already included in the approved label for metaxalone and the proposed prescribing information.

9. Advisory Committee Meeting

Not applicable. No Advisory Committee Meeting was convened for this application.

10. Pediatrics

Pertinent pediatric issues were addressed during the first cycle review. No new pediatric information was submitted with this re-submission. If approved, CorePharma's metaxalone tablet, will be recommended for patients 12 years of age and older. While the nominal dose of CorePharma's metaxalone tablet is different from the nominal dose of the listed drug, the exposure is the same and the dose and dosing regimen is within the range of the approved doses and the dosing of Skelaxin. Therefore, on May 05, 2010, PeRC determined that approval of this NDA does not trigger Pediatric Research Equity Act and thus, no pediatric assessment is required.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**

No issues were identified to trigger the AIP.

- **Exclusivity or patent issues of concern**

Pertinent patent and exclusivity issues were addressed during the first review cycle and re-submissions. No new information on patents or exclusivity has been provided in this re-submission. At the time of the original submission, there were three patents listed in the orange

book for the listed drug, Skelaxin, and CorePharma had been granted a patent license to the listed patents (6407128, expiration 12/3/21; 6683102, expiration 12/3/21; and 7122566, expiration 2/6/26) by agreement with King Pharmaceuticals, Inc., the owner of the patents. Based on orange book review, at this time patents 6407128 and 6683102 no longer appear, but patent 7714006 appears with the same expiration date of 12/3/21. No unexpired exclusivity exists for Skelaxin. With the previous re-submission, CorePharma provided paragraph IV certification along with notification to the NDA holder as well as proof that the notification was sent to the NDA holder and each patent holder.

- **Financial disclosures**—No issues.
- **Other GCP issues**—No issues.
- **DSI audits**—No issues.
- **Other discipline consults**—Not applicable.
- **Any other outstanding regulatory issues**—No issues.

12. Labeling

- **Proprietary name**

On June 26, 2013, during the previous review cycle, the applicant informed the Agency that they would not submit a proprietary name for this NDA prior to approval [REDACTED] (b) (4). At the time of this review, no acceptable proprietary name had yet been submitted or agreed upon.

- **Address important issues raised by brief discussion of DDMAC and OSE Division comments**

Not applicable. See Physician labeling section below.

- **Physician labeling**

CorePharma submitted labeling in Physician Labeling Rule (PLR) format. The content of the proposed label follows closely the content of labeling of Skelaxin, with minor differences due to the lack of a trade name, different nominal dose, and new clinical pharmacology information. Additional edits were implemented by the review team for consistency with the current labeling practices and for clarity.

- **Carton and immediate container labels (if problems are noted)**

No problems noted.

- **Patient labeling/Medication guide (if considered or required)**

None required. No new safety signals were identified in the application or in the review of postmarketing case reports with Skelaxin.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

NDA 22-503 provided adequate evidence that CorePharma 640 mg metaxalone tablets are bioequivalent to the Listed Drug (LD), Skelaxin. Therefore, the Agency's previous finding of safety and efficacy for the LD may be extrapolated to apply to the CorePharma metaxalone product. The facilities inspection deficiencies identified during the previous review cycles have been addressed and the pre-approval inspection has found facilities acceptable. With this, all of the deficiencies which were the basis for the complete response action on June 11, 2010 and December 18, 2013 have been addressed and I recommend approval of the NDA.

- **Risk Benefit Assessment**

The overall risk:benefit profile of CorePharma's 640 mg metaxalone tablets remains unchanged from the first review cycle and is acceptable.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**

No postmarketing risk evaluation and mitigation strategies are warranted for this product, for the reasons mentioned above.

- **Recommendation for other Postmarketing Requirements and Commitments**

No postmarketing requirements are recommended by the review team.

One post-marketing commitment (PMC) for comparative dissolution data (determined by f2 metrics) between [REDACTED]^{(b) (4)} metaxalone tablets using the approved dissolution method was recommended by the CMC team as discussed above in Section 3, CMC. On March 30, 2015, the applicant submitted timetable, to conduct this study according to the following schedule:

Study Completion: October 2015
Final Report Submission: November 2015

- **Recommended Comments to Applicant**

No issues remain that warrant comments.

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/s/

NIKOLAY P NIKOLOV
05/28/2015