CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022503Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	June 1, 2015
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	22-503
Applicant Name:	CorePharma, LLC
Date of Submission:	December 15, 2014, (original submission was on August 18, 2009; second cycle resubmission on June 18, 2013)
PDUFA Goal Date:	June 15, 2015
Proprietary Name:	None
Established Name:	Metaxalone
Dosage form:	Tablets
Strength:	640 mg
Proposed Indications:	Adjunct to rest, physical therapy, and other measures of relief of discomfort associated with acute, painful musculoskeletal conditions
Action:	Approval

1. Introduction

CorePharma submitted their 505(b)(2) application for metaxalone tablets, as an adjunct to rest, physical therapy, and other measures of relief of discomfort associated with acute, painful musculoskeletal conditions in patients 12 years of age and older. The application refers to King Pharmaceuticals metaxalone tablet (marketed as Skelaxin, NDA 13-217) as the listed drug and relies on a clinical pharmacology study to show bioequivalence (BE) to Skelaxin. The original application was submitted on August 18, 2009, and received a Complete Response action on June 11, 2010, because of a failed inspection of the drug product manufacturing facility at New Jersey. In addition, CorePharma did not provide appropriate patent certification for applicable patents and failed to comply with the statutory requirements for sending notice of paragraph IV certification to the NDA holder and each patent owner.

CorePharma resubmitted the application on June 18, 2013, and in that resubmission CorePharma stated that the deficiencies identified in the Complete Response were adequately addressed. However, when FDA attempted to schedule re-inspection for that NDA resubmission, CorePharma stated that the New Jersey site was not ready for re-inspection. The Office of Compliance therefore retained the withhold recommendation. With the submission of June 18, 2010, 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. The Division took a second Complete Response action on December 18, 2013, due to Withhold recommendation from Office

of Compliance. The current resubmission addressed the manufacturing inspection deficiencies adequately and the Office of Compliance recommends approval.

2. Background

Metaxalone was originally approved in 1962 (NDA 13-217, King Pharmaceuticals) with the trade name Skelaxin. Metaxalone underwent DESI review in 1970 and was originally determined to be ineffective based on data submitted[1,2], but with review of additional data[3] in 1974, metaxalone was determined to be effective.

The formulation of CorePharma's product is different compared to Skelaxin. CorePharma's product contains a lower nominal dose, with systemic exposure similar to the Skelaxin, with a lesser food effect (discussed further in sections 3 and 5 below). This product will provide patients with a choice of another formulation of metaxalone. The appropriateness of 505(b)(2) regulatory pathway versus a 505(j) pathway for this product was discussed with the Office of Regulatory Policy (who consulted with the Office of Chief Council). It was determined that 505(b)(2) regulatory pathway is appropriate for this application.

3. Chemistry, Manufacturing, and Controls

The proposed commercial drug product is a tablet formulation that contains 640 mg metaxalone with standard compendial excipients. Unlike Skelaxin, the drug substance in CorePharma's product is (b) (4) which seems to impact the gastrointestinal absorption (see section 5 below). The drug product is proposed to be packaged in HDPE bottles containing 100 tablets. The active pharmaceutical ingredient will be manufactured at (b) (4) The drug product will be manufactured, packaged, released, and stability tested at CorePharma facilities in New Jersey, USA. The Office of Compliance has an Acceptable recommendation for the drug product manufacturing facility at New Jersey as discussed in section 1 above. The various DMFs associated with the manufacture of the product are adequate. An expiry date of 36 months is supported by submitted stability data.

4. Nonclinical Pharmacology and Toxicology

No new non-clinical toxicology studies were required or performed for this application.

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[1] Fathie K. A second look at skeletal muscle relaxant: A double-blind study of metaxalone. Curr Ther Res 1964; 6:677-83.

[2] Diamond S. Double-blind study of metaxalone use as a skeletal muscle relaxant. JAMA 1966; 195:479-80.

5. Clinical Pharmacology and Biopharmaceutics

The pivotal clinical pharmacology study is a single-dose four-way crossover study in 47 healthy adult volunteers that compared 640 mg of the CorePharma's metaxalone to the listed drug (Skelaxin 800 mg marketed by King Pharmaceuticals) under fasting and fed conditions (Study R08-0838). The clinical pharmacology study showed that the 90% CI for the CorePharma's metaxalone 640 mg to Skelaxin ratios for the primary PK parameters of Cmax and AUC in the fasted state were within the 80-125% BE limits, thus demonstrating equivalent systemic exposure between CorePharma's product and the listed drug. CorePharma's product was outside the BE limit under fed state, however, BE under fed state is not required as Skelaxin has no specific instructions regarding administration with or without food (Table 1). The data suggest that Skelaxin has a food effect that CorePharma's product does not appear to have (Figures 1 and 2).

Table 1. Key PK parameters for CorePharma metaxalone vs Skelaxin

	CorePharma Metaxalone 640 mg	King Pharma Skelaxin 800 mg	% Ratio	90% CI
Fasted State				
Cmax	1798.83	1735.28	103.66	88.64, 121.24
AUC_{0-t} (ng.hr/mL)	13686.84	13907.27	98.41	90.74, 105.74
AUC_{0-inf} (ng hr/mL)	13988.59	14866.84	94.09	87.12, 101.62
Fed State				
Cmax	2207.56	3046.51	72.46	61.96, 84.75
AUC_{0-t} (ng.hr/mL)	14600.21	19359.95	75.41	69.53, 81.80
AUC_{0-inf} (ng hr/mL)	14840.39	19624.22	75.62	70.02, 81.67

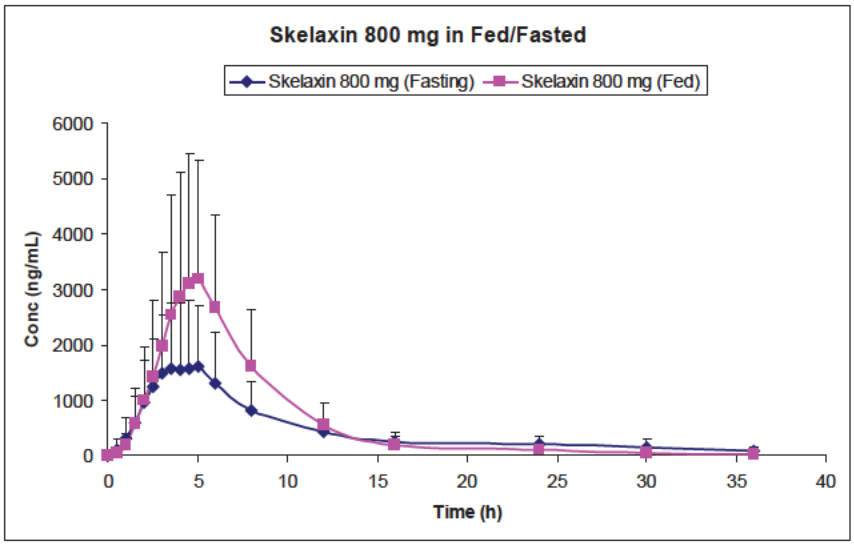

Figure 1. King Pharmaceutical's Skelaxin 800 mg (RLD) food effect (from Dr. Al Habet's review)

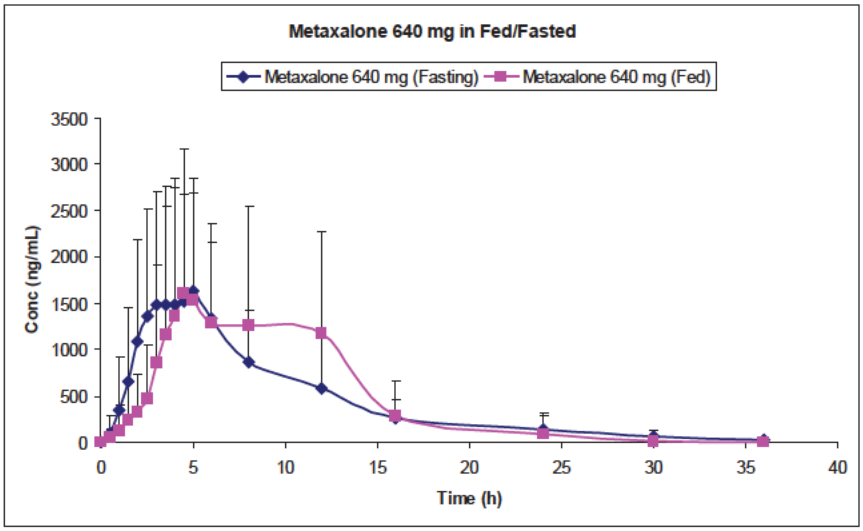

Figure 2. CorePharma's metaxalone 640 mg food effect (from Dr. Al Habet's review)

6. Clinical Microbiology

The final product is not sterile, which is acceptable for an orally administered product. The manufacturing process is adequate from a microbiological perspective.

7. Clinical and Statistical – Efficacy

No clinical studies were required or conducted to support this application. The entire program was based on a bioequivalent study as discussed in the clinical pharmacology section above.

8. Safety

The safety database for CorePharma's metaxalone includes data from the clinical pharmacology study, supplemented by review of post-marketing safety reports, and review of the literature. There were no new or unique findings that are not already described in the approved Skelaxin product label.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Metaxalone is a known drug substance; there were no specific issues to warrant discussion at an Advisory Committee Meeting.

10. Pediatric

Pertinent pediatric issues were addressed during earlier cycle reviews. No new pediatric information was submitted with this re-submission. 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

a. DSI Audits

DSI conducted an audit of the pivotal clinical pharmacology study. The inspection did not reveal any significant deficiencies. During review of this submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements.

c. Others

There are no outstanding issues with consult reviews received from OPDP, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

The applicant initially proposed the trade name [redacted] (b) (4) for the product, and later revised the trade name to [redacted] (b) (4) DMEPA rejected both trade names because [redacted] (b) (4) The applicant has not submitted another trade name for consideration.

b. Physician Labeling

With the original application, CorePharma submitted a label in the Physician's Labeling Rule format that closely mirrors Skelaxin label with minor changes to account for the lack of a trade name, different nominal dose, and description of the clinical pharmacology study discussed in section 5 above. The labeling was reviewed previously with the original submission.

c. Carton and Immediate Container Labels

These were reviewed during the original application review by various disciplines of this Division, and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

There is no separate patient labeling and medication guide for this product.

13. Action and Risk Benefit Assessment

a. Regulatory Action

CorePharma has submitted adequate data to support approval of metaxalone 640 mg tablets for use as an adjunct to rest, physical therapy, and other measures of relief of discomfort associated with acute, painful musculoskeletal conditions in patients 12 years of age and older.

b. Risk Benefit Assessment

The overall risk and benefit assessment of metaxalone 640 mg for the indication stated above (section 1 and 13a) supports its approval. The risk benefit assessment of this product is expected to be the same as Skelaxin since the two products are bioequivalent. The observed apparent lack of food effect of the CorePharma's metaxalone compared to Skelaxin is not expected to alter the risk benefit assessment. The efficacy will not be negatively impacted and systemic safety is not expected to be any worse with lower exposure.

c. Post-marketing Risk Management Activities

None.

d. Post-marketing Study Commitments

One post-marketing commitment (PMC) for comparative dissolution data (determined by f2 metrics) between (b) (4) metaxalone tablets using the approved dissolution method was recommended by the CMC team. 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.

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06/01/2015