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RESEARCH**

APPLICATION NUMBER:

022503Orig1s000

MEDICAL REVIEW(S)

Clinical Investigator Financial Disclosure
Review Template

Application Number: **NDA 22503**

Submission Dates: **Original NDA August 20, 2009, Resubmission: December 15, 2014**

Applicant: **CorePharma, LLC**

Product: **Metaxalone Tablet**

Reviewer: **Nikolay P. Nikolov, M.D.**

Date of Review: **May 15, 2015**

Covered Clinical Study (Name and/or Number): **R08-0838, an open-label, single-dose, randomized, four-period, four-treatment crossover study under fasting and fed conditions comparing CorePharma's drug product Metaxalone Tablet, 640 mg against the listed drug Skelaxin Tablet 800 mg.**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>4</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N.A.</u></p> <p>Significant payments of other sorts: <u>N.A.</u></p> <p>Proprietary interest in the product tested held by investigator: <u>N.A.</u></p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>N.A.</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>4</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Reviewer's Comment: The applicant has adequately disclosed financial interests and/or arrangements with clinical investigators by having submitted a signed Form FDA 3454 stating that none of the 4 investigators had a financial agreement with the sponsor or financial interest in the company.

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/s/

NIKOLAY P NIKOLOV
05/15/2015

SUMMARY REVIEW OF REGULATORY ACTION

Date: December 18, 2013

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: June 18, 2013 (original submission was on August 18, 2009)

PDUFA Goal Date: December 18, 2013

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: Complete Response

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.

The current resubmission to the Complete Response dated June 18, 2013, stated that CorePharma considers the deficiencies identified with the complete response adequately addressed. However, when FDA attempted to schedule re-inspection for this NDA resubmission, CorePharma stated that the New Jersey site was not ready for re-inspection. The Office of Compliance is therefore retaining the withhold recommendation. With this resubmission, 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.

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 data³ 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 the 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 a withhold 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 (b) (4) 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.

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

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.

parameters of C_{max} 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				
C _{max}	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				
C _{max}	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

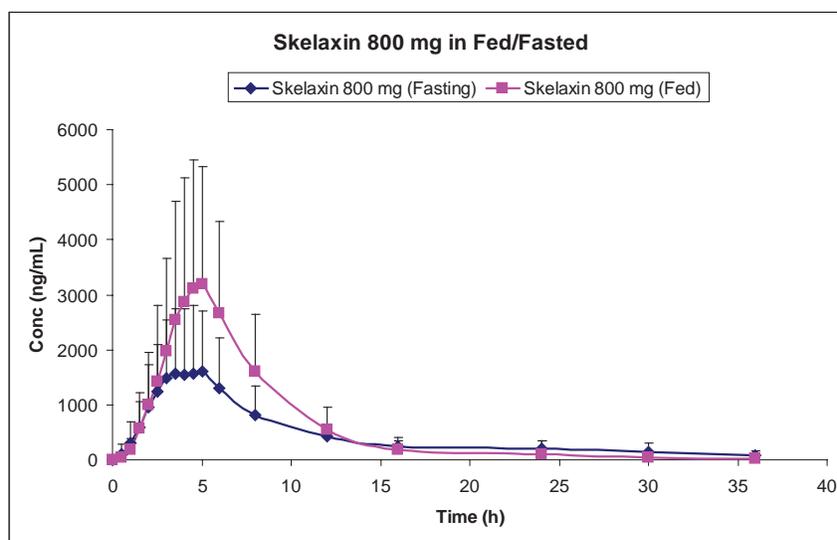


Figure 1. King Pharmaceutical's Skelaxin 800 mg (RLD) food effect (from Dr. Al Habet's review)

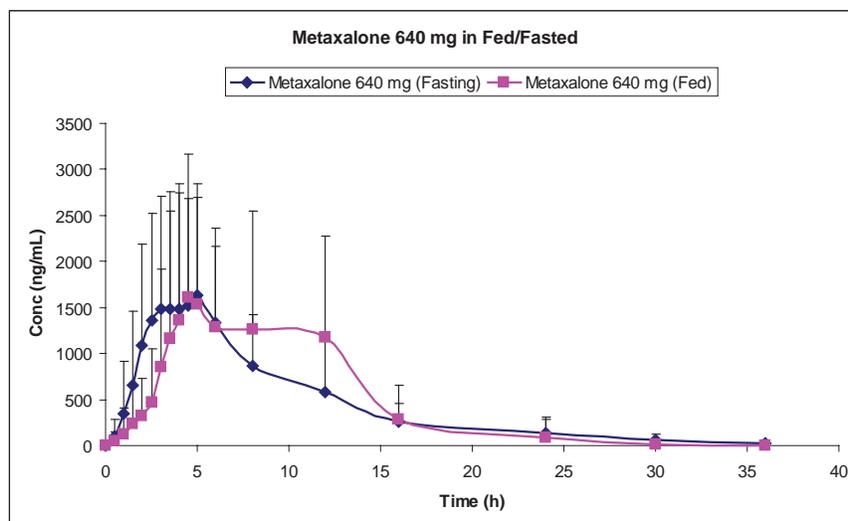


Figure 2. CorePharma's metaxalone 640 mg food effect (from Dr. Al Habet's review)

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

The applicant requested a waiver of pediatric studies in children below 12 years of age on the grounds that the product does not represent a meaningful therapeutic benefit over existing treatment for young pediatric patients. This is a reasonable request. Furthermore, this class of drug is not routinely recommended in young pediatric patients.

Musculoskeletal injuries are common in young patients, but they are usually self limiting and respond to rest and analgesics. This application was discussed at a PeRC meeting held on May 5, 2010. The PeRC agreed to waive pediatric study requirements below 12 years of age.

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 (b) (4) for the product, and later revised the trade name to (b) (4). DMEPA rejected both trade names because (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. Labeling was not finalized because the application will not be approved in this review cycle.

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 with minor changes.

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. However, the application cannot be approved because of a failed inspection of the drug product manufacturing facility.

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

Not relevant in this review cycle because the application will not be approved. During the original review it was tentatively decided that no specific risk management activities will be necessary.

d. Post-marketing Study Commitments

Not relevant in this review cycle because this application will not be approved. During the original review it was tentatively decided that there would be no post-marketing studies (PMR or PMC).

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/s/

BADRUL A CHOWDHURY
12/18/2013

Cross-Discipline Team Leader Review

Date	December 02, 2013
From	Nikolay Nikolov, M.D. Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Subject	Cross-Discipline Team Leader Review Update
NDA/BLA # Supplement#	NDA 22-503
Applicant	CorePharma, LLC
Date of Submission	June 18, 2013
PDUFA Goal Date	December 18, 2013
Proprietary Name / Established (USAN) names	METAXALONE/ 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:	Complete Response due to manufacturing inspection deficiencies

1. Introduction

This document updates the cross discipline team leader review of the NDA 22,503 for CorePharma's metaxalone product, which was originally submitted on August 18, 2009 and received a complete response action on June 11, 2010 due to manufacturing site inspection deficiencies pertaining to the CorePharma, Middlesex, New Jersey drug product finishing facility. The original application 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. Since the complete response (CR) action, the sponsor submitted two CR resubmission extension requests, on June 1, 2011 and May 29, 2012, which were granted.

The current CR resubmission was submitted on June 18, 2013, with a cover letter stating that the sponsor considers the deficiencies identified with the complete response 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 has found that the firm was not ready for pre-approval inspection of NDA 22,503 (b) (4) and has demonstrated a lack of capacity to manufacture the drug products (CPGM 7346.832, Part V Item 1). In a

letter, dated September 13, 2013, CorePharma, LLC has stated they were not ready for pre-approval inspection for NDA 22,503 [REDACTED] ^{(b) (4)} and no proposed date for readiness has been provided. The sponsor has not provided any indication that it would be ready prior to the December 18th, 2013, the PDUFA goal date for NDA 22,503. The Office of Compliance has determined the need for a follow-up inspection with pre-approval specific coverage. Based on the available information, the CDER, Office of Compliance, Division of Good Manufacturing Practice Assessment (DGMPA) has recommended withholding approval for these applications, including NDA 22,503. I concur with DGMPA's recommendation.

2. Background

Refer to Section 1, Introduction.

3. CMC/Device

Primary CMC Reviewer: Edwin Jao, Ph.D.
CMC Supervisor: Prasad Peri, Ph.D.

No new CMC information was provided in this submission.

- **Facilities review/inspection**

Compliance Officer: Robert H. Wittorf, Pharm.D.
NDMAB Acting Team Leader: Mahesh Ramanadham, Pharm.D.
NDMAB Branch Chief: Tara Gooen

A manufacturing inspection at CorePharma, LLC facility by the New Jersey District Office (NWJ-DO) from September 11 to 13, 2013 has found that the firm was not ready for pre-approval inspection of NDA 22,503 and has demonstrated a lack of capacity to manufacture the drug products. In a letter, dated September 13, 2013, CorePharma, LLC has stated they were not ready for pre-approval inspection for NDA 22,503 and no proposed date for readiness has been provided. The sponsor has not provided any indication that it would be ready prior to the December 18th, 2013, the PDUFA goal date for NDA 22,503. The Office of Compliance has determined the need for a follow-up inspection with pre-approval specific coverage. Based on the available information, the CDER, Office of Compliance, Division of Good Manufacturing Practice Assessment (DGMPA) has recommended withholding approval for these applications, including NDA 22,503. I concur with DGMPA's recommendation.

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 application. 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 exposure), but bioequivalence under fed conditions was not considered necessary for approval, as the Skelaxin does not have any specific instructions regarding administration with or without food.

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

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

The sponsor has no ongoing clinical program; however in this submission the sponsor has provided a safety update from the published literature. Dr. Keith's 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 package label. I concur with Dr. Keith's assessment of the updated safety information and conclusions.

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 application

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**

No issues were identified to trigger the AIP.

- **Exclusivity or patent issues of concern**

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. The applicant submitted Form 3542a attesting that there are no relevant patents for which a claim of patent infringement could be reasonably asserted. In any case, because this application will not be approved, patent or exclusivity issues are moot.

- **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, the applicant informed the Agency that they would not submit a proprietary name for this NDA prior to approval [REDACTED] (b) (4)

[REDACTED] 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**

Revised labeling and container labels were provided in this resubmission. However, because agreed-upon labeling was negotiated with the sponsor in the first review cycle, and because of an anticipated complete response action due to the outstanding inspection deficiencies, no additional labeling edits were discussed with the sponsor at this time. Labeling edits will be negotiated with the sponsor in the next review cycle should the sponsor submit a new application.

- **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 review team has found that the sponsor is not ready for a pre-approval facilities inspection which would preclude approval of this NDA, and I concur. Should these deficiencies be addressed 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 or commitments are recommended by the review team.

- **Recommended Comments to Applicant**

No issues remain that warrant comment, with the exception of inspection of the manufacturing facilities. Comments pertaining to this issue will be relayed as they are finalized.

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/s/

NIKOLAY P NIKOLOV
12/02/2013

CLINICAL REVIEW

Application Type NDA
Submission Number 22-503 (response to CR)

Letter Date June 18, 2013
Stamp Date June 18, 2013
PDUFA Goal Date December 18, 2013

Reviewer Name Keith M Hull, MD, PhD
Review Completion Date October 8, 2013

Established Name metaxalone
(Proposed) Trade Name TBD
Therapeutic Class Muscle Relaxant
Applicant Corepharma LLC
Priority Designation S

Formulation 640 mg tablets

Proposed Dosing Regimen Adults & Children >12 yo: 640 mg p.o. QID

Indication Adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions

Intended Population Adults and children older than 12 years with musculoskeletal pain

TABLE OF CONTENTS

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	3
1.1	Recommendation on Regulatory Action.....	3
1.2	Risk-Benefit Assessment.....	4
1.3	Recommendations for Postmarketing Risk Management Activities	4
2	INTRODUCTION AND REGULATORY BACKGROUND.....	5
2.1	Product Information.....	5
2.2	Currently Available Treatments for Proposed Indications	6
2.3	Availability of Proposed Active Ingredient in the United States.....	6
2.4	Important Safety Issues with Consideration to Related Drugs	6
3	ETHICS AND GOOD CLINICAL PRACTICES	7
3.1	Submission Quality and Integrity	7
3.2	Compliance with Good Clinical Practices	7
3.3	Financial Disclosures.....	7
4	SIGNIFICANT EFFICACY OR SAFETY FINDINGS RELATED TO OTHER REVIEW DISCIPLINES.....	8
4.1	Chemistry Manufacturing and Controls	8
4.2	Clinical Microbiology.....	8
4.3	Preclinical Pharmacology/Toxicology.....	8
4.4	Clinical Pharmacology	8
5	SOURCES OF CLINICAL DATA AND REVIEW STRATEGY	11
5.1	Review Strategy.....	11
5.2	Discussion of Individual Studies	11
6	REVIEW OF EFFICACY	13
7	REVIEW OF SAFETY.....	15
8	POST-MARKETING EXPERIENCE	17
9	APPENDICES	19
9.1	Literature Review/References	19
9.2	Labeling Recommendations	20
9.3	Advisory Committee Meeting	20

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This marketing application is for approval of metaxalone 640 mg (proposed trade name to be determined) as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified but may be related to its sedative properties. The application was filed under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and consists of a single bioavailability study in 48 healthy volunteers comparing metaxalone 640 mg to the reference listed drug (RLD), Skelaxin 800 mg. On June 11, 2010 the sponsor was notified that their application was receiving a Complete Response action due to deficiencies related to facility inspections. The sponsor has submitted a Complete Response resubmission that they believe adequately addresses the deficiencies. However, the facilities re-inspection is pending at the time of this review. The sponsor has also included a safety update from the published literature regarding the safety of metaxalone, as they have no ongoing clinical studies or trials with their metaxalone product. Review of the additional data did not demonstrate any new safety signals and is consistent with information already included in the approved label for metaxalone and the proposed package label.

Results from the bioavailability study, submitted in the original NDA, demonstrated that the metaxalone 640 mg formulation is bioequivalent to Skelaxin 800 mg in the fasted state; however, in the fed state, the C_{max} and AUC concentrations of the metaxalone 640 mg formulation are lower than Skelaxin 800 mg. Thus, in regards to the fed state, the two drugs are not bioequivalent. 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. Therefore, the Agency's standard for bioequivalence in the fasted state, and extrapolation of efficacy based on meeting this standard, could reasonably be applied in this case.

Safety analyses were provided on data from the Applicant's pharmacokinetic (PK) studies, and through a search of the FDA Adverse Events Reporting System (AERS) database. Given that serum concentrations of the metaxalone 640 mg formulation are either equivalent or lower than the approved formulation of Skelaxin 800 mg, an increased risk of toxicity to patients would not be anticipated. Overall, no new safety signals were identified with the metaxalone 640 mg formulation or the RLD, Skelaxin.

Therefore, from a clinical standpoint, this reviewer believes that the data submitted in this application are adequate to approve metaxalone 640 mg tablets with labeling that

mirrors the RLD, Skelaxin; provided that the inspectional deficiencies have been adequately addressed.

1.2 Risk-Benefit Assessment

The data presented in this application support the conclusion that metaxalone 640 mg tablets taken 3 to 4 times daily would have a similar risk-benefit profile to the RLD, Skelaxin, or could even exhibit a better safety profile with respect to concomitant food ingestion, given its relative lack of food effect compared to the RLD. However, the potential exists for medical errors related to confusion regarding the different nominal dose. This would be limited to instances where a prescriber or patient might errantly conclude that the 640 mg tablet should be taken as 1.5 tablets to approximate the effect of 800 mg Skelaxin. In these instances, a patient may experience excess sedation or other common adverse effects of metaxalone, but this is unlikely to be life-threatening. The package insert and patient information for the 640 mg metaxalone tablet would need to adequately address and warn against this scenario.

1.3 Recommendations for Postmarketing Risk Management Activities

Given the long history of clinical use of Skelaxin (metaxalone), the well-known adverse event (AE) profile associated with the drug, and the lack of additional safety signals in this review, no additional postmarketing risk management activities are required for the proposed indication.

2 Introduction and Regulatory Background

Skelaxin was originally approved by the Agency in 1962 for the relief of discomfort associated with acute musculoskeletal conditions. However, in 1970 as part of the Agency's Drug Efficacy Study Implementation (DESI) program, the FDA concluded that there was a lack of substantial evidence demonstrating the efficacy of Skelaxin based on a report received from the National Academy of Sciences/National Research Council. In 1972, the Agency proposed to withdraw approval of Skelaxin but permitted interested parties the opportunity to request a hearing in support of allowing Skelaxin to remain in the marketplace. In 1974, King Pharmaceuticals successfully presented evidence to the FDA demonstrating the effectiveness of Skelaxin for the relief of the discomfort associated with acute painful musculoskeletal conditions and Skelaxin was permitted to be marketed. Skelaxin is currently available as an 800 mg tablet containing the active ingredient metaxalone.

Corepharma LLC has submitted the present NDA under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for an alternative formulation of metaxalone (Skelaxin[®]) 640 mg tablets (as opposed to the currently market 800 mg tablets) for an indication as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. With the exception of changes specific to the new 640 mg formulation in relevant sections (i.e., Strengths, Description, Clinical Pharmacology, and How Supplied/Storage and Handling), the proposed package insert for the 640 mg metaxalone product is (b) (4)

2.1 Product Information

Chemically, metaxalone is 5-[(3,5-dimethylphenoxy) methyl]-2-oxazolidone with an empiric formula of $C_{12}H_{15}NO_3$ and a molecular weight of 221.25. Metaxalone is a white to almost white, odorless crystalline powder freely soluble in chloroform, soluble in methanol and in 96% ethanol but insoluble in water. The current product formulation consists of a tablet containing the active ingredients (b) (4) metaxalone (b) (4) and metaxalone (b) (4). Inactive ingredients include lactose monohydrate, FD&C Yellow #6, propylene glycol alginate, alginic acid, povidone, magnesium stearate, (b) (4)

The mechanism of action of metaxalone in humans has not been established but may be due to general nervous system depression. Metaxalone has no direct action on the contractile mechanism of striated muscle, the motor end plate, or the nerve fiber.

2.2 Currently Available Treatments for Proposed Indications

Numerous treatments are currently used for the discomfort associated with musculoskeletal pain and selection of therapy depends on many factors including the underlying etiology of the discomfort. However, musculoskeletal pain related to injury, strains/sprains, or repetitive use syndromes are typically treated with analgesics such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., ibuprofen, naproxen), opioids (e.g., hydrocodone) or so-called “muscle relaxants” (e.g. cyclobenzaprine). Metaxalone represents one of a number of drugs from the “muscle relaxant” class of therapeutics and is typically used in conjunction with non-pharmacologic therapies such as physical therapy.

2.3 Availability of Proposed Active Ingredient in the United States

Skelaxin was originally approved by the Agency in 1962 for the relief of discomfort associated with acute musculoskeletal conditions and has been available from the manufacturer King Pharmaceuticals as an 800 mg tablet.

2.4 Important Safety Issues with Consideration to Related Drugs

Metaxalone is generally well-tolerated with a favorable risk-benefit ratio. The most serious safety issue with metaxalone appears to be its ability to enhance the effects of alcohol and other CNS depressants and potentially impairing mental and/or physical abilities required for performance of hazardous tasks. The most frequent adverse effects reported with metaxalone include drowsiness, dizziness, headache, nervousness, nausea/vomiting, and gastrointestinal upset. Hypersensitivity, leucopenia, hemolytic anemia, and jaundice have been reported. Deaths have resulted due to deliberate/accidental overdoses especially when used in combination with antidepressants and alcohol.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The application was complete, well-organized, and uncomplicated in hyperlinking references as necessary. The Division of Scientific Investigations (DSI) audited two sites: Cetero Research, East Grand Forks, MN (clinical site) and [REDACTED] (b) (4) (analytical site). No issues were identified at the East Grand Forks site; however, at the [REDACTED] (b) (4) site, DSI reported two minor deficiencies as follows:

- failure to establish written procedures for the assessment of instrumental carryover during chromatographic analysis of study samples and for criteria to determine reprocessing of chromatographic data in analytic runs
- failure to document justification for changing chromatogram integration parameters during validation and study.

In their final report, DSI concluded that data from Study R08-0838 are acceptable for Agency review and that the [REDACTED] (b) (4) must document justifications of chromatogram re-integration and run reprocessing for future studies.

3.2 Compliance with Good Clinical Practices

The Applicant certified that submitted clinical study was conducted in compliance with good clinical practice guidelines. Quality control procedures to insure that the study was conducted, and that the data were generated, documented, and reported in compliance with the protocol, GCP and applicable regulatory documents.

3.3 Financial Disclosures

The sponsor has adequately disclosed financial arrangements with the main clinical investigator and sub-investigators as recommended in the FDA guidance for industry and no potential conflicts of interest were identified.

4 Significant Efficacy or Safety Findings Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry Manufacturing and Control's portion of this application was reviewed by Elsbeth Chikhale, PhD who recommended approval of the application. Please refer to Dr. Chikhale's review for further discussion of the Chemistry Manufacturing and Controls portion of this application.

4.2 Clinical Microbiology

Not applicable to this application.

4.3 Preclinical Pharmacology/Toxicology

The Pharmacology/Toxicology portion of this application was reviewed by Jay Chang, PhD who recommended approval of the application. Please refer to Dr. Chang's review for further discussion of the non-clinical program of this application.

4.4 Clinical Pharmacology

The Clinical Pharmacology portion of this application was reviewed by Sayed Al Habet, RPh, PhD. Please refer to Dr. Sayed Al Habet's review for further discussion of the clinical pharmacology portion of this application.

Briefly, Study R08-0838 assessed equivalency in terms of C_{max} and AUC between the test product, metaxalone 640 mg tablets, to the RLD, Skelaxin 800 mg tablets. The study was conducted in 47 healthy volunteers in fasted and fed conditions as follows:

- Treatment A (Fasted, Study Drug): Single dose of 640 mg metaxalone tablets after an over night fast
- Treatment B (Fed, Study Drug): Single dose of 640 mg metaxalone tablets 30 min after a high-fat breakfast
- Treatment C (Fasted, RLD): Single dose of 800 mg Skelaxin® tablets after an over night fast
- Treatment D (Fed, RLD): Single dose of 800 mg of Skelaxin® tablets 30 min after a high-fat breakfast

Blood samples were collected at appropriate time-points over 36 hours.

Results from the study demonstrated that the plasma concentration-time profiles of metaxalone 640 mg were comparable to Skelaxin 800 mg tablets under fasted conditions (Table 1). The 90% CI for both the C_{max} and AUC were within the 80% to 125% bioequivalence (BE) limits in both treatment arms in the fasted state.

Table 1. Pharmacokinetic Parameters Following Metaxalone 640 mg and Skelaxin 800 mg Tablets in Fasted Subjects.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	Metaxalone Tablets (640 mg) Fasting	SKELAXIN® Tablets (800 mg) Fasting	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	13686.84	13907.27	98.41	(90.74, 106.74)
AUC _{0-inf} (ng·hr/mL)	13988.59	14866.84	94.09	(87.12, 101.62)
C _{max} (ng/mL)	1798.83	1735.28	103.66	(88.64, 121.24)

In contrast to the fasted state, the plasma concentration-time profile of metaxalone 640 mg metaxalone tablets was significantly lower than that of Skelaxin 800 mg tablets in subjects in the fed state (Table 2). The C_{max} and AUC in the fed state were approximately 28% and 25% lower after metaxalone 640 mg metaxalone compared to Skelaxin 800 mg, respectively. In the fed state, the 90% CI for both C_{max} and AUC were outside the 80% to 125% BE limits.

In contrast to the metaxalone 640 mg tablet, food substantially increased the absorption of the RLD, Skelaxin 800 mg tablet (Table 2). The C_{max} and AUC were approximately 75% and 30% higher in fed state than in fasted state, respectively. The food effect related to Skelaxin 800 mg tablets is already documented in the currently approved label and food effect data from application is consistent with what is already included in the RLD label. When the metaxalone 640 mg tablet was given with food, the absorption phase seemed to be extended; however, the T_{max} in fasted and fed conditions appears to occur at the same time.

Table 2. Pharmacokinetic Parameters Following Metaxalone 640 mg and Skelaxin 800 mg Tablets in Fed Subjects.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	SKELAXIN® Tablets (800 mg) Fed	% Ratio	90% CI
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)
C _{max} (ng/mL)	2207.56	3046.51	72.46	(61.96, 84.75)

Overall, metaxalone 640 mg tablet is equivalent to Skelaxin 800 mg only under fasted conditions and not under fed conditions. Food increased the C_{max} after metaxalone

640 mg tablet by approximately 23% with no change in the AUC compared to that after fasted condition while food increased the C_{max} and AUC of the Skelaxin 800 mg tablet by approximately 75% and 30%, respectively. The data from this study is in general consistent with the food effect in the currently approved label for Skelaxin 800 mg tablet. Additionally, the two products are not bioequivalent when administered in either females or males alone or under fed/fasted conditions; however, this is not an issue as the Agency BA/BE guidance discourages stratification of the bioequivalence data by gender. Thus, the combined data from all fasted subjects (n=47) is considered adequate to conclude that the two products exhibit equivalent systemic exposure only under fasted condition. Overall, the data derived from the pharmacokinetic studies appear to be extrapolable to the clinical setting. The efficacy of the metaxalone 640 mg tablets should be relatively equivalent to the RLD, and theoretically, the safety profile could be better given that metaxalone 640 mg tablet bioavailability is constant regarding food intake in contrast to the increased concentrations of Skelaxin 800 mg tablets in the fed state. Labeling language in reference to substitution issues between Skelaxin 800mg and metaxalone 640 mg tablets need to be addressed in the package insert as appropriate in light of different nominal doses between the two products.

5 Sources of Clinical Data and Review Strategy

5.1 Review Strategy

The data in this application are derived from a single bioavailability study which was designed as a randomized, single-dose, four-way, open-labeled, crossover trial evaluating fasted and fed subjects and comparing Corepharma's drug product (b) (4) metaxalone 640 mg with the RLD, Skelaxin® 800 mg tablets. The primary focus of the clinical review is on the safety data generated from the 48 subjects enrolled in the single PK study submitted in the application and review of the Agency's Adverse Event Reporting System (AERS) database.

5.2 Discussion of Individual Studies

Study R08-0838, entitled "A Relative Bioavailability Study of 640 mg Metaxalone Tablets versus 800 mg Skelaxin® Tablets under Fasting and Fed Conditions", was a randomized, single-dose, four-way, open-label, crossover bioavailability study that enrolled 48 healthy adult volunteers (29 males and 18 females). Subjects were randomized equally to one of four treatment arms:

- Treatment A (fasted): metaxalone 640 mg p.o.
- Treatment B (fed): metaxalone 640 mg p.o. (high fat breakfast)
- Treatment C (fasted): Skelaxin 800 mg p.o.
- Treatment D (fed): Skelaxin 800 mg p.o. (high fat breakfast)

Throughout the study subjects were re-allocated to a different treatment arm with a minimum of a 7 day washout period between drug administration based on the following randomization sequence :

- Sequence 1: ABCD
- Sequence 2: BDAC
- Sequence 3: CADB
- Sequence 4: DCBA

Major Inclusion and Exclusion data included:

- Able to competently agree and sign the improved consent form
- Complete screening process within 4 weeks prior to Period 1 dosing
- Healthy male and female subjects ≥18 years of age
- Body Mass Index between 18-32 kg/m², inclusive, and weigh ≥110 lbs
- Generally healthy with no presence or history of disease involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, neurologic systems, or abnormal laboratory values

- Female subjects of childbearing potential must be practicing an acceptable method of birth control as judged by the investigator or be postmenopausal for ≥ 1 year and if < 55 years of age has a documented FSH level ≥ 30 mIU/mL or is surgically sterile
- Could not have received an investigational drug within 28 days of Period 1 dosing
- Could not have an active infection including HBV, HCV, or HIV
- Could not have a positive drug screen or history of alcohol or drug abuse within the past year
- Could not have a history of clinically significant allergies to foods or drugs
- Females Could not be pregnant or breastfeeding over the course of the study

Subjects were monitored throughout the confinement portion of the study and included vitals signs, physical exam, clinical laboratory tests (CBC, Clinical Chemistry, HBV, HCV, and HIV antibody screening, pregnancy screening), and urinalysis at baseline and at the end of the study period. Additionally, vital signs, and adverse events queries were performed after testing period and again at the completion of the study. The demographic characteristics of the enrolled subjects are shown in Table 3.

Table 3. Demographic Characteristics of Subjects Enrolled in Study R08-0838

	Subjects (n=48)
Age (Years) Mean \pm SD	35 \pm 14
Sex, n (%) Male	30 (63%)
Race, n (%) White Native American/Hawaiian/Pacific Islander Black Asian	40 (85%) 5 (10%) 2 (4%) 1 (2%)
BMI Mean \pm SD	25 \pm 4

6 Review of Efficacy

Efficacy Summary

The application contains a single bioequivalence study that was not designed with an efficacy component. No clinical trials of metaxalone 640 mg tablets were performed to assess efficacy. As mentioned in Section 2, above, the RLD, Skelaxin, underwent the DESI process and was ultimately determined to be effective. The randomized, controlled studies that formed the basis of this efficacy assessment are described in Table 4, below. The primary study supporting the determination that Skelaxin was effective for the currently approved indication was the 1974 study by Dent, et al.

Table 4. Referenced Literature used for the Regulatory Actions of Skelaxin

Study author (year ¹)	Design	Treatment Groups	Endpoints	Results
Dent ² (1974)	R, DB, MC 8-day study in patients with acute muscle spasm (≤ 14 days duration)	1) Skelaxin 800 mg QID (dose can be decreased to 400 mg QID) (n=113) 2) Placebo (n=115)	23 total endpoints 1) <u>16 endpoints</u> : assessed by patient and investigator on a 0-4 scale (absent, mild, moderate, severe, very severe) at Days 2 & 8: muscle spasm, limitation of motion, local pain or tenderness, & interference with daily activities 2) <u>4 endpoints</u> : on Days 2 & 8 assessed by investigator and patient global (recovered, much better, better, same, worse) 3) <u>2 endpoints</u> : need for physiotherapy or analgesics on Days 2 & 8 4) <u>1 endpoint</u> : patient satisfaction on Day 8	FDA medical reviewer felt that this study was an adequate and well controlled study <u>Efficacy</u> : Greater improvement in the Skelaxin group compared to placebo group in spasm, motion, pain, activities, and global. <u>Safety</u> : No SAEs <u>Adverse reactions</u> : sedation, nausea
Diamond ³ (1966)	R, DB, PC, 10-day study of patients with acute muscle spasm, pain, tenderness, and restriction of motion	N=100 1) Metaxalone 800 mg QID 2) Placebo QID	Multiple endpoints including muscle spasm relief, pain relief	<u>Efficacy</u> : No difference in muscle spasm relief and no difference in pain relief <u>Safety</u> : No SAEs
Fathie ⁴ (1964)	R, DB, PC, 7-day study of patients with LBP	N=100 1) Metaxalone 800 mg QID 2) Placebo QID	Multiple endpoints including muscle spasm and range of motion	FDA reviewer stated that this study could not serve as an adequate and well-controlled study and could not support the efficacy of Skelaxin because of multiple design issues <u>Safety</u> : No SAEs

Source: Eric Brodsky, M.D.

In summary, results from the bioavailability study demonstrated that the metaxalone 640 mg formulation is bioequivalent to Skelaxin 800 mg in the fasted state; however, in the fed state, the C_{max} and AUC concentrations of the metaxalone 640 mg formulation are lower than Skelaxin 800 mg. Thus, in regards to the fed state, the two drugs are not bioequivalent. 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. Therefore, the Agency's standard for bioequivalence in the fasted state, and extrapolation of efficacy based on meeting this standard, could reasonably be applied in this case.

7 Review of Safety

An adverse event (AE) was defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient administered study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not the event was considered causally related to the use of the product.

Subjects in Study R08-0838 were monitored for clinical and laboratory evidence of AEs throughout the study. The investigators also assessed and recorded any AE in detail including the date of onset, description, severity, time course, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for events not considered "probably related" to study drug, final diagnosis (if known), and any action(s) taken. For AEs to be considered sporadic, the events must be of similar nature and severity. All AEs were recorded regardless of if the response was due to a query, observed by site personnel, or reported spontaneously by the patient. All AEs were followed to a satisfactory conclusion.

Serious adverse events (SAE) were defined as any event that met any one of the following criteria:

- Life-threatening
- Hospitalization
- Prolongation of hospitalization
- Congenital anomaly
- Persistent of significant disability/incapacity
- Important medical event requiring medical or surgical intervention to prevent a serious outcome
- Spontaneous abortion
- Elective abortion

There were no deaths or SAEs reported in Study R08-0838 and no subjects were discontinued due to an AE. Subject 003 withdrew from the study due to personal reasons following a single dose of study drug. This subject was included in the safety analysis of the study but was not included in the pharmacokinetic/bioavailability analyses.

Overall, eight subjects experienced 14 AEs, all of which were mild to moderate in severity (Table 2).

TABLE 2. Study R08-0838 Adverse Events by Treatment Group

Body System/AE	AE Incidence by Treatment Group			
	Treatment A (n=48)	Treatment B (n=47)	Treatment C (n=47)	Treatment D (n=47)
Eye Disorders				
Eye irritation	-	-	1 (2%)	-
Gastrointestinal				
Abdominal pain	-	-	-	1 (2%)
Diarrhea	-	1 (2%)	-	-
Nausea	1 (2%)	-	-	-
Vomiting	-	1 (2%)	-	-
General Disorders				
Fatigue	-	1 (2%)	-	-
Musculoskeletal & Connective Tissue				
Muscle spasm	1 (2%)	-	-	-
Myalgia	1 (2%)	-	-	-
Nervous System				
Dizziness	-	-	2 (4%)	1 (2%)
Headache	-	-	1 (2%)	-
Lethargy	-	-	1 (2%)	-
Skin & Subcutaneous Tissue				
Rash	-	-	1 (2%)	-
Total	3 (6%)	1 (2%)	5 (11%)	2 (4%)

Adverse events were similar in metaxalone-treated subjects (6 AEs) compared to the referenced licensed drug Skelaxin (8 AEs). No significant changes in laboratory values were noted. All AEs reported during Study R0-0838 are listed in the current Skelaxin label and no new safety signals were identified.

In summary, safety analyses were based on data from the Applicant's PK studies, and through a search of the FDA AERS database. Given that serum concentrations of the metaxalone 640 mg formulation are either equivalent or lower than the approved formulation of Skelaxin 800 mg, an increased risk of toxicity to patients would not be anticipated. Overall, no new safety signals were identified with the metaxalone 640 mg formulation or the RLD, Skelaxin; however, the potential exists for medical errors related to confusion regarding the different nominal dose. This would be limited to instances where a prescriber or patient might errantly conclude that the 640 mg tablet should be taken as 1.5 tablets to approximate the effect of 800 mg Skelaxin. In these instances, a patient may experience excess sedation or other common adverse effects of metaxalone, but this is unlikely to be life-threatening. The package insert and patient information for the 640 mg metaxalone tablet would need to adequately address and warn against this scenario.

8 Post-Marketing Experience

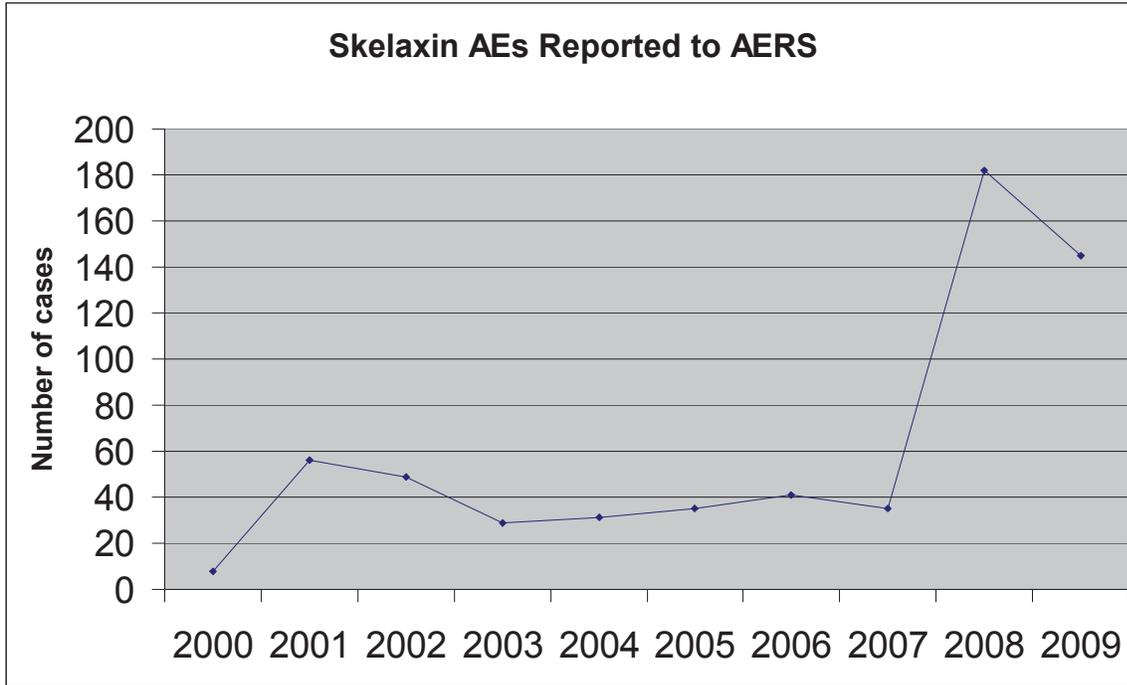
Given the limitations associated with safety data derived from this small bioavailability study in healthy volunteers, a search of the Agency's Adverse Event Reporting System (AERS) database was undertaken to better understand the rate of SAE and AEs associated with the referenced licensed drug Skelaxin.

An AERS search of the U.S. post-marketing AEs was performed for the period from January 2000 to April 2010 to determine the overall reporting rate of AEs associated with metaxalone.

After eliminating duplicates, cases that were clearly not related to Skelaxin, and cases associated with Skelaxin overdose, there were 42 SAEs reported over the period (approximately 5 SAEs per year). Of the 42 SAEs, 17 cases were related to allergic events, 2 were cases of liver failure, and 2 were cases of idiopathic thrombocytopenic purpura. The remainder of cases were single occurrences of unexpected events, e.g., sepsis, myocardial infarction, eye redness. In most cases, concomitant medications were taken and the temporal relationship of Skelaxin use and the event was not clear. None of the 42 cases reported an association between an AE and fasted/fed state of the individual; thus, it was not possible to determine a relationship between metaxalone exposure and fasted or fed states. Approximately (b) (4) Skelaxin prescriptions are dispensed yearly, thus the approximate annual reporting rate is 5 SAE cases per (b) (4) (b) (4) prescriptions dispensed.

From 2000 to 2007 the rate of AEs averaged between 30 to 60 AE reports per year (Figure 1). In 2007, the rate of reported AEs spiked to over 180 mostly as a result of reports submitted by the manufacturer. No change in formulation or manufacturing process occurred to explain this increase; however the increase in reports appeared to coincide with Citizen Petitions submitted to the Agency pertaining to Skelaxin. Review of the AEs were consistent with the approved label and most frequently included reports of drowsiness, dizziness, headache, nervousness, nausea, vomiting, and gastrointestinal upset. No new safety signals were identified.

Figure 1. AERS Database Adverse Event Reports for Skelaxin from 1/1/2000 to 4/1/2010



9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

In general, the metaxalone 640 mg tablet label can mirror the Skelaxin 800 mg tablet label given the PK data; however, labeling language in reference to substitution issues between Skelaxin 800 mg and metaxalone 640 mg tablets need to be addressed in the package insert as appropriate in light of different nominal doses between the two products. For example, “patients should not exceed 640 mg metaxalone or use metaxalone in combination with Skelaxin”.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was conducted for this application.

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/s/

KEITH M HULL
10/10/2013

SUMMARY REVIEW OF REGULATORY ACTION

Date: June 11, 2010

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: August 18, 2009

PDUFA Goal Date: June 20, 2010

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: Complete Response

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 reference listed drug (RLD) and relies on a clinical pharmacology study to show bioequivalence (BE) to the RLD. This summary review provides an overview of the application. The application cannot be approved because of a failed inspection of the final drug product manufacturing facility. Also, CorePharma has not provided 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.

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 data³ in 1974, metaxalone was determined to be effective.

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.

The formulation of CorePharma's product is different compared to the RLD. CorePharma's product contains a lower nominal dose, with systemic exposure similar to the RLD, and 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. However, CorePharma has not provided appropriate patent certifications and failed to comply with the statutory requirements for sending notice of paragraph IV certification to the NDA holder and each patent owner, .

3. Chemistry, Manufacturing, and Controls

The proposed commercial drug product is a tablet formulation that contains 640 mg metaxalone with standard compendial excipients. Unlike the RLD, the drug substance in CorePharma's product is (b) (4)

(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 a withhold recommendation for the drug product manufacturing facility at New Jersey because of a failed inspection. The various DMFs associated with the manufacture of the product are adequate. An expiry date of (b) (4) months is supported by submitted stability data.

4. Nonclinical Pharmacology and Toxicology

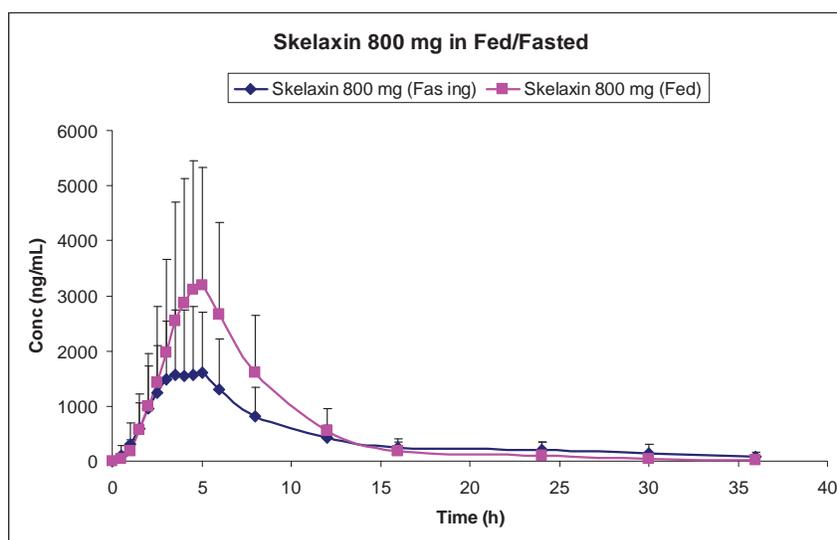
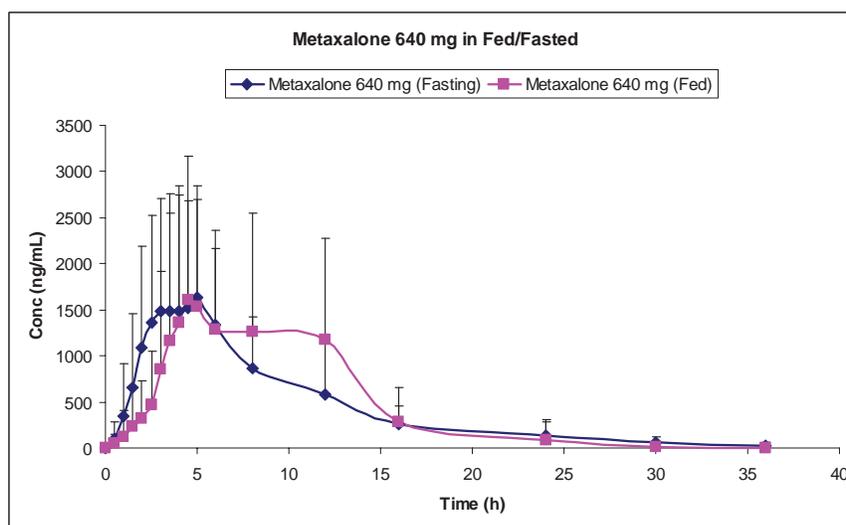
No new non-clinical toxicology studies were required or performed for this application.

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 RLD (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 RLD 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 the CorePharma's product and the RLD. The CorePharma's product was outside the BE limit under fed state, however, BE under fed state is not required as the RLD has no specific instructions regarding administration with or without food (Table 1). The data suggest that the RLD 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 RLD metaxalone

	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

The applicant requested a waiver of pediatric studies in children below 12 years of age on the grounds that the product does not represent a meaningful therapeutic benefit over existing treatment for young pediatric patients. This is a reasonable request. Furthermore, this class of drug is not routinely recommended in young pediatric patients. Musculoskeletal injuries are common in young patients, but they are usually self limiting and respond to rest and analgesics. This application does not trigger PREA requirements. This application was discussed at a PeRC meeting held on May 5, 2010. The PeRC agreed to waive pediatric study requirements below 12 years of age.

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 DDMAC, or from other groups in CDER, except from DMEPA as discussed below under proprietary name.

12. Labeling

a. Proprietary Name

The applicant initially proposed the trade name (b) (4) for the product, and later revised the trade name to (b) (4). The Division of Medication Error and Prevention Analysis (DMEPA) rejected both the trade names (b) (4). The applicant has not submitted another trade name for consideration.

b. Physician Labeling

The applicant submitted a label in the Physician's Labeling Rule format that closely mirrors the RLD 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 by various disciplines of the Division and by DDMAC. Major labeling comments were communicated to the CorePharma and they agreed with the suggested changes. Labeling was not finalized because the application will not be approved in this review cycle.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, , and DMEPA, and found to be acceptable with minor changes.

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. However, the application cannot be approved because of a failed inspection of the drug product manufacturing facility. In addition, the applicant has not provided appropriate patent certifications and failed to comply with the statutory requirements for sending notice of paragraph IV certification to the NDA and each patent holder.

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 the RLD since the two products are bioequivalent. The observed apparent lack of food effect of the CorePharma's metaxalone compared to

the RLD 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

No specific risk management activities are necessary.

d. Post-marketing Study Commitments

There will be no post-marketing studies (PMR or PMC).

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22503

ORIG-1

COREPHARMA
LLC

 (b) (4)
640MG
(METAXALONE)

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

/s/

BADRUL A CHOWDHURY
06/11/2010

Cross-Discipline Team Leader Review

Date	May 21, 2010
From	Sarah Okada, M.D. Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22-503
Applicant	CorePharma, LLC
Date of Submission	August 18, 2009
PDUFA Goal Date	June 18, 2010
Proprietary Name / Established (USAN) names	To be determined / metaxalone
Dosage forms / Strength	640 mg tabs
Proposed Indication(s)	1. Adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful, musculoskeletal conditions
Recommended:	Approval, with revisions to proposed labeling

1. Introduction

The indication “relief of discomfort associated with acute painful musculoskeletal conditions” has historically been granted to muscle relaxants on the basis of demonstrated efficacy in clinical trials of acute musculoskeletal low back pain. In the United States, low back pain is the 5th most common reason for physician office visits, and 80% of primary care patients with low back pain were prescribed at least one medication at their initial office visit [Chou 2007]. Metaxalone comprises approximately (b) (4)% of the total market share of prescriptions for muscle relaxants (b) (4)

The muscle relaxant metaxalone was originally approved in 1962 (NDA 13-217) with the proprietary name, Skelaxin. The current NDA holder for NDA 13-217 is King Pharmaceuticals. Skelaxin underwent DESI review in 1970 and was initially determined ineffective, but with additional data presented by the sponsor, was given the final determination of effective “for the relief of discomforts associated with acute painful musculoskeletal conditions” in 1974. For various reasons, including a patented food-effect, no generic metaxalone products have yet been approved. (b) (4)

Table 1 Metaxalone ANDAs currently under review

Sponsor	ANDA	Dose	Submission Date
(b) (4)			

NDA 22-503 is a 505(b)(2) application for CorePharma’s 640 mg metaxalone tablets (proprietary name to be determined). This product, comprised of (b) (4) metaxalone, results in higher bioavailability than the reference listed drug (RLD), Skelaxin. Thus, the lower nominal dose in the applicant’s product results in similar fasted exposure as the RLD. Based on bioequivalence in the fasted state, the applicant proposes to market their metaxalone product with the same indication and similar labeling as the RLD. The proposed indication is: “as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute painful musculoskeletal conditions.” Although the nominal dose is different, exposure is similar, thus the applicant proposes to maintain the RLD dosing instruction of one tablet three to four times a day, for adults and children over 12 years of age.

The NDA contains a single clinical study: Study #R08-0838, is a four-way crossover relative bioavailability (BA) study in 47 healthy subjects comparing the 640 mg test product (CorePharma’s metaxalone) and the RLD, 800 mg Skelaxin® after ingestion of single-doses of each product under fasted and fed conditions. Review of NDA 22-503 focused on the following issues:

- Whether Study #R08-0838 provided adequate evidence that CorePharma’s 640 mg tablets are bioequivalent to the RLD, based on standard criteria
- Whether the difference in food-effect between the product and the RLD raised efficacy, safety, or regulatory issues that would preclude approval
- Legal and regulatory implications of approving a product of a different nominal dose but with similar exposure as a reference listed drug.

The submitted bioavailability study for CorePharma’s 640 mg metaxalone tablets was not conducted under IND. No pre-submission regulatory contact occurred between the applicant and the Division.

2. Background

Refer to Section 1, Introduction.

3. CMC/Device

CMC Reviewer: Elsbeth Chikhale, Ph.D.

CMC Team Leader: Prasad Peri, Ph.D.

This section is largely excerpted/adapted from Dr. Chikhale's review.

Summary: Dr. Chikhale did not identify any issues that would prevent approval of this application, pending final recommendations from the Office of Compliance regarding the cGMP status of the manufacturing, testing, and packaging facilities. No CMC-related Phase 4 commitments are recommended.

- **General product quality considerations**

1. Drug Product

The proposed drug product is an immediate release tablet, indicated for the relief of discomforts associated with acute, painful musculoskeletal conditions. The tablet is a 640 mg oval, (b) (4) peach tablet, debossed on one side (b) (4) and plain on the other side. The route of administration is oral. The proposed commercial drug product is manufactured by Corepharma LLC., in Middlesex, NJ. It is formulated as an (b) (4) immediate release tablet manufactured by (b) (4). The tablets are packaged in HDPE bottles with child resistant closures for direct sale to the user (150 cc bottles containing 100 tablets) (b) (4). The excipients consist of lactose monohydrate NF, FD&C yellow #6 (b) (4), propylene glycol alginate NF, alginic acid NF, povidone USP, and magnesium stearate NF.

The proposed storage condition for the drug product is at controlled room temperature (i.e. store at 20 °C - 25 °C (68 °F - 77 °F) (b) (4) (see USP controlled room temperature). The provided stability data support a shelf life of (b) (4) months (NOT the proposed (b) (4) months) when stored at room temperature conditions.

2. Drug Substance

The drug substance, metaxalone, is a previously approved drug substance, produced by chemical synthesis, with the chemical name of 5-(3,5-dimethylphenoxy)methyl]-2-oxazolidone. Metaxalone has a low aqueous solubility across pH range 1 to 7.5. The major difference, compared to the RLD, is (b) (4). All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of metaxalone are provided in the Drug Master Files (DMFs) (b) (4) held by (b) (4). A Letter of Authorization (LOA) allowing the Agency to refer to DMF (b) (4) was provided in the NDA. DMF (b) (4) was reviewed on 1/25/2010 (see separate review #9 by Elsbeth Chikhale, Ph.D.) and found adequate to support this NDA. The drug substance is manufactured in (b) (4).

- **Facilities review/inspection**

Manufacturing facilities were inspected in January 2010, and a Form 483 was issued. A final determination from the Office of Compliance regarding the acceptability of the inspection results and Form 483 response is still pending as of the time of this review.

- **Other notable issues (resolved or outstanding)**

Although the applicant proposed a (b) (4) month expiry, stability data support a shelf-life of (b) (4) months when stored at room temperature.

4. Nonclinical Pharmacology/Toxicology

Primary Pharmacology/Toxicology Reviewer: Jay H. Chang, Ph.D.

Pharmacology/Toxicology Supervisor: Adam Wasserman, Ph.D.

This section is largely excerpted/adapted from Dr. Chang's review.

Summary: Drs. Chang and Wasserman agree that there are no pharmacology/toxicology-related issues with NDA 22-503 that would preclude approval. If approved, the language from the RLD label pertaining to nonclinical information would be utilized. They are not recommending any requirements for additional nonclinical studies.

- **General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).**

As previously noted, NDA 22-503 was submitted via the 505(b)(2) pathway, with the RLD being King Pharmaceutical's Skelaxin 800 mg tablets (NDA 13-217). Prior to NDA submission, no INDs were submitted and no meetings were held with the Agency. No nonclinical studies were submitted with the NDA. This was determined to be acceptable by the Agency's pharmacology/toxicology team since the CorePharma metaxalone product is intended to be bioequivalent to the Skelaxin RLD, with the same indication and similar labeling to the RLD. The primary issues arising from the proposed formulation of the CorePharma metaxalone product are related to the levels of two excipients—propylene glycol alginate (PGA) and povidone (b) (4)—when ingested at the maximum recommended daily dose (MRDD). See "Other notable issues" section below.

- **Carcinogenicity**

No carcinogenicity studies were submitted with this NDA. According to the RLD Skelaxin® label, "the carcinogenic potential of metaxalone has not been determined." The same language is proposed for the CorePharma metaxalone label.

- **Reproductive toxicology**

No reproductive toxicology studies were submitted with this NDA. According to the RLD Skelaxin® label, "Reproduction studies in rats have not revealed evidence of impaired fertility or harm to the fetus due to metaxalone. Post marketing experience has not revealed evidence of fetal injury, but such experience cannot exclude the possibility of infrequent or subtle

damage to the human fetus. Safe use of metaxalone has not been established with regard to possible adverse effects upon fetal development. Therefore, metaxalone tablets should not be used in women who are or may become pregnant and particularly during early pregnancy unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.”

(b) (4)

- **Other notable issues (resolved or outstanding)**

The NDA applicant was advised via comments sent in the 74-day letter that nonclinical data and/or additional information would be required to justify the total daily intake (TDI) of the excipients propylene glycol alginate (PGA) and povidone (b) (4) which would result from consuming the maximum recommended daily dose (MRDD) of four CorePharma metaxalone tablets. Note that both of these inactive ingredients are present in marketed drugs approved in the U.S. for oral use and are within the maximum concentrations listed in the FDA Inactive Ingredient Guide (IIG) when considering a single CorePharma metaxalone tablet. However, the two excipients are in excess of the IIG-listed maximum concentrations when considering the MRDD of four tablets of CorePharma’s metaxalone product.

The NDA applicant subsequently submitted additional information from the literature to justify the levels of these two excipients. This included World Health Organization (WHO) Technical Reports which assigned a human “Acceptable Daily Intake” (ADI) of 70 mg/kg per body weight for PGA and an ADI of 50 mg/kg per body weight for povidone (specific K-grade not specified) based on a review of the available existing clinical literature and nonclinical toxicity study data. For an adult weighing 70 kg, the total daily intake (TDI) of the excipients from the proposed MRDD of CorePharma’s metaxalone tablets would translate to approximately (b) (4) % of the ADI set forth by the WHO for PGA and (b) (4) % of the ADI for povidone.

Dr. Chang also noted that the TDI of both PGA and povidone (b) (4) from the consumption of 4 CorePharma’s metaxalone tablets are exceeded in currently marketed FDA-approved drugs when used as recommended by their respective labels, which indicates that the Agency has previously determined that such levels are acceptable. For example, the TDI of PGA in CorePharma’s metaxalone tablets is more than (b) (4) lower than the level contained at the MRDD of the currently marketed drug Questran Light®, which contains cholestyramine, a drug that is administered orally to bind bile acids for the treatment of hypercholesterolemia. The TDI of povidone from 4 CorePharma metaxalone tablets is more than (b) (4) lower than the amount found at the MRDD of Colestid®, which is another approved orally administered bile acid sequestrant for the treatment of primary hypercholesterolemia. The Pharmacology/Toxicology review team concluded that, together, the information above provides adequate qualification for the levels of the inactive ingredients contained in the MRDD of CorePharma’s metaxalone tablets.

5. Clinical Pharmacology/Biopharmaceutics

Primary Clinical Pharmacology Reviewer: Sayed (Sam) Al Habet, R.Ph., Ph.D.

Clinical Pharmacology Team Leader: Suresh Doddapaneni, Ph.D.

ONDQA Biopharmaceutics Primary Reviewer: Sandra Suarez-Sharp, Ph.D.

ONDQA Biopharmaceutics Team Leader: Angelica Dorantes, Ph.D.

ONDQA Biopharmaceutics Supervisor: Patrick Marroum, Ph.D.

This section is excerpted/adapted from the reviews of Drs. Al Habet and Suarez-Sharp

Summary: The clinical pharmacology and biopharmaceutics review teams have found no issues that would preclude approval of NDA 22-503, presuming agreement can be reached with the NDA applicant on labeling revisions. No Phase 4 commitments are recommended by the clinical pharmacology and biopharmaceutics teams.

- **General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.**

The pivotal study demonstrating the bioequivalence of CorePharma's metaxalone product to the RLD was Study #R08-0838, a four-way relative bioavailability study in fed and fasted healthy subjects comparing the 640 mg test product (CorePharma's metaxalone) and the RLD, 800 mg Skelaxin®.

This was a single-dose, 4-period, 4-treatment, four-way crossover study in 47 healthy subjects with a minimum washout period of 7 days between treatments as follows:

- Treatment A (Fasted, Test): Single dose of 640 mg CorePharma metaxalone tablets after an overnight fast
- Treatment B (Fed, Test): Single dose of 640 mg CorePharma metaxalone tablets 30 min after high-fat breakfast
- Treatment C (Fasted, RLD): Single dose of 800 mg Skelaxin® tablets after an overnight fast
- Treatment D (Fed, RLD): Single dose of 800 mg of Skelaxin® tablets 30 min after high-fat breakfast

In each study period, serial blood samples for pharmacokinetic (PK) testing were collected over 36 hours for the determination of metaxalone concentrations in plasma.

Bioavailability Results, Fasted State

Results of this study confirmed the CorePharma 640 mg tablet metaxalone product met standard criteria for bioequivalence compared to the RLD, Skelaxin 800 mg tablets. Specifically, the 90% confidence interval (CI) for both C_{max} and AUC were within the 80% to 125% BE limits in the fasted state (see Table 2, below).

Table 2 Key PK Parameters for CorePharma’s Metaxalone Tablets vs. Skelaxin Tablets, Fasted State

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	Metaxalone Tablets (640 mg) Fasting	SKELAXIN® Tablets (800 mg) Fasting	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	13686.84	13907.27	98.41	(90.74, 106.74)
AUC _{0-inf} (ng·hr/mL)	13988.59	14866.84	94.09	(87.12, 101.62)
C _{max} (ng/mL)	1798.83	1735.28	103.66	(88.64, 121.24)

Source: Table 1.3.1 of Dr. Al Habet’s review

Bioavailability Results, Fed State

The CorePharma product was not bioequivalent to the RLD under fed conditions, however bioequivalence under fed conditions is not required in this case, as the RLD label has no specific instructions regarding administration of the RLD with or without food. Under fed conditions, the plasma concentration-time profile of metaxalone following 640 mg metaxalone tablet ingestion was significantly lower than after 800 mg Skelaxin® tablet ingestion (See Table 3 below). The C_{max} and AUC in fed state were approximately 28% and 25% lower after 640 mg metaxalone tablets compared to 800 mg Skelaxin® tablets, respectively. The 90% CI for both C_{max} and AUC were outside the 80% to 125% BE limits.

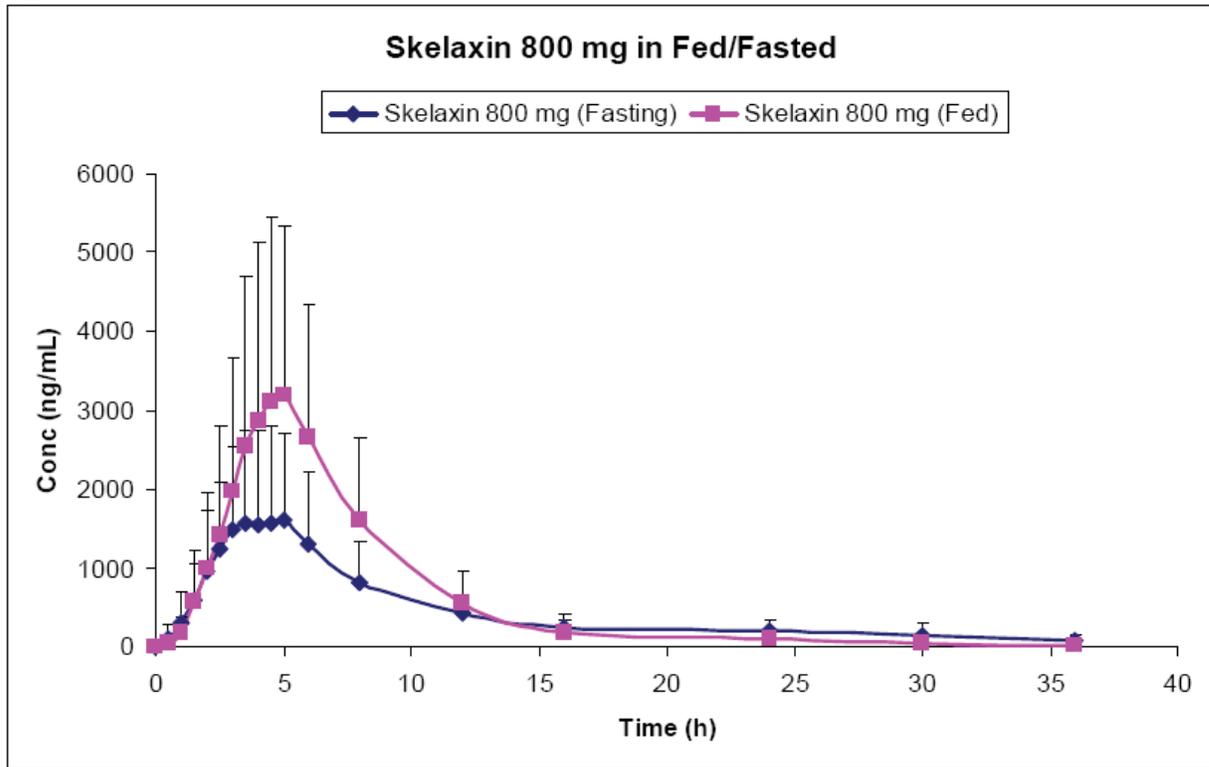
Table 3 Key PK Parameters for CorePharma’s Metaxalone Tablets vs. Skelaxin Tablets, Fed State

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	SKELAXIN® Tablets (800 mg) Fed	% Ratio	90% CI
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)
C _{max} (ng/mL)	2207.56	3046.51	72.46	(61.96, 84.75)

Source: Table 1.3.2 of Dr. Al Habet’s review

The RLD, Skelaxin, has a known large food effect, which reportedly has been patented by the innovator. As per results in the RLD label, ingestion of Skelaxin with food led to an almost doubling of C_{max} (177% in one study, 194% in a second study) with a lesser but still marked increase in AUC parameters as well. These results are consistent with results for Skelaxin in Study R08-0838 (see Figure 1, below). Despite this large food effect, the RLD label does not contain instructions or restrictions pertaining to ingestion of Skelaxin relative to food. This is likely due to a lack of exposure-response information for metaxalone to support a need for a restriction relative to food. Additionally, there is no evidence to suggest a significant safety issue pertaining to this food effect, as discussed in Section 8 below.

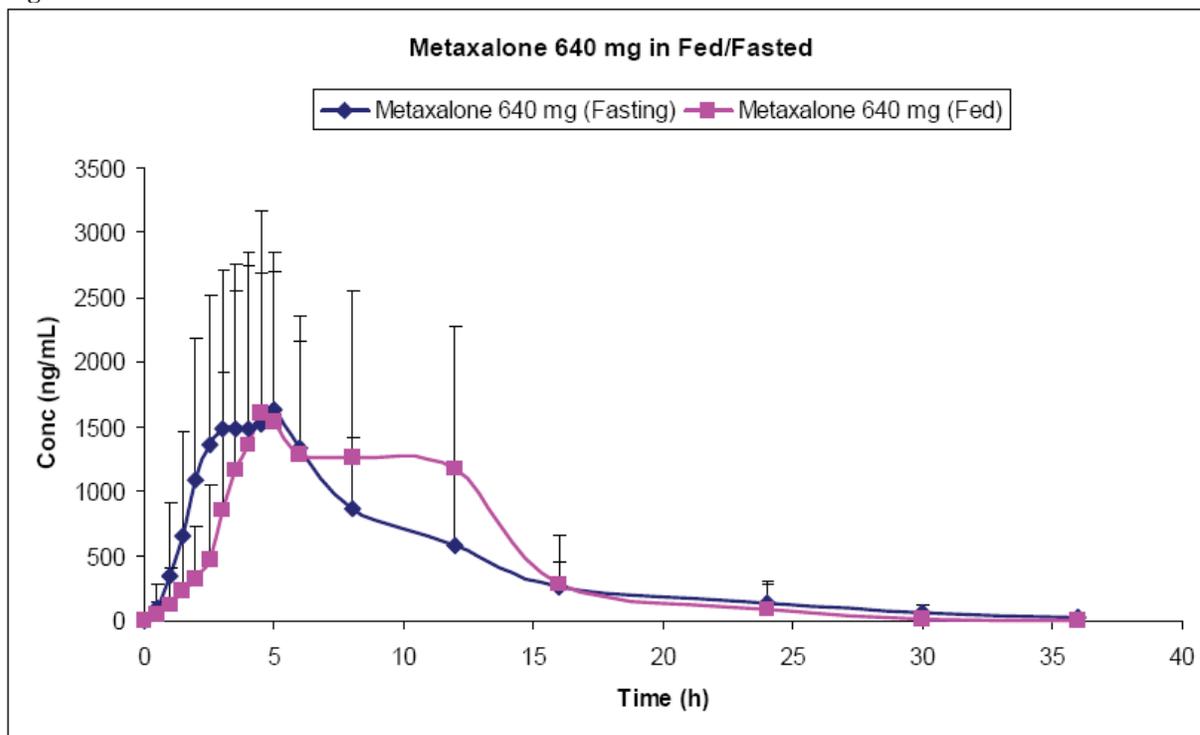
Figure 1 RLD (Skelaxin) Food Effect



Source: Figure 1.3.3 of Dr. Al Habet's review

In contrast, ingestion of CorePharma's metaxalone 640 mg tablets with food does not appear to result in greatly increased exposure (see Figure 2 below). Peak exposure is essentially the same as for ingestion in the fasted state, with a small delay to peak exposure and flattening of the curve near peak concentrations. This would not be expected to effect efficacy, which has not been linked to the higher exposures associated with Skelaxin's food effect. The lower food-effect exposure associated with CorePharma's metaxalone tablets would not be expected to worsen the safety profile of this product; if anything the profile would be expected to be similar or better compared to the RLD.

Figure 2 CorePharma’s Metaxalone Tablets Food Effect



Source: Figure 1.3.4 of Dr. Al Habet’s review

CorePharma’s Metaxalone Product is Intended as an Immediate Release Formulation

CorePharma’s Metaxalone is an immediate release formulation intended for ingestion three to four times a day, similar to the RLD. The time to peak concentration (T_{max}) of the CorePharma 640 mg metaxalone tablets is approximately 3.5 hours when ingested in the fasted state, with a terminal half-life ($T_{1/2}$) of 5 hours. This profile is similar to the RLD, which has a T_{max} of 3.0 hours and $T_{1/2}$ of 8 hours. “Delayed Release” drug products are dosage forms that release the drug at a time later than immediately after administration (i.e., these products exhibit a lag time in quantifiable plasma concentrations). Typically, coatings (e.g., enteric coatings) are intended to delay the release of medication until the dosage form has passed through the acidic medium of the stomach. There are no established criteria for demonstrating delayed release characteristics of a product in vivo. However in vivo comparative data (e.g., of T_{max} or T_{lag}) between a given delayed release formulation and an immediate release solid, solution or suspension formulation of a drug may be utilized as supportive information. Such data have not been submitted by the applicant, as the CorePharma product is not intended as a delayed release formulation.

- **Drug-drug interactions/Extrinsic factors**

No specific studies were conducted to investigate the effect of extrinsic factors on the disposition of metaxalone. The RLD label notes that, “Hepatic Cytochrome P450 enzymes play a role in the metabolism of metaxalone. Specifically, CYP1A2, CYP2D6, CYP2E1, and CYP3A4 and, to a lesser extent, CYP2C8, CYP2C9 and CYP2C19 appear to metabolize

metaxalone. Metaxalone does not significantly inhibit major CYP enzymes such as CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Metaxalone does not significantly induce major CYP enzymes such as CYP1A2, CYP2B6, and CYP3A4 in vitro.”

- **Pathway of elimination**

No new information was submitted with the NDA. The RLD label notes that metaxalone is, “metabolized by the liver and excreted in the urine as unidentified metabolites.”

- **Intrinsic factors**

No formal special population studies were conducted or submitted with the NDA.

1) Age: The RLD label contains the results of a study assessing the bioavailability of metaxalone under fasted and fed conditions in three groups of healthy volunteers, with a mean age of 26, 39, and 72 years. The results of this study suggested that the PK of metaxalone is more affected by age under fasted conditions, due to increased bioavailability under fasted conditions with increasing age. The RLD label contains a precaution that “Taking Skelaxin with food may enhance general CNS depression; elderly patients may be especially susceptible to this CNS effect.” With respect to pediatric age ranges, the RLD label states, “The safety and effectiveness in children 12 years of age and below have not been established.” No new pediatric data were submitted in NDA 22-503.

2) Gender: The RLD label describes the results of a PK study of two 400 mg Skelaxin tablets (800 mg total dose) in 48 healthy volunteers (24 males and 24 females) under fasted conditions. This study showed a higher bioavailability of metaxalone in females compared to males (1.4-fold higher C_{max} and 1.7-fold higher AUC_∞). Results of the pivotal BE study submitted in NDA 22-503 were consistent with results described in the RLD label. With respect to both C_{max} and AUC, under both fed and fasted conditions, females demonstrated higher exposures as compared to males following single doses of the test product (CorePharma’s metaxalone 640 mg tablets) and the reference product (Skelaxin 800 mg tablets). Exposure ranged from 1.2 to 1.4 fold higher in females depending on the product, PK parameter, and test condition. (See Figures 2.3.1.5 and 2.3.1.6 in Dr. Al Habet’s review for additional details.)

The CorePharma metaxalone product and the RLD Skelaxin did not meet bioequivalence criteria in either gender subgroup when subgroups were assessed separately; however, as noted in the Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products, the Agency does not require that BA/BE studies be sufficiently powered to draw conclusions for subgroups. BE criteria were met for each gender subgroup under fasted conditions with respect to AUC, but not C_{max}. However, results of the entire population, when grouped together, did meet BE criteria, as noted above.

3) Hepatic or Renal impairment: No new information was submitted in the NDA. The RLD label states, “The impact of hepatic and renal disease on the pharmacokinetics of metaxalone

has not been determined. In the absence of such information, Skelaxin should be used with caution in patients with hepatic and/or renal impairment.” (b) (4)

- **Thorough QT study or other QT assessment**

No formal QTc study was performed for or submitted in NDA 22-503. QT assessment was not routinely required at the time of approval of the RLD, and the RLD label contains no information regarding the effect of metaxalone on QT intervals. However, in the 48 years of clinical experience with the RLD, QT-related safety concerns have not been detected.

- **Other notable issues (resolved or outstanding)**

Study #R08-0838 provided adequate evidence that CorePharma’s 640 mg metaxalone tablet is equivalent to 800 mg Skelaxin®, based on the Agency’s standard bioequivalence criteria under fasted conditions. CorePharma’s metaxalone 640 mg tablets are not bioequivalent to the RLD under fed conditions—the RLD is associated with a marked increase in exposure following ingestion with food, and the CorePharma metaxalone product is not. However bioequivalence under fed conditions is not required in this case, as the RLD label has no specific instructions regarding administration of the RLD with or without food. The clinical pharmacology sections of the proposed label for the CorePharma metaxalone product will need to be revised to include the product-specific results from Study R08-0838, rather than the information specific to the RLD.

ONDQA biopharmaceutics reviewers noted that the dissolution method and acceptance criteria proposed by the applicant for their product is the same as that for the RLD product, Skelaxin.

Table 4 Proposed Dissolution Method and Acceptance Criteria

Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criteria
Immediate release tablet	II (Paddle)	100	0.5% SLS in water	900	Q= (b) (4)% in 90 min

Source: Dr. Suarez-Sharp’s review

Although the proposed method has already been approved to assess Skelaxin, and is acceptable, ONDQA biopharmaceutics reviewers believe that the acceptance criteria may not be optimal to assess the CorePharma metaxalone product (b) (4)

They recommend the addition of a specification at 30 minutes (no more than (b) (4)%) and an increase in the acceptable amount dissolved (“Q”) at 90 minutes (Q= (b) (4)%). This recommendation was relayed to the applicant, who accepted the new specifications and agreed to submit dissolution information for stability batches under these new specifications, as requested by the Agency.

6. Clinical Microbiology

Not Applicable.

7. Clinical/Statistical- Efficacy

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

No efficacy studies were submitted in the NDA. This 505(b)(2) application relies on the Agency's previous finding of efficacy for the RLD, Skelaxin. Skelaxin was originally approved in 1962 on the basis of safety. After passage of the 1962 Kefauver-Harris amendment to the Federal Food, Drug, and Cosmetic Act, Skelaxin underwent review via the DESI process to determine its efficacy. This initial review, concluded in 1970, determined Skelaxin to be ineffective (FR Volume 35, Number 26, February 6, 1970). At that time, two randomized controlled trials were available in the published literature (Diamond, 1966 and Fathie, 1964). Features and results of these trials are summarized in Table 5 below. Of these two studies, the Fathie study was positive but was found to have multiple design issues that precluded definitive conclusions, and the Diamond study showed no difference between Skelaxin and placebo with respect to the major efficacy endpoints. The NDA holder was allowed to present additional evidence at a final hearing on the matter, by which time, the Dent study had been completed (published in 1975). This study was determined to be of adequate design and showed a treatment benefit in favor of Skelaxin. Skelaxin was ultimately determined to be effective for the indication of "relief of discomforts associated with acute, painful musculoskeletal conditions." (FR August 15, 1974).

Table 5 Summary of Randomized Controlled Studies of Skelaxin

Study author (year ¹)	Design	Treatment Groups	Endpoints	Results
Dent ² (1974)	R, DB, MC 8-day study in patients with acute muscle spasm (≤ 14 days duration)	1) Skelaxin 800 mg QID (dose can be decreased to 400 mg QID) (n=113) 2) Placebo (n=115)	23 total endpoints 1) <u>16 endpoints</u> : assessed by patient and investigator on a 0-4 scale (absent, mild, moderate, severe, very severe) at Days 2 & 8: muscle spasm, limitation of motion, local pain or tenderness, & interference with daily activities 2) <u>4 endpoints</u> : on Days 2 & 8 assessed by investigator and patient global (recovered, much better, better, same, worse) 3) <u>2 endpoints</u> : need for physiotherapy or analgesics on Days 2 & 8 4) <u>1 endpoint</u> : patient satisfaction on Day 8	FDA medical reviewer felt that this study was an adequate and well controlled study <u>Efficacy</u> : Greater improvement in the Skelaxin group compared to placebo group in spasm, motion, pain, activities, and global. <u>Safety</u> : No SAEs <u>Adverse reactions</u> : sedation, nausea
Diamond ³ (1966)	R, DB, PC, 10-day study of patients with acute muscle spasm, pain, tenderness, and restriction of motion	N=100 1) Metaxalone 800 mg QID 2) Placebo QID	Multiple endpoints including muscle spasm relief, pain relief	<u>Efficacy</u> : No difference in muscle spasm relief and no difference in pain relief <u>Safety</u> : No SAEs
Fathie ⁴ (1964)	R, DB, PC, 7-day study of patients with LBP	N=100 1) Metaxalone 800 mg QID 2) Placebo QID	Multiple endpoints including muscle spasm and range of motion	FDA reviewer stated that this study could not serve as an adequate and well-controlled study and could not support the efficacy of Skelaxin because of multiple design issues <u>Safety</u> : No SAEs

Source: Eric Brodsky, M.D.

R = randomized; DB = double-blind, MC = multi-center

1 year article was published

2 Dent RW, Ervin DK. 1975. A study of metaxalone (Skelaxin) vs. placebo in acute musculoskeletal disorders: a cooperative study. *Curr Ther Res Clin Exp* 1975;18(3):443-440.

3 Diamond S. Double-blind study of metaxalone use as skeletal muscle relaxant. *JAMA* 1966;195(6):479-480.

4 Fathie K. A second look at a skeletal muscle relaxant: A double-blind study of metaxalone. *Curr Ther Res* 1964;6(11):677-683.

- **Includes discussion of both the statistical reviewer review and the clinical efficacy review with explanation for CDTL’s conclusions and ways that any disagreements were addressed.**

Not applicable

- **Includes discussion of notable efficacy issues both resolved and outstanding**

As described, the evidence for the efficacy of metaxalone is limited to what is available in the published literature. These data, while determined to be adequate to support the efficacy of metaxalone, lack a number of details that would be germane to the assessment of CorePharma’s metaxalone product. The primary issues are as follows:

1. Exposure-Efficacy Response Relationship. No PK data are available from efficacy studies of metaxalone that would allow an assessment of the exposure-response relationship with respect to efficacy. Therefore, we can only conclude that the efficacy of metaxalone would apply to the broad range of exposures observed with Skelaxin. As the CorePharma metaxalone product has demonstrated bioequivalence with Skelaxin in the fasted state, it is reasonable to conclude that evidence for efficacy of Skelaxin would apply to the exposures associated with the CorePharma metaxalone product.
2. Food Effect. The RLD Skelaxin is associated with a large increase in exposure when ingested with food, whereas the CorePharma metaxalone product is not (see Section 5, above). The RLD's food-effect has reportedly been patented by the innovator, which is likely to impede the ability to approve a generic metaxalone product with a similar food-effect profile. However, the RLD label contains no instruction or restriction with regard to ingestion relative to food; neither is relevant information from the clinical studies available to address this issue. Skelaxin has been marketed for 48 years and there has not been even anecdotal evidence that the product must be taken with food in order to be effective. Therefore, it is reasonable to conclude that the increased exposure observed with Skelaxin when ingested with food is not necessary for its efficacy. This, combined with the lack of exposure-efficacy response data, supports the extrapolation of the evidence of efficacy of Skelaxin to support the CorePharma product, despite the lack of food-effect noted with the CorePharma product.

8. Safety

- **Discuss the adequacy of the database, major findings/signals, special studies, foreign marketing experience, if any, and plans for postmarketing as discussed in the Pre-Approval Safety Conference (if NME will be approved)**

The bulk of the evidence of safety for the CorePharma metaxalone product lies in the Agency's previous finding of safety for the RLD Skelaxin. Therefore an AERS search of the U.S. post-marketing AEs was performed for the period from January 2000 to April 2010 to determine the overall reporting rate of AEs associated with metaxalone. After eliminating duplicates, cases that were clearly not related to Skelaxin, and cases associated with Skelaxin overdose, there were 42 SAEs reported over the period (approximately 5 SAEs per year). Of the 42 SAEs, 17 cases were related to allergic events, 2 were cases of liver failure, and 2 were cases of idiopathic thrombocytopenic purpura. The remainder of cases were single occurrences of unexpected events, e.g., sepsis, myocardial infarction, eye redness. In most cases, concomitant medications were taken and the temporal relationship of Skelaxin use and the event was not clear. None of the 42 cases reported an association between an AE and fasted/fed state of the individual; thus, it was not possible to determine a relationship between metaxalone exposure and fasted or fed states. Approximately (b)(4) Skelaxin prescriptions are dispensed yearly, thus the approximate annual reporting rate is 5 SAE cases per (b)(4) prescriptions dispensed. AEs overall were consistent with the approved label and included

reports of drowsiness, dizziness, headache, nervousness, nausea, vomiting, and gastrointestinal upset. No new safety signals were identified.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests**

There were limited safety data provided by BA Study R08-0838, which enrolled 48 healthy adult volunteers for exposure to single doses of CorePharma's metaxalone and Skelaxin under fasted and fed conditions—a total of four doses of metaxalone (2 doses of each product) per participant. As expected, no deaths or SAEs were reported in Study R08-0838 and no subjects were discontinued due to an AE. A single subject discontinued the study, for personal reasons. Eight subjects experienced 14 adverse events in this study, with the most common adverse events being dizziness, headache, and lethargy. GI symptoms and fatigue were also reported commonly. Adverse events were similar for the CorePharma product as for the RLD, and were consistent with the approved label. No new safety signals were identified. For additional details, refer to Section 7 in the clinical review by Dr. Keith Hull.

- **Immunogenicity**—Not applicable.
- **Special safety concerns**—Not applicable.
- **Discussion of primary reviewer's comments and conclusions**

Dr. Hull has concluded that the safety profile of CorePharma's 640 mg metaxalone tablets is similar to the known safety profile of the RLD, Skelaxin 800 mg tablets. No new safety signals were identified in Study R08-0838. I agree with Dr. Hull's conclusions.

- **Highlight differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed**—Not applicable.
- **Discussion of notable safety issues (resolved or outstanding)**

No notable safety issues were identified.

9. Advisory Committee Meeting

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

10. Pediatrics

- **A brief documentation of the scientific data supporting extrapolation if extrapolation from one population to another is used to support efficacy.**

The RLD label notes, “The recommended dose for adults and children over 12 years of age is one 800 mg tablet three to four times a day,” and CorePharma is proposing to similarly label their product for children over 12 years of age at the same adult dose (640 mg three to four times a day). The exact date, circumstances, or basis upon which Skelaxin was approved for children over 12 years of age is not known, but appears to have occurred in the 1980’s. In any case, Skelaxin has been approved for use in children over 12 years of age for several decades now, although usage is likely low, given that skeletal muscle relaxants are not routinely recommended for pediatric patients with back pain (treatment recommendations include adjunctive therapy and nonsteroidal anti-inflammatory drugs [NSAIDs]) and Skelaxin is not effective for the treatment of spasticity (approved treatments—baclofen, dantrolene, and tizanidine).

We conducted a brief search of the FDA Adverse Event Reporting System (AERS) database for adverse events associated with Skelaxin of the last 10 years (2000-2009 inclusive). Out of a total of 611 AERS reports, 5 cases were reported for children under 18—3 cases in 14-year-olds and 2 cases in 16-year-olds. Cases reported labeled adverse events, to include dizziness, nausea, and leukopenia, with one case describing new muscle spasms.

Because the CorePharma product is bioequivalent to the reference listed drug, Skelaxin, and because there are no formulation-specific reasons to believe the drug would behave differently in children over 12 years of age, it is reasonable to allow the CorePharma product label to mirror Skelaxin’s approved label, including the indication for children over 12 years of age.

- **Peds exclusivity board review - PPSR/WR**—Not applicable.
- **PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, peds assessment**

NDA 22-503 was discussed at the Pediatric Review Committee (PeRC) meeting on May 5, 2010. At this meeting, PeRC concluded that this NDA does not trigger Pediatric Research Equity Act (PREA) requirements, as it does not pertain to a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. Therefore, no pediatric assessment is required in this case. Nonetheless, the applicant did submit a waiver request for pediatric patients ages 0 to 11 years, on the grounds that the product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients. The Division agreed in principle with this waiver request because skeletal muscle relaxants are not routinely recommended in children under 12 years of age. While musculoskeletal injuries are not uncommon, particularly in older children (i.e., ages 6 to 11), the conditions are self-limited and typically respond to rest, adjunctive therapies and analgesics. Furthermore, metaxalone is not efficacious for conditions involving spasticity, which is the most likely disorder requiring muscle relaxant treatment in this age group. This was discussed at the PeRC meeting for this NDA, and the Committee also agreed in principle that a waiver would be appropriate for children under 12 years.

- **Consults**—Not applicable.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**

No issues were identified to trigger the AIP.

- **Exclusivity or patent issues of concern**

As of the date of the filing of NDA 22-503, there were three United States Patents listed in the Orange Book for the RLD, Skelaxin® Tablets, 800 mg, held by King Pharmaceuticals, NDA # 013217. CorePharma has been granted a patent license to the below listed patents by agreement with King Pharmaceuticals, Inc., the owner of US Patents 6,407,128 (expiration December 3, 2021) and 6,683,102 (expiration December 3, 2021) and licensee (with the right to sublicense CorePharma) to US Patent 7,122,566 (expiration February 6, 2026). The patent holder for patent no. 7122566 is Pharmaceutical IP Holdings, Inc.

In accordance with 21 USC 355(b)(2)(A)(iv), the applicant certified that the approval, manufacture, use, or sale of its metaxalone product will not infringe on the patents listed for King Pharmaceutical's Skelaxin Tablets. A letter of authorization from King Pharmaceuticals was provided by the applicant. No unexpired exclusivity exists for Skelaxin.

- **Financial disclosures**—No issues.
- **Other GCP issues**—No issues.
- **DSI audits**

The clinical portion of Study #R08-0838 was conducted at Cetero research in East Grand Forks, Minnesota and the analytical portion was conducted at (b) (4) facility. Study records and reserve samples were stored at the (b) (4) facility; therefore review of clinical study records took place at this facility (b) (4). A separate inspection was conducted at the East Grand Forks facility (March 29, 2010).

No significant issues were found at the East Grand Forks site. The (b) (4) site was cited for:

1. Failure to establish written procedures for the following:
 - Assessment of instrumental carryover during chromatographic analysis of study samples, and
 - Criteria to determine re-processing of chromatographic data in analytical runs.
2. Failure to document justification for changing chromatogram integration parameters during validation and study. Most validation and study runs had the integration parameters modified. However, there was no documentation of the reason for changing the parameters.

Neither item was found to have significantly impacted study results; therefore a Voluntary Action Indicated (VAI) determination was given for the (b) (4) facility. The firm

acknowledged the Agency's determination in their response to the Form 483 and has implemented corrective action.

The Division of Scientific Investigation (DSI) reviewer (Carol Rivera-Lopez, Ph.D.) concluded that data from Study R08-0838 are acceptable for Agency review.

- **Other discipline consults**—Not applicable.
- **Any other outstanding regulatory issues**

The Division convened an internal meeting on May 6, 2010 to discuss the legal and regulatory issues associated with this application. This meeting included the NDA 22-503 review team and members of the Office of Regulatory Policy (Nancy Boocker, Michael Bernstein, and Jane Baluss) and the Office of Generic Drugs [REDACTED] (b)(6). Meeting participants discussed the legal and regulatory precedents for approving a product with a different nominal dose, but that is otherwise bioequivalent to an approved product; and whether there were any existing legal or regulatory impediments to approving the application.

After discussion at the meeting and confirmation with the Office of Chief Counsel, it was concluded that if the application provided adequate evidence that the CorePharma product meets Agency standards for safety and effectiveness, which in this case is via bioequivalence to the RLD, there is no legal or regulatory impediment to approving the application. Although confusion between the RLD and the CorePharma product is likely, if one medication is errantly substituted for the other, no safety concern would arise as the products are bioequivalent when taken as prescribed—which is one tablet three to four times a day for both products. Precedent exists for having multiple nominal doses producing similar exposure with various fenofibrate products which have been approved by the Agency.

12. Labeling

- **Proprietary name**

The applicant initially proposed the name [REDACTED] (b)(4) for their 640 mg tablets. This was rejected by the Division of Medication Error Prevention and Analysis (DMEPA) due to [REDACTED] (b)(4). The applicant then submitted a proposal for the name, [REDACTED] (b)(4) which was rejected [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**

The applicant's proposed label closely mirrored the RLD label, with minor changes to account for the CorePharma metaxalone tradename and dose. The RLD label does not contain efficacy information and contains limited, descriptive safety information. Input for the CorePharma label was sought from the Division of Drug Marketing, Advertising, and Communication

(DDMAC) and the Office of Surveillance and Epidemiology (OSE). OSE did not have any comments regarding CorePharma's proposed label. DDMAC's comments regarding the proposed CorePharma label pertain primarily to language that is present in the RLD label that has been taken verbatim for use in the CorePharma label. Their major issues pertain to the lack of an acute use limitation found in labels of other approved muscle relaxants (e.g., carisoprodol and cyclobenzaprine products), and the use of some descriptors that could lead to vague or promotional interpretation, such as "rare" or "significantly."

Labeling negotiations have not yet been completed, but DDMAC's suggested changes will be addressed in the label to be forwarded to the applicant. These changes would be applicable to the RLD labeling as well; however there are no safety issues that warrant mandatory labeling changes to the RLD label. Because CorePharma's 640 mg metaxalone product is new and will be the first metaxalone label in PLR format, DDMAC's changes could reasonably be incorporated as an improvement over the RLD label.

- **Physician labeling**

See above section on DDMAC comments for the label. The applicant's proposed label closely mirrored the RLD label, with minor changes to account for the CorePharma metaxalone tradename and dose. The clinical pharmacology review team has recommended replacing the RLD clinical pharmacology information with the results from Study #R08-0838, and I concur.

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review.**

No major issues have been identified, however the CorePharma proposed label requires revisions from the RLD label and labeling negotiations have not yet been completed.

- **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 the RLD.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

NDA 22-503 provided adequate evidence that CorePharma 640 mg metaxalone tablets are bioequivalent to the RLD Skelaxin. Therefore, the Agency's previous finding of safety and efficacy for the RLD may be extrapolated to apply to the CorePharma metaxalone product. The review team has found no issues that would preclude approval of this NDA, and I concur.

I recommend approval of the NDA, provided that the manufacturing facilities are cleared by the Office of Compliance and that agreement can be reached on revisions to the proposed label.

- **Risk Benefit Assessment**

The risk-benefit profile of CorePharma 640 mg metaxalone tablets is anticipated to be similar to the risk-benefit profile of the RLD, since the two products are bioequivalent in the fasted state. Although the CorePharma product is not bioequivalent to the RLD in the fed state, the exposures observed with ingestion of the CorePharma 640 mg tablets in the fed state are lower than those observed with ingestion of the RLD in the fed state; therefore this bioinequivalence would, if anything, result in less toxicity compared to RLD.

The risk of having two products available with different nominal doses but similar exposures was assessed during review of this NDA (See Section 11, Other Regulatory Issues). If one medication is errantly substituted for the other, no safety concern would arise as the products are bioequivalent when taken as prescribed—one tablet three to four times a day for both products. Even if a patient were to attempt to take 800 mg of the CorePharma product, e.g., by taking 1 and 1/3 tablets, the toxicities resulting from this additional exposure would likely be limited to non-life-threatening effects such as excess sedation, dizziness, or GI symptoms. Metaxalone is not a narrow therapeutic index drug; doses up to 44,000 mg (mostly associated with suicide attempts) have been tolerated without permanent sequelae [Forrester 2009]. Thus, the possibility that patients would errantly try to use 800 mg of the CorePharma product would not be so dangerous as to preclude approval.

Therefore, overall, the risk:benefit profile of CorePharma's 640 mg metaxalone tablets 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 or commitments are recommended by the review team.

- **Recommended Comments to Applicant**

No issues remain that warrant comment, with the exception of the label and results from inspection of the manufacturing facilities. Comments pertaining to these two issues will be relayed as they are finalized.

References

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Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22503

ORIG-1

COREPHARMA
LLC

 (b) (4)
640MG
(METAXALONE)

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

/s/

SARAH K OKADA
05/24/2010

CLINICAL REVIEW

Application Type NDA
Submission Number 22-503

Letter Date August 20, 2009
Stamp Date August 20, 2009
PDUFA Goal Date June 20, 2010

Reviewer Name Keith M Hull, MD, PhD
Review Completion Date May 4, 2010

Established Name metaxalone
(Proposed) Trade Name TBD
Therapeutic Class Muscle Relaxant
Applicant Corepharma LLC
Priority Designation S

Formulation 640 mg tablets

Proposed Dosing Regimen Adults & Children >12 yo: 640 mg p.o. QID

Indication Adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions

Intended Population Adults and children older than 12 years with musculoskeletal pain

TABLE OF CONTENTS

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	3
1.1	Recommendation on Regulatory Action.....	3
1.2	Risk-Benefit Assessment.....	3
1.3	Recommendations for Postmarketing Risk Management Activities	4
2	INTRODUCTION AND REGULATORY BACKGROUND.....	5
2.1	Product Information.....	5
2.2	Currently Available Treatments for Proposed Indications	6
2.3	Availability of Proposed Active Ingredient in the United States.....	6
2.4	Important Safety Issues with Consideration to Related Drugs	6
3	ETHICS AND GOOD CLINICAL PRACTICES	7
3.1	Submission Quality and Integrity	7
3.2	Compliance with Good Clinical Practices	7
3.3	Financial Disclosures.....	7
4	SIGNIFICANT EFFICACY OR SAFETY FINDINGS RELATED TO OTHER REVIEW DISCIPLINES.....	8
4.1	Chemistry Manufacturing and Controls	8
4.2	Clinical Microbiology.....	8
4.3	Preclinical Pharmacology/Toxicology.....	8
4.4	Clinical Pharmacology	8
5	SOURCES OF CLINICAL DATA AND REVIEW STRATEGY	11
5.1	Review Strategy.....	11
5.2	Discussion of Individual Studies	11
6	REVIEW OF EFFICACY	13
7	REVIEW OF SAFETY.....	15
8	POST-MARKETING EXPERIENCE	17
9	APPENDICES	19
9.1	Literature Review/References	19
9.2	Labeling Recommendations	20
9.3	Advisory Committee Meeting	20

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This marketing application is for approval of metaxalone 640 mg (proposed trade name to be determined) as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified but may be related to its sedative properties. The application was filed under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and consists of a single bioavailability study in 48 healthy volunteers comparing metaxalone 640 mg to the reference listed drug (RLD), Skelaxin 800 mg.

Results from the bioavailability study demonstrated that the metaxalone 640 mg formulation is bioequivalent to Skelaxin 800 mg in the fasted state; however, in the fed state, the C_{max} and AUC concentrations of the metaxalone 640 mg formulation are lower than Skelaxin 800 mg. Thus, in regards to the fed state, the two drugs are not bioequivalent. 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. Therefore, the Agency's standard for bioequivalence in the fasted state, and extrapolation of efficacy based on meeting this standard, could reasonably be applied in this case.

Safety analyses were provided on data from the Applicant's pharmacokinetic (PK) studies, and through a search of the FDA Adverse Events Reporting System (AERS) database. Given that serum concentrations of the metaxalone 640 mg formulation are either equivalent or lower than the approved formulation of Skelaxin 800 mg, an increased risk of toxicity to patients would not be anticipated. Overall, no new safety signals were identified with the metaxalone 640 mg formulation or the RLD, Skelaxin.

Therefore, from a clinical standpoint, this reviewer believes that the data submitted in this application are adequate to approve metaxalone 640 mg tablets with labeling that mirrors the RLD, Skelaxin.

1.2 Risk-Benefit Assessment

The data presented in this submission support the conclusion that metaxalone 640 mg tablets taken 3 to 4 times daily would have a similar risk-benefit profile to the RLD, Skelaxin, or could even exhibit a better safety profile with respect to concomitant food ingestion, given its relative lack of food effect compared to the RLD. However, the

potential exists for medical errors related to confusion regarding the different nominal dose. This would be limited to instances where a prescriber or patient might errantly conclude that the 640 mg tablet should be taken as 1.5 tablets to approximate the effect of 800 mg Skelaxin. In these instances, a patient may experience excess sedation or other common adverse effects of metaxalone, but this is unlikely to be life-threatening. The package insert and patient information for the 640 mg metaxalone tablet would need to adequately address and warn against this scenario.

1.3 Recommendations for Postmarketing Risk Management Activities

Given the long history of clinical use of Skelaxin (metaxalone), the well-known adverse event (AE) profile associated with the drug, and the lack of identification of additional safety signals in this review, no additional postmarketing risk management activities are required for the proposed indication.

2 Introduction and Regulatory Background

Skelaxin was originally approved by the Agency in 1962 for the relief of discomfort associated with acute musculoskeletal conditions. However, in 1970 as part of the Agency's Drug Efficacy Study Implementation (DESI) program, the FDA concluded that there was a lack of substantial evidence demonstrating the efficacy of Skelaxin based on a report received from the National Academy of Sciences/National Research Council. In 1972, the Agency proposed to withdraw approval of Skelaxin but permitted interested parties the opportunity to request a hearing in support of allowing Skelaxin to remain in the marketplace. In 1974, King Pharmaceuticals successfully presented evidence to the FDA demonstrating the effectiveness of Skelaxin for the relief of the discomfort associated with acute painful musculoskeletal conditions and Skelaxin was permitted to be marketed. Skelaxin is currently available as an 800 mg tablet containing the active ingredient metaxalone.

Corepharma LLC has submitted the present NDA under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for an alternative formulation of metaxalone (Skelaxin[®]) 640 mg tablets (as opposed to the currently market 800 mg tablets) for an indication as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. With the exception of changes specific to the new 640 mg formulation in relevant sections (i.e., Strengths, Description, Clinical Pharmacology, and How Supplied/Storage and Handling), the proposed package insert for the 640 mg metaxalone product is (b) (4)

2.1 Product Information

Chemically, metaxalone is 5-[(3,5-dimethylphenoxy) methyl]-2-oxazolidone with an empiric formula of $C_{12}H_{15}NO_3$ and a molecular weight of 221.25. Metaxalone is a white to almost white, odorless crystalline powder freely soluble in chloroform, soluble in methanol and in 96% ethanol but insoluble in water. The current product formulation consists of a tablet containing the active ingredients (b) (4) metaxalone (b) (4) and metaxalone (b) (4). Inactive ingredients include lactose monohydrate, FD&C Yellow #6, propylene glycol alginate, alginic acid, povidone, magnesium stearate, (b) (4)

The mechanism of action of metaxalone in humans has not been established but may be due to general nervous system depression. Metaxalone has no direct action on the contractile mechanism of striated muscle, the motor end plate, or the nerve fiber.

2.2 Currently Available Treatments for Proposed Indications

Numerous treatments are currently used for the discomfort associated with musculoskeletal pain and selection of therapy depends on many factors including the underlying etiology of the discomfort. However, musculoskeletal pain related to injury, strains/sprains, or repetitive use syndromes are typically treated with analgesics such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., ibuprofen, naproxen), opioids (e.g., hydrocodone) or so-called “muscle relaxants” (e.g. cyclobenzaprine). Metaxalone represents one of a number of drugs from the “muscle relaxant” class of therapeutics and is typically used in conjunction with non-pharmacologic therapies such as physical therapy.

2.3 Availability of Proposed Active Ingredient in the United States

Skelaxin was originally approved by the Agency in 1962 for the relief of discomfort associated with acute musculoskeletal conditions and has been available from the manufacturer King Pharmaceuticals as an 800 mg tablet.

2.4 Important Safety Issues with Consideration to Related Drugs

Metaxalone is generally well-tolerated with a favorable risk-benefit ratio. The most serious safety issue with metaxalone appears to be its ability to enhance the effects of alcohol and other CNS depressants and potentially impairing mental and/or physical abilities required for performance of hazardous tasks. The most frequent adverse effects reported with metaxalone include drowsiness, dizziness, headache, nervousness, nausea/vomiting, and gastrointestinal upset. Hypersensitivity, leucopenia, hemolytic anemia, and jaundice have been reported. Deaths have resulted due to deliberate/accidental overdoses especially when used in combination with antidepressants and alcohol.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The application was complete, well-organized, and uncomplicated in hyperlinking references as necessary. The Division of Scientific Investigations (DSI) audited two sites: Cetero Research, East Grand Forks, MN (clinical site) and [REDACTED] (b) (4) [REDACTED] (analytical site). No issues were identified at the East Grand Forks site; however, at the [REDACTED] (b) (4) site, DSI reported two minor deficiencies as follows:

- failure to establish written procedures for the assessment of instrumental carryover during chromatographic analysis of study samples and for criteria to determine reprocessing of chromatographic data in analytic runs
- failure to document justification for changing chromatogram integration parameters during validation and study.

In their final report, DSI concluded that data from Study R08-0838 are acceptable for Agency review and that the [REDACTED] (b) (4) must document justifications of chromatogram re-integration and run reprocessing for future studies.

3.2 Compliance with Good Clinical Practices

The Applicant certified that submitted clinical study was conducted in compliance with good clinical practice guidelines. Quality control procedures to insure that the study was conducted, and that the data were generated, documented, and reported in compliance with the protocol, GCP and applicable regulatory documents.

3.3 Financial Disclosures

The sponsor has adequately disclosed financial arrangements with the main clinical investigator and sub-investigators as recommended in the FDA guidance for industry and no potential conflicts of interest were identified.

4 Significant Efficacy or Safety Findings Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry Manufacturing and Control's portion of this application was reviewed by Elsbeth Chikhale, PhD who recommended approval of the application. Please refer to Dr. Chikhale's review for further discussion of the Chemistry Manufacturing and Controls portion of this application.

4.2 Clinical Microbiology

Not applicable to this application.

4.3 Preclinical Pharmacology/Toxicology

The Pharmacology/Toxicology portion of this application was reviewed by Jay Chang, PhD who recommended approval of the application. Please refer to Dr. Chang's review for further discussion of the non-clinical program of this application.

4.4 Clinical Pharmacology

The Clinical Pharmacology portion of this application was reviewed by Sayed Al Habet, RPh, PhD. Please refer to Dr. Sayed Al Habet's review for further discussion of the clinical pharmacology portion of this application.

Briefly, Study R08-0838 assessed equivalency in terms of C_{max} and AUC between the test product, metaxalone 640 mg tablets, to the RLD, Skelaxin 800 mg tablets. The study was conducted in 47 healthy volunteers in fasted and fed conditions as follows:

- Treatment A (Fasted, Study Drug): Single dose of 640 mg metaxalone tablets after an over night fast
- Treatment B (Fed, Study Drug): Single dose of 640 mg metaxalone tablets 30 min after a high-fat breakfast
- Treatment C (Fasted, RLD): Single dose of 800 mg Skelaxin® tablets after an over night fast
- Treatment D (Fed, RLD): Single dose of 800 mg of Skelaxin® tablets 30 min after a high-fat breakfast

Blood samples were collected at appropriate time-points over 36 hours.

Results from the study demonstrated that the plasma concentration-time profiles of metaxalone 640 mg were comparable to Skelaxin 800 mg tablets under fasted conditions (Table 1). The 90% CI for both the C_{max} and AUC were within the 80% to 125% bioequivalence (BE) limits in both treatment arms in the fasted state.

Table 1. Pharmacokinetic Parameters Following Metaxalone 640 mg and Skelaxin 800 mg Tablets in Fasted Subjects.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	Metaxalone Tablets (640 mg) Fasting	SKELAXIN [®] Tablets (800 mg) Fasting	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	13686.84	13907.27	98.41	(90.74, 106.74)
AUC _{0-inf} (ng·hr/mL)	13988.59	14866.84	94.09	(87.12, 101.62)
C _{max} (ng/mL)	1798.83	1735.28	103.66	(88.64, 121.24)

In contrast to the fasted state, the plasma concentration-time profile of metaxalone 640 mg metaxalone tablets was significantly lower than that of Skelaxin 800 mg tablets in subjects in the fed state (Table 2). The C_{max} and AUC in the fed state were approximately 28% and 25% lower after metaxalone 640 mg metaxalone compared to Skelaxin 800 mg, respectively. In the fed state, the 90% CI for both C_{max} and AUC were outside the 80% to 125% BE limits.

In contrast to the metaxalone 640 mg tablet, food substantially increased the absorption of the RLD, Skelaxin 800 mg tablet (Table 2). The C_{max} and AUC were approximately 75% and 30% higher in fed state than in fasted state, respectively. The food effect related to Skelaxin 800 mg tablets is already documented in the currently approved label and food effect data from current submission is consistent with what is already included in the RLD label. When the metaxalone 640 mg tablet was given with food, the absorption phase seemed to be extended; however, the T_{max} in fasted and fed conditions appears to occur at the same time.

Table 2. Pharmacokinetic Parameters Following Metaxalone 640 mg and Skelaxin 800 mg Tablets in Fed Subjects.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	SKELAXIN [®] Tablets (800 mg) Fed	% Ratio	90% CI
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)
C _{max} (ng/mL)	2207.56	3046.51	72.46	(61.96, 84.75)

Overall, metaxalone 640 mg tablet is equivalent to Skelaxin 800 mg only under fasted conditions and not under fed conditions. Food increased the C_{max} after metaxalone

640 mg tablet by approximately 23% with no change in the AUC compared to that after fasted condition while food increased the C_{max} and AUC of the Skelaxin 800 mg tablet by approximately 75% and 30%, respectively. The data from this study is in general consistent with the food effect in the currently approved label for Skelaxin 800 mg tablet. Additionally, the two products are not bioequivalent when administered in either females or males alone or under fed/fasted conditions; however, this is not an issue as the Agency BA/BE guidance discourages stratification of the bioequivalence data by gender. Thus, the combined data from all fasted subjects (n=47) is considered adequate to conclude that the two products exhibit equivalent systemic exposure only under fasted condition. Overall, the data derived from the pharmacokinetic studies appear to be extrapolable to the clinical setting. The efficacy of the metaxalone 640 mg tablets should be relatively equivalent to the RLD, and theoretically, the safety profile could be better given that metaxalone 640 mg tablet bioavailability is constant regarding food intake in contrast to the increased concentrations of Skelaxin 800 mg tablets in the fed state. Labeling language in reference to substitution issues between Skelaxin 800mg and metaxalone 640 mg tablets need to be addressed in the package insert as appropriate in light of different nominal doses between the two products.

5 Sources of Clinical Data and Review Strategy

5.1 Review Strategy

The data in this application are derived from a single bioavailability study which was designed as a randomized, single-dose, four-way, open-labeled, crossover trial evaluating fasted and fed subjects and comparing Corepharma's drug product (b) (4) metaxalone 640 mg with the RLD, Skelaxin[®] 800 mg tablets. The primary focus of the clinical review is on the safety data generated from the 48 subjects enrolled in the single PK study submitted in the application and review of the Agency's Adverse Event Reporting System (AERS) database.

5.2 Discussion of Individual Studies

Study R08-0838, entitled "A Relative Bioavailability Study of 640 mg Metaxalone Tablets versus 800 mg Skelaxin[®] Tablets under Fasting and Fed Conditions", was a randomized, single-dose, four-way, open-label, crossover bioavailability study that enrolled 48 healthy adult volunteers (29 males and 18 females). Subjects were randomized equally to one of four treatment arms:

- Treatment A (fasted): metaxalone 640 mg p.o.
- Treatment B (fed): metaxalone 640 mg p.o. (high fat breakfast)
- Treatment C (fasted): Skelaxin 800 mg p.o.
- Treatment D (fed): Skelaxin 800 mg p.o. (high fat breakfast)

Throughout the study subjects were re-allocated to a different treatment arm with a minimum of a 7 day washout period between drug administration based on the following randomization sequence :

- Sequence 1: ABCD
- Sequence 2: BDAC
- Sequence 3: CADB
- Sequence 4: DCBA

Major Inclusion and Exclusion data included:

- Able to competently agree and sign the improved consent form
- Complete screening process within 4 weeks prior to Period 1 dosing
- Healthy male and female subjects ≥ 18 years of age
- Body Mass Index between 18-32 kg/m², inclusive, and weigh ≥ 110 lbs
- Generally healthy with no presence or history of disease involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, neurologic systems, or abnormal laboratory values

- Female subjects of childbearing potential must be practicing an acceptable method of birth control as judged by the investigator or be postmenopausal for ≥ 1 year and if < 55 years of age has a documented FSH level ≥ 30 mIU/mL or is surgically sterile
- Could not have received an investigational drug within 28 days of Period 1 dosing
- Could not have an active infection including HBV, HCV, or HIV
- Could not have a positive drug screen or history of alcohol or drug abuse within the past year
- Could not have a history of clinically significant allergies to foods or drugs
- Females Could not be pregnant or breastfeeding over the course of the study

Subjects were monitored throughout the confinement portion of the study and included vitals signs, physical exam, clinical laboratory tests (CBC, Clinical Chemistry, HBV, HCV, and HIV antibody screening, pregnancy screening), and urinalysis at baseline and at the end of the study period. Additionally, vital signs, and adverse events queries were performed after testing period and again at the completion of the study. The demographic characteristics of the enrolled subjects are shown in Table 3.

Table 3. Demographic Characteristics of Subjects Enrolled in Study R08-0838

	Subjects (n=48)
Age (Years) Mean \pm SD	35 \pm 14
Sex, n (%) Male	30 (63%)
Race, n (%) White Native American/Hawaiian/Pacific Islander Black Asian	40 (85%) 5 (10%) 2 (4%) 1 (2%)
BMI Mean \pm SD	25 \pm 4

6 Review of Efficacy

Efficacy Summary

The current submission contains a single bioequivalence study that was not designed with an efficacy component. No clinical trials of metaxalone 640 mg tablets were performed to assess efficacy. As mentioned in Section 2, above, the RLD, Skelaxin, underwent the DESI process and was ultimately determined to be effective. The randomized, controlled studies that formed the basis of this efficacy assessment are described in Table 4, below. The primary study supporting the determination that Skelaxin was effective for the currently approved indication was the 1974 study by Dent, et al.

Table 4. Referenced Literature used for the Regulatory Actions of Skelaxin

Study author (year ¹)	Design	Treatment Groups	Endpoints	Results
Dent ² (1974)	R, DB, MC 8-day study in patients with acute muscle spasm (≤ 14 days duration)	1) Skelaxin 800 mg QID (dose can be decreased to 400 mg QID) (n=113) 2) Placebo (n=115)	23 total endpoints 1) 16 endpoints: assessed by patient and investigator on a 0-4 scale (absent, mild, moderate, severe, very severe) at Days 2 & 8: muscle spasm, limitation of motion, local pain or tenderness, & interference with daily activities 2) 4 endpoints: on Days 2 & 8 assessed by investigator and patient global (recovered, much better, better, same, worse) 3) 2 endpoints: need for physiotherapy or analgesics on Days 2 & 8 4) 1 endpoint: patient satisfaction on Day 8	FDA medical reviewer felt that this study was an adequate and well controlled study <u>Efficacy</u> : Greater improvement in the Skelaxin group compared to placebo group in spasm, motion, pain, activities, and global. <u>Safety</u> : No SAEs <u>Adverse reactions</u> : sedation, nausea
Diamond ³ (1966)	R, DB, PC, 10-day study of patients with acute muscle spasm, pain, tenderness, and restriction of motion	N=100 1) Metaxalone 800 mg QID 2) Placebo QID	Multiple endpoints including muscle spasm relief, pain relief	<u>Efficacy</u> : No difference in muscle spasm relief and no difference in pain relief <u>Safety</u> : No SAEs
Fathie ⁴ (1964)	R, DB, PC, 7-day study of patients with LBP	N=100 1) Metaxalone 800 mg QID 2) Placebo QID	Multiple endpoints including muscle spasm and range of motion	FDA reviewer stated that this study could not serve as an adequate and well-controlled study and could not support the efficacy of Skelaxin because of multiple design issues <u>Safety</u> : No SAEs

Source: Eric Brodsky, M.D.

In summary, results from the bioavailability study demonstrated that the metaxalone 640 mg formulation is bioequivalent to Skelaxin 800 mg in the fasted state; however, in the fed state, the C_{max} and AUC concentrations of the metaxalone 640 mg formulation are lower than Skelaxin 800 mg. Thus, in regards to the fed state, the two drugs are not bioequivalent. 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. Therefore, the Agency's standard for bioequivalence in the fasted state, and extrapolation of efficacy based on meeting this standard, could reasonably be applied in this case.

7 Review of Safety

An adverse event (AE) was defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient administered study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not the event was considered causally related to the use of the product.

Subjects in Study R08-0838 were monitored for clinical and laboratory evidence of AEs throughout the study. The investigators also assessed and recorded any AE in detail including the date of onset, description, severity, time course, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for events not considered "probably related" to study drug, final diagnosis (if known), and any action(s) taken. For AEs to be considered sporadic, the events must be of similar nature and severity. All AEs were recorded regardless of if the response was due to a query, observed by site personnel, or reported spontaneously by the patient. All AEs were followed to a satisfactory conclusion.

Serious adverse events (SAE) were defined as any event that met any one of the following criteria:

- Life-threatening
- Hospitalization
- Prolongation of hospitalization
- Congenital anomaly
- Persistent of significant disability/incapacity
- Important medical event requiring medical or surgical intervention to prevent a serious outcome
- Spontaneous abortion
- Elective abortion

There were no deaths or SAEs reported in Study R08-0838 and no subjects were discontinued due to an AE. Subject 003 withdrew from the study due to personal reasons following a single dose of study drug. This subject was included in the safety analysis of the study but was not included in the pharmacokinetic/bioavailability analyses.

Overall, eight subjects experienced 14 AEs, all of which were mild to moderate in severity (Table 2).

TABLE 2. Study R08-0838 Adverse Events by Treatment Group

Body System/AE	AE Incidence by Treatment Group			
	Treatment A (n=48)	Treatment B (n=47)	Treatment C (n=47)	Treatment D (n=47)
Eye Disorders				
Eye irritation	-	-	1 (2%)	-
Gastrointestinal				
Abdominal pain	-	-	-	1 (2%)
Diarrhea	-	1 (2%)	-	-
Nausea	1 (2%)	-	-	-
Vomiting	-	1 (2%)	-	-
General Disorders				
Fatigue	-	1 (2%)	-	-
Musculoskeletal & Connective Tissue				
Muscle spasm	1 (2%)	-	-	-
Myalgia	1 (2%)	-	-	-
Nervous System				
Dizziness	-	-	2 (4%)	1 (2%)
Headache	-	-	1 (2%)	-
Lethargy	-	-	1 (2%)	-
Skin & Subcutaneous Tissue				
Rash	-	-	1 (2%)	-
Total	3 (6%)	1 (2%)	5 (11%)	2 (4%)

Adverse events were similar in metaxalone-treated subjects (6 AEs) compared to the referenced licensed drug Skelaxin (8 AEs). No significant changes in laboratory values were noted. All AEs reported during Study R0-0838 are listed in the current Skelaxin label and no new safety signals were identified.

In summary, safety analyses were based on data from the Applicant's PK studies, and through a search of the FDA AERS database. Given that serum concentrations of the metaxalone 640 mg formulation are either equivalent or lower than the approved formulation of Skelaxin 800 mg, an increased risk of toxicity to patients would not be anticipated. Overall, no new safety signals were identified with the metaxalone 640 mg formulation or the RLD, Skelaxin; however, the potential exists for medical errors related to confusion regarding the different nominal dose. This would be limited to instances where a prescriber or patient might errantly conclude that the 640 mg tablet should be taken as 1.5 tablets to approximate the effect of 800 mg Skelaxin. In these instances, a patient may experience excess sedation or other common adverse effects of metaxalone, but this is unlikely to be life-threatening. The package insert and patient information for the 640 mg metaxalone tablet would need to adequately address and warn against this scenario.

8 Post-Marketing Experience

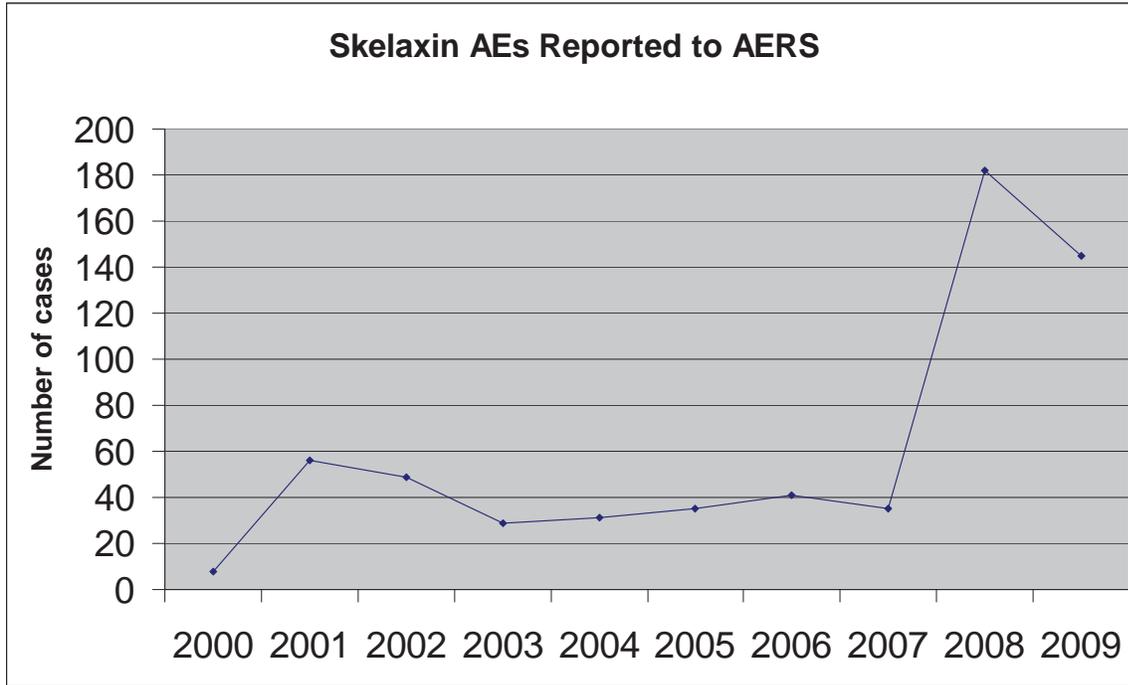
Given the limitations associated with safety data derived from this small bioavailability study in healthy volunteers, a search of the Agency's Adverse Event Reporting System (AERS) database was undertaken to better understand the rate of SAE and AEs associated with the referenced licensed drug Skelaxin.

An AERS search of the U.S. post-marketing AEs was performed for the period from January 2000 to April 2010 to determine the overall reporting rate of AEs associated with metaxalone.

After eliminating duplicates, cases that were clearly not related to Skelaxin, and cases associated with Skelaxin overdose, there were 42 SAEs reported over the period (approximately 5 SAEs per year). Of the 42 SAEs, 17 cases were related to allergic events, 2 were cases of liver failure, and 2 were cases of idiopathic thrombocytopenic purpura. The remainder of cases were single occurrences of unexpected events, e.g., sepsis, myocardial infarction, eye redness. In most cases, concomitant medications were taken and the temporal relationship of Skelaxin use and the event was not clear. None of the 42 cases reported an association between an AE and fasted/fed state of the individual; thus, it was not possible to determine a relationship between metaxalone exposure and fasted or fed states. Approximately (b) (4) Skelaxin prescriptions are dispensed yearly, thus the approximate annual reporting rate is 5 SAE cases per (b) (4) (b) (4) prescriptions dispensed.

From 2000 to 2007 the rate of AEs averaged between 30 to 60 AE reports per year (Figure 1). In 2007, the rate of reported AEs spiked to over 180 mostly as a result of reports submitted by the manufacturer. No change in formulation or manufacturing process occurred to explain this increase; however the increase in reports appeared to coincide with Citizen Petitions submitted to the Agency pertaining to Skelaxin. Review of the AEs were consistent with the approved label and most frequently included reports of drowsiness, dizziness, headache, nervousness, nausea, vomiting, and gastrointestinal upset. No new safety signals were identified.

Figure 1. AERS Database Adverse Event Reports for Skelaxin from 1/1/2000 to 4/1/2010



9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

In general, the metaxalone 640 mg tablet label can mirror the Skelaxin 800 mg tablet label given the PK data; however, labeling language in reference to substitution issues between Skelaxin 800 mg and metaxalone 640 mg tablets need to be addressed in the package insert as appropriate in light of different nominal doses between the two products. For example, “patients should not exceed 640 mg metaxalone or use metaxalone in combination with Skelaxin”.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was conducted for this application.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22503	ORIG-1	COREPHARMA LLC	(b) (4) 640MG (METAXALONE)

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

/s/

KEITH M HULL
05/10/2010

SARAH K OKADA
05/17/2010

I concur with Dr. Hull's conclusions. See my cross-discipline team leader review for details.

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?		X		

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer

Date

Clinical Team Leader

Date

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22503

ORIG-1

COREPHARMA
LLC

 (b) (4)
640MG
(METAXALONE)

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

/s/

KEITH M HULL
05/13/2010