

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022503Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

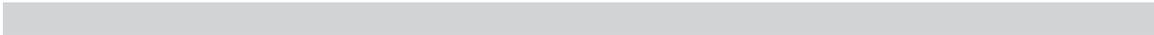
Application Information		
NDA # 22503	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Metaxalone Dosage Form: tablets Strengths: 640 mg		
Applicant: CorePharma, LLC		
Date of Receipt: Dec 15, 2014		
PDUFA Goal Date: June 15, 2015		Action Goal Date (if different): June 1, 2015
RPM: Jessica Lee		
Proposed Indication(s): Adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions		

GENERAL INFORMATION

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

YES NO

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



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

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

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 13217 Skelaxin	Assess equivalency (Cmax and AUC)
Literature	Non-clinical

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

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

The sponsor submitted data from a 4-way, crossover, relative bioavailability study (R08-0838) linking their product to already approved and marketed NDA 13-217 for Skelaxin (Metaxalone Tablets 800 mg). The plasma concentration-time profiles of metaxalone were comparable following 640 mg Metaxalone Tablets and 800 mg Skelaxin under fasted state (i.e., the 90% CI for both Cmax and AUC were within the 80% to 125% bioequivalence limits in fasted state).

RELIANCE ON PUBLISHED LITERATURE

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

YES NO

If "NO," proceed to question #5.

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

YES NO

If "NO," proceed to question #5.

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

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

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

YES NO

APPEARS THIS WAY ON ORIGINAL

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

RELIANCE ON LISTED DRUG(S)

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

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

YES NO

If "NO," proceed to question #10.

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

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Skelaxin 800 mg tablets	NDA 13217	Yes

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

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

N/A YES NO

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

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

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

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

YES NO

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

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

- b) Approved by the DESI process?

YES NO

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

Name of drug(s) approved via the DESI process: Skelaxin 800 mg tablets, NDA 13217

- c) Described in a final OTC drug monograph?

YES NO

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

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

d) Discontinued from marketing?

YES NO

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

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

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

YES NO

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

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

The formulation is different compared to Skelaxin in that it contains a lower nominal dose, with systemic exposure similar to the reference listed drug, and a lesser food effect.

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

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

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

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

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

YES NO

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

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.
If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

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

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

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

YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

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

A203399 metaxalone 800 mg tablet by Amneal Pharms

A040486 metaxalone 400 mg tablet by CorePharma

A040445 metaxalone 800 mg tablet by Sandoz

PATENT CERTIFICATION/STATEMENTS

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

6407128* (delisted)

6683102* (delisted)

7122566

7714006

No patents listed proceed to question #14

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

YES NO

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

Listed drug/Patent number(s):

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

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

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

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the

application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

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

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

- (a) Patent number(s): 7122566 and 7714006; 6407128* (delisted) and 6683102* (delisted)
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO

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

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO

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

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

Date(s): June 7, 2010

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

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

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

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

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/s/

JESSICA K LEE
06/01/2015

LABEL AND LABELING REVIEW MEMORANDUM

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

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

Date of This Review: May 15, 2015
Requesting Office or Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number: NDA 022503
Product Name and Strength: Metaxalone Tablets 640 mg
Product Type: Single-Ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: CorePharma, LLC
Submission Date: December 15, 2014
OSE RCM #: 2013-1524
DMEPA Primary Reviewer: Teresa McMillan, PharmD
DMEPA Team Leader: Kendra Worthy, PharmD

1 REASON FOR REVIEW

This review responds to a request from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to evaluate the proposed Prescribing Information and container labels for Metaxalone, NDA 022503 for areas of vulnerability that could lead to medication errors.

This is a resubmission of the 505(b) (2) application for Metaxalone Tablets, 640 mg in response to a complete response (CR) issued on December 18, 2013. All label and labeling recommendations made in previous DMEPA reviews (see appendix B) were implemented.

2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

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

3 CONCLUSION & RECOMMENDATIONS

A review of the proposed labels and labeling did not identify any potential areas of confusion. Therefore, DMEPA concludes that the proposed Prescribing Information (PI) and container labels are acceptable. Also, we do not have any additional recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Metaxalone that CorePharma, LLC submitted on March 24, 2015, and the listed drug (LD).

Table 2. Relevant Product Information for Metaxalone and the Listed Drug		
Product Name	Metaxalone	Skelaxin
Initial Approval Date	N/A	1962
Active Ingredient	Metaxalone	Metaxalone
Indication	Indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions.	Indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions.
Route of Administration	oral	oral
Dosage Form	tablet	tablet
Strength	640 mg	800 mg
Dose and Frequency	640 mg three to four times a day	800 mg three to four times a day
How Supplied	Available as oval, peach-colored tablet, debossed on one side with cor 324 and plain on the other side. Bottle of 100 tablets	Available as an 800 mg oval, scored pink tablet inscribed with 8667 on the scored side and "S" on the other. Bottles of 100 and 500 tablets
Storage	Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]	Controlled Room Temperature, between 15°C and 30 °C (59 °F and 86 °F).

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 28, 2015, we searched the L:drive and AIMS using the terms, Metaxalone and (b) (4) to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified three previous reviews¹, and we confirmed that our previous recommendations were implemented.

¹ McMillan, T. Label Labeling and Packing Review for Metaxalone. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 August 20. 7 p. OSE RCM No.: 2013-1524.

Turner T. Proprietary Name Review for (b) (4) Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2010 May 13. 4 p. OSE RCM No.: 2010-533 2009-2136.

Oleszczuk, Z. Label Labeling and Packing Review for (b) (4) Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2010 May 27. 5 p. OSE RCM No.: 2009-2137.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,² along with postmarket medication error data, we reviewed the following Metaxalone labels submitted by CorePharma on 5/7/15.

- Container label

G.2 Label and Labeling Images



² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

TERESA S MCMILLAN
05/15/2015

KENDRA C WORTHY
05/18/2015

NDA/BLA # 22-503
Product Name: Metaxalone Tablets

PMC #1 Description: Submit the results of comparative dissolution data (determined by f2 metrics) between (b) (4) metaxalone tablets using the approved dissolution method in a Changes Being Effected (CBE) Supplement.

PMC Schedule Milestones: Final Protocol Submission: 08/31/2015
Study Completion: 10/31/2015
Final Report Submission: 11/30/2015
Other: _____

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The safety and efficacy of metaxalone tablets has been established. However, the drug product is (b) (4) FDA has requested that the sponsor (b) (4) and provide comparative dissolution data. Since the application is ready for approval and otherwise safe and effective, (b) (4) can be done post-approval.

2. Describe the particular review issue and the goal of the study.

The tablet has (b) (4) The applicant agreed to (b) (4) (b) (4). Since the drug product is ready to be approved based on data collected from (b) (4) the applicant needs to manufacture batches (b) (4) test and submit data to support that the tablets (b) (4) have consistent performance characteristics.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery

- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Provide comparative dissolution data (determined by f2 metrics) between [REDACTED] (b) (4) tablets ([REDACTED] (b) (4)) using the approved dissolution method.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

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/s/

SALLY M SEYMOUR
05/11/2015

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

*****Pre-decisional Agency Information*****

Memorandum

Date: March 17, 2015

To: Jessica Lee, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Roberta Szydlo, Senior Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: NDA 022503
OPDP labeling comments for Metaxalone tablets for oral use
(Metaxalone)

In response to DPARP's consult request dated January 16, 2015, OPDP has reviewed the draft labeling (Package Insert [PI], and Carton/Container Labeling) for Metaxalone.

OPDP's comments on the PI are provided directly below and are based on the draft labeling titled "NDA 22503 Metaxalone SCPI_TMed_Track.doc" (attached) that was provided via email from DPARP on March 13, 2015.

OPDP has also reviewed the proposed container labeling submitted by the sponsor on June 18, 2013 (attached). We have no comments at this time on the proposed container labeling.

Thank you for your consult. If you have any questions, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

8 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

ROBERTA T SZYDLO
03/17/2015

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

*****Pre-decisional Agency Information*****

Memorandum

Date: December 3, 2013

To: Carol Hill, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Roberta Szydlo, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 022503, Metaxalone 640 mg Tablets

OPDP acknowledges receipt of your July 10, 2013, consult request for the proposed Package Insert and Carton/Container Labeling for Metaxalone 640 mg Tablets. Reference is made to the Cross-Discipline Team Leader Review dated December 2, 2013, that indicates that labeling will not be finalized during the current review cycle and that a Complete Response letter will be issued. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DPARP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions, please contact Roberta Szydlo at 301-796-5389 or roberta.szydlo@fda.hhs.gov.

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/s/

ROBERTA T SZYDLO
12/03/2013



Memorandum

Date 24-Oct-2013

From Robert H. Wittorf, PharmD
Division of Good Manufacturing Practice Assessment (DGMPA)

Subject Concurrence with New Jersey District Office (NWJ-DO) Withhold Recommendation for:

NDA 022503, (b) (4) (Metaxalone) (b) (4) Tablets, 640 mg
Non Responsive



Thru Tara Goen Bizjak, Branch Chief (Acting)
New Drug Manufacturing Assessment Branch
Division of Good Manufacturing Practice Assessment

To NDA and ANDA Application Files

Applicant: CorePharma, LLC.
215 Wood Avenue
Middlesex, NJ 08846

Establishment: CorePharma, LLC.
215 Wood Avenue
Middlesex, NJ 08846
FEI: 3002535019

The Division of Good Manufacturing Practice Assessment (DGMPA) has completed a review of documentation covering a pre-approval inspection (PAI) by NWJ-DO investigators from 11-Sep-2013 to 13-Sep-2013 at the CorePharma, LLC. facility. This inspection was initiated by NWJ-DO to provide pre-approval coverage of (b) (4) **Non Responsive** (b) (4). The scope of this concurrence memo also covers all other pending NDA (b) (4) applications manufactured at the CorePharma, LLC facility (FEI: 3002535019).

DGMPA concurs with the NWJ District Office's withhold recommendation for the above pending (b) (4) NDA applications due to the following deficiency:

1. NWJ-DO investigators arrived at CorePharma, LLC for a pre-approval inspection. At the time NWJ-DO investigators found that the firm was not ready for pre-approval inspection. A 483 was not issued at the time of inspection. As pre-approval inspection requirements could not be completed, the NWJ-DO stated to CorePharma, LLC that a withhold recommendation would be submitted for (b) (4) applications. NWJ-DO recommended a follow-up inspection be conducted prior to a decision (b) (4).

(b) (4) letters were submitted by CorePharma, LLC management to NWJ-DO. (b) (4) (b) (4) It also provided a list of (b) (4) pending applications and stated that CorePharma would provide periodic updates on readiness for these applications.

In (b) (4) letter, dated 13-Sep-2013, CorePharma, LLC stated they were not ready for pre-approval inspection for (b) (4) applications. The firm asserted that it would provide notice to NWJ-DO when the firm was ready for re-inspection. No proposed date for readiness was provided. The firm did not provide any indication that it would be ready prior to the December 18th, 2013 PDUFA date for NDA 022503.

DGMPA has reviewed information entered in EES by the district and the letters provided by CorePharma, LLC to NWJ-DO. OMPQ concurs with the need for a follow-up inspection with pre-approval specific coverage. The inspection findings hold that the site demonstrated a lack of capacity to manufacture the drug products (CPGM 7346.832, Part V Item 1).

CDER/OC/OMPQ/DGMPA Recommendation:

Based on the above assessment of the inspection findings and the firm's response to pre-approval inspections, DGMPA concurs with NWJ-DO's recommendation to withhold approval of:

NDA 022503, (b) (4) (Metaxalone) (b) (4) Tablets, 640 mg,

Non Responsive

CorePharma LLC. (b) (4)
NDA 22-503 (b) (4) (Metaxalone) (b) (4) Tablets, 640 mg), et. al.

Non Responsive

DGMPA recommends that an on-site evaluation of the firm (per Compliance Program Guidance Manual 7346.832, Pre-Approval Inspections) for manufacturing operations listed in this application be performed prior to a change in approval status (b) (4). Alternatively, the firm can be withdrawn from an application if there is an alternate facility to perform the listed function.

If you have any questions, please contact me at 240-402-3113 or by email at robert.wittorf@fda.hhs.gov.

Robert H. Wittorf, PharmD
Compliance Officer

CorePharma LLC.
NDA 22-503 (b) (4) (Metaxalone) (b) (4) Tablets, 640 mg), et. al.

cc:

New Jersey District Office (NWJ-DO)- Pre-Approval Manager (PAM), Karen D'Orazio
NDMAB Acting Team Leader, Mahesh Ramanadham
CMS case #: (b) (4)

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/s/

ROBERT H WITTORF
10/24/2013

TARA R GOOEN
10/24/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 22503

Application Type: Resubmitted NDA

Name of Drug: Metaxalone tablets, 640 mg

Applicant: CorePharma, LLC

Submission Date: June 18, 2013

Receipt Date: June 18, 2013

1.0 Regulatory History and Applicant's Main Proposals

The original NDA was submitted as a 505(b)(2) application on August 18, 2009 for treatment as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. A Complete Response letter was issued on June 11, 2010 which included labeling revisions.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix), the Label Review Tool, April 2013 and the CR letter issued on June 11, 2013.

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix. NOTE: The applicant revised the PI to address the labeling deficiencies listed in the CR letter dated June 11, 2013.

In addition, the following labeling issues were identified:

1. In the Indications and Usage section, the (s) on the word limitations should be removed.
2. In the Indications and Usage section, the sentence below the Important Limitations for Use should be unbolded.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed during label negotiations. The applicant will be asked to correct these deficiencies and the resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *The length of HL page must be less than or equal to one-half page. The applicant will be requested to reduce the length of the HL to length that does not exceed one-half.*

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is

Selected Requirements of Prescribing Information (SRPI)

the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

NO

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment: *The bolded HL LS is not on the line immediately beneath the HL heading; the applicant will be requested to place the HL LS on the line immediately beneath the HL heading. Also the applicant will be requested to remove the dosage form and strength from the HL LS.*

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

- N/A** 12. All text must be **bolded**.

Comment:

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment: *Will request that the applicant remove this section of the label since it is an original NDA and no recent changes have been made.*

N/A

18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A

19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

N/A

20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

Selected Requirements of Prescribing Information (SRPI)

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- NO** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: Adverse reaction reporting statement includes the applicant's web address. Applicant will be asked to remove the web address from the statement.

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

Selected Requirements of Prescribing Information (SRPI)

- YES** 28. A horizontal line must separate TOC from the FPI.
Comment:
- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.
Comment:
- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS

Selected Requirements of Prescribing Information (SRPI)

7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- N/A** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

Selected Requirements of Prescribing Information (SRPI)

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- N/A** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- N/A** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

CAROL F HILL
08/23/2013

LADAN JAFARI
08/28/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: August 20, 2013

Reviewer: Teresa McMillan, PharmD
Division of Medication Error Prevention & Analysis

Team Leader: Lubna Merchant, PharmD
Division of Medication Error Prevention & Analysis

Drug Name: Metaxalone Tablets

Strength: 640 mg

Application Type/Number: NDA 022503

Applicant/sponsor: CorePharma, LLC

OSE RCM #: 2013-1524

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1	Introduction	1
1.1	Background and Regulatory History	1
1.2	Product Information	1
2	Medication Error Risk Assessment of the Labels and Labeling	1
2.1	Faers Selection of Medication Error Cases	2
2.2	Literature Search	2
3	Conclusion and Recommendations	2
	Appendices.....	3

1 INTRODUCTION

This review is in response to a consult from the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) to evaluate the revised container labels and insert labeling for Metaxalone Tablets, 640 mg, NDA 022503 for areas of vulnerability that could lead to medication errors. Skelaxin (Metaxalone) Tablets, 800 mg, held by King Pharmaceuticals, is the referenced listed drug (RLD).

1.1 BACKGROUND AND REGULATORY HISTORY

This is a resubmission of the 505(b) (2) application for Metaxalone Tablets, 640 mg in response to a complete response (CR) issued on June 11, 2010. All aspects of the submission remained the same, the deficiencies noted in the CR letter were addressed and the label and labeling recommendations made by DMEPA in OSE review 2009-2137 were implemented. Additionally, on June 26, 2013, the applicant informed the Agency that they would not submit a proprietary name for this NDA prior to approval and they may reconsider submitting a proprietary name after the product is launched.

1.2 PRODUCT INFORMATION

The following product information is provided in the June 18, 2013 proprietary name submission.

- Active Ingredient: Metaxalone
- Indication of Use: As an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions in adults and children over 12 years of age
- Route of Administration: Oral
- Dosage Form: Tablet
- Strength: 640 mg
- Dose and Frequency: 640 mg three to four times daily
- How Supplied: Bulk bottles of 100 count (b) (4)

According to the Clinical Pharmacology review team, Skelaxin 800 mg and Metaxalone 640 mg are bioequivalent under fasting conditions. However, under fed conditions Skelaxin 800 mg has higher bioavailability than Metaxalone 640 mg. Therefore, depending upon meal conditions, a patient taking Metaxalone 640 mg may or may not receive the same exposure as Skelaxin 800 mg.

2 MEDICATION ERROR RISK ASSESSMENT OF THE LABELS AND LABELING

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database and literature for Metaxalone medication error reports (See Appendix A for description of FAERS database). We also reviewed the revised container labels (See Appendix B for images) and insert labeling (no image) submitted by the Applicant and OSE Label and

Labeling Review #2009-2137, May 27, 2010 to see if our recommendations were implemented and whether the revisions adequately addressed our concerns.

2.1 FAERS SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 1. All cases were excluded due to the following: duplicate cases, cases that listed Metaxalone as a concomitant medication, intentional overdose, and adverse events unrelated to a medication error.

Table 1: FAERS Search Strategy	
Date	Start date: April 28, 2010 (date of last AERS search in OSE Review# 2009-2137) End date: July 23, 2013
Drug Names	(active ingredient) *METAZALONE* (trade name) * (b) (4) *
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

2.2 LITERATURE SEARCH

We searched the ISMP publications on July 25, 2013 for additional cases and actions concerning Metaxalone and none were identified.

3 CONCLUSIONS AND RECOMMENDATIONS

No new label and labeling deficiencies were identified. Additionally, the revised labels and labeling addressed all of DMEPA's concerns and we have no additional comments.

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager at 301-796-3904.

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

REFERENCES

1. OSE Review #2009-2137, Label and Labeling Review for (b) (4) (Metazalone), May 27, 2010, Oleszczuk, Z.

Appendix B: Container Labels



(b) (4)

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/s/

TERESA S MCMILLAN
08/21/2013

LUBNA A MERCHANT
08/21/2013

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-503
APPLICANT	Corepharma
DRUG NAME	[TRADENAME] (metaxalone)
SUBMISSION DATE	August 20, 2009
SEALD REVIEW DATE	June 1, 2010
SEALD REVIEWER(S)	Jeanne M. Delasko, RN, MS

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22503

ORIG-1

COREPHARMA
LLC

(b) (4)
640MG
(METAXALONE)

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/s/

JEANNE M DELASKO
06/01/2010

LAURIE B BURKE
06/02/2010

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 22-503 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: Metaxalone Dosage Form: Tablets Strengths: 640 mg		
Applicant: CorePharma Agent for Applicant (if applicable):		
Date of Application: August 18, 2009 Date of Receipt: August 21, 2009 Date clock started after UN:		
PDUFA Goal Date: June 20, 2010		Action Goal Date (if different): June 18, 2010
Filing Date: October 01, 2009 Date of Filing Meeting: September 24, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed Indication(s): Relief of discomforts associated with acute, painful musculoskeletal conditions.		
Type of Original NDA: AND (if applicable)		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)
Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Refer to Appendix A for further information.		
Review Classification:		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal?	<input type="checkbox"/>	
Resubmission after refuse to file?	<input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR	

601.42)	
Collaborative Review Division (if OTC product):	
List referenced IND Number(s):	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ora/compliance_ref/aip.html If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status Comments:	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p> <p>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES # years requested: (b) (4) <input checked="" type="checkbox"/> NO
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<input type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
505(b)(2) (NDA/NDA Efficacy Supplements only)	
<ol style="list-style-type: none"> 1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)). 3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? 	<input type="checkbox"/> Not applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	
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<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	
<p>If yes, please list below:</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
Format and Content			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>		<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>			
<p>If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p> <p>If not, explain (e.g., waiver granted):</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments: Submitted in a letter.</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>sign the certification.</p> <p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> <p>Comments:</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
PREA	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) 	<p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p>Comments: A request for a partial waiver and deferral is</p>	

included but the Sponsor did not include a pediatric plan.	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i> Comments:	<input type="checkbox"/> YES <input type="checkbox"/> NO
Prescription Labeling	
Check all types of labeling submitted. Comments:	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i> Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Package insert (PI) submitted in PLR format? If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request? <i>If no, request in 74-day letter.</i> Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REMS consulted to OSE/DRISK? Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 09-24-09

NDA/BLA #: 22-503

PROPRIETARY/ESTABLISHED NAMES: (b) (4) (Metaxalone)

APPLICANT: CorePharma

BACKGROUND:

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Ramani Sista	Y
	CPMS/TL:	Parinda Jani\Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Sarah Okada		Y
Clinical	Reviewer:	Keith Hull	Y
	TL:		
Social Scientist Review <i>(for OTC products)</i>	Reviewer:		
	TL:		
Labeling Review <i>(for OTC products)</i>	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology <i>(for antimicrobial products)</i>	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sayed Al Habet	Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:	Dionne Price	Y
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jay Chang	Y
	TL:	Adam Wasserman	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Elsbeth Chikhale	Y
	TL:	Danae Christodoulou	Y
Facility (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Carol Rivera-Lopez	Y
	TL:		
Other reviewers			

OTHER ATTENDEES:

505(b)(2) filing issues? If yes, list issues:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Per reviewers, are all parts in English or English translation? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>Electronic Submission comments</p> <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Establishment(s) ready for inspection? <ul style="list-style-type: none"> Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Sterile product? 	<input type="checkbox"/> YES <input type="checkbox"/> NO

<p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>FACILITY (BLAs only)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Dr. Badrul A. Chowdhury</p> <p>GRMP Timeline Milestones:</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <ul style="list-style-type: none"> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22503

ORIG-1

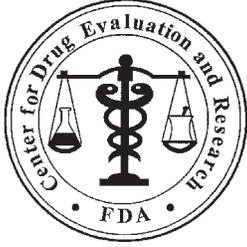
COREPHARMA
LLC

(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/

RAMANI V SISTA
05/28/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: May 27, 2010

To: Badrul Chowdhury, M.D., Director
Division of Pulmonary, Allergy, and Rheumatology Products

Through: Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Zachary Oleszczuk, Pharm.D., Acting Team Leader
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): (b) (4)
(Metaxalone) Tablets
640 mg

Application Type/Number: NDA 022503

Applicant: CorePharma LLC

OSE RCM #: 2009-2137

EXECUTIVE SUMMARY

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA) evaluation of the proposed container labels and insert labeling for (b) (4) (Metaxalone) Tablets 640 mg.

1 INTRODUCTION

This review responds to a request from the Division of Pulmonary, Allergy, and Rheumatology Products for DMEPA to evaluate container label and insert labeling for (b) (4) (Metaxalone) Tablets.

1.1 REGULATORY HISTORY

(b) (4) (640 mg) is being reviewed by the Agency as a 505(b)(2) application. Skelaxin 800 mg, held by King Pharmaceuticals, is the reference listed drug (RLD).

1.2 PRODUCT INFORMATION

(b) (4) (640 mg) is proposed for the same indication as Skelaxin 800 mg, as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. However, the proposed product is a new formulation and a new strength of Metaxalone (see Appendix A). The formulation consists of Metaxalone (b) (4) and Metaxalone (b) (4) for a total strength of 640 mg. The recommended dose for adults and children over 12 years of age is one 640 mg tablet orally three to four times a day. The proposed product will be supplied in bulk bottles of 100 (b) (4).

According to the Clinical Pharmacology review team, Skelaxin 800 mg and (b) (4) (640 mg) are bioequivalent under fasting conditions. However, under fed conditions Skelaxin 800 mg has higher bioavailability than (b) (4) (640 mg). Therefore, depending upon meal conditions, a patient taking (b) (4) (640 mg) may or may not receive the same exposure of Skelaxin 800 mg.

2 METHODS AND MATERIALS

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

Since, Skelaxin is currently marketed as an 800 mg tablet, DMEPA conducted a search of the Adverse Event Reporting System (AERS) on April 28, 2010, using active ingredients "Metaxalone", trade name "Skelaxin" and verbatim substance names "metax%" and "skel%", along with the MedDRA reaction terms "Medication Errors" (HLGT), "Product Quality Issue" (PT) and "Product Label Issues" (HLT).

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were grouped together into cases. If an error occurred, the staff reviewed the cases to determine if the root cause could be associated with the labels, labeling, or packaging configuration of the product, and thus pertinent to this review. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

This search strategy identified 52 cases, however none of the cases are relevant to this review. The medication errors identified were intentional overdose (n=34), complaints of a the drug being in effective (n=3), expired medication being consumed that did not lead to an adverse event (n=3), multiple drug overdoses that did not provide enough information to determine the cause of the error (n=3), adverse events that were not associated with a medication error (n=2), cases that stated an unspecified medication error occurred but did not provide an other details (n=2), errors where the wrong patient was given another patient's medication in a nursing home (n=1), , a transcription error by a pharmacy where the prescription stated to take 1 tablet and the pharmacy wrote take 2 tablets on the prescription label (n=1), a complaint that the currently marketed Skelaxin tablet looks like candy with no patient involvement (n=1), a complaint that a patient confused one of the Skelaxin tablets for their daily vitamin and took two Skelaxin tablets (n=1) and a patient mistakenly taking two tablets, but no other information was given (n=1).

2.2 LABELS AND LABELING

Using Failure Mode and Effects Analysis (FMEA)¹, the Division of Medication Error Prevention and Analysis (DMEPA) evaluates the proposed container labels (see Appendix A) and package insert labeling (no image) submitted by the Applicant on March 2, 2010.

3 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation noted concerns with the size of the Applicant's logo which competes with more important information on the labels and also recommend changes to the presentation of information in the package insert to help minimize this risk of confusion that can lead to medication errors. We provide our recommendations for the presentation of the proprietary name and package insert labeling in Section 3.1 *Comments to the Division* and for the container labels in Section 3.2, *Comments to the Applicant*. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Carolyn Volpe, OSE Regulatory Project manager, at 301-796-5204.

3.1 COMMENTS TO THE DIVISION

1. The labels and labeling include a proprietary name (b) (4) which was found unacceptable by DMEPA in OSE Review #2010-553, dated May 13, 2010. The container labels and package insert should be revised to remove all instances of the proposed proprietary name (b) (4)
2. The *Dosage Forms and Strength* section of the highlights and the full prescribing information contains information that is not required as stated in 21 CFR 201.57(a)(8) and 21 CFR 201.57(c)(4) such as the NDC numbers and how this product is supplied. Revise these sections to include only information that is in accordance with 21 CFR 201.57(a)(8) and 21 CFR 201.57(c)(4).
3. Revise the presentation of strength (640mg) in section 2, *Dosage Forms and Strengths* to include a read space between the number (640) and the unit of measure (mg). The presentation should be as follows:

640 mg

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4. The presentation of the NDC numbers in section 16, *How Supplied* does not include the letters ‘NDC’ immediately before the numbers. Without the letters ‘NDC’ before the number patients and healthcare providers may be confused as to what these numbers represent. To make the NDC numbers more clear include the letters ‘NDC’ immediately before the NDC numbers as follows:

(NDC 64720-324-10) [REDACTED] (b) (4)

3.2 COMMENTS TO THE APPLICANT

1. The labels and labeling include a proprietary name [REDACTED] (b) (4) which we found unacceptable and communicated this decision to you via a letter dated May 27, 2010. The container labels and package insert should be revised to remove all instances of the proposed proprietary name [REDACTED] (b) (4).
2. Your logo on the principal display panel of the container labels is large, distracting, and competes for prominence with both the proposed proprietary name and established name of the drug. Delete or reduce the size of your logo and relocate it away from the proposed proprietary name and established name so that it does not compete with prominence with the propose proprietary name or the established name.
3. The ‘Rx Only’ statement and the net quantity statement ‘100 Tablets’ [REDACTED] (b) (4) [REDACTED] is distracting from more vital information on the PDP of your container labels such as the name of the of product and the strength. Decrease the prominence of these statements by unbolding the font or decreasing the size of the statement.
4. The usual dose is located on the side panel of the container labels. Revise this statement to include the word [REDACTED] (b) (4) at the beginning of the statement. The revised statement should read “**USUAL DOSAGE:** The recommended dose for adults and children over 12 years of ages is one tablet (640 mg) three to four times a day”.
5. The side panel of the container labels instruct pharmacists to [REDACTED] (b) (4) [REDACTED] however this product should also be dispensed in a container that is also unless otherwise specified by the patient. Revise the statement to read “Dispense in a well-closed child-resistant container”.

APPENDICES

Appendix A: Container Labels (134% Magnification)



(b) (4)

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

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/s/

ZACHARY A OLESZCZUK
05/27/2010

DENISE P TOYER
05/27/2010

CAROL A HOLQUIST
05/27/2010

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 20, 2010

To: Ramani Sista, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Roberta Szydlo, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

Through: Lisa Hubbard, Professional Group Leader

CC: Sangeeta Vaswani, DTC Group Leader
Robyn Tyler, Regulatory Review Officer
Wayne Amchin, Regulatory Health Project Manager
(DDMAC)

Subject: NDA # 022503
DDMAC labeling comments for Metaxalone 640 mg tablet for oral
administration

DDMAC has reviewed the proposed product labeling (PI) for NDA 022503 submitted for consult on November 6, 2009. DDMAC's comments are based on the proposed draft marked-up labeling titled "N22503_CP and CMC_27Apr10.doc" that was sent via email from DPARP to DDMAC on May 18, 2010.

DDMAC's comments on the PI are provided directly in the marked-up document attached (see below).

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PI, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22503

ORIG-1

COREPHARMA
LLC

 (b) (4)
640MG
(METAXALONE)

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/s/

ROBERTA T SZYDLO
05/20/2010

MEMORANDUM

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

DATE: April 22, 2010

TO: Bob A. Rappaport, M.D.
Director
Division of Anesthesia and Analgesia Products (DAAP)

FROM: Carol M. Rivera-Lopez, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 4/22/10*
Acting Team Leader, Bioequivalence
GLP and Bioequivalence Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 22-503, (b)(4)
(Metaxalone) Tablets, 640 mg, sponsored by Corepharma
LLC.

At the request of the Division of Anesthesia and Analgesia Products (DAAP), the Division of Scientific Investigations (DSI) conducted an audit of the clinical and analytical portions of the following study:

Study # R08-0838

Title: "A Relative Bioavailability Study of 640 mg Metaxalone Tablets versus 800 mg Skelaxin[®] Tablets under Fasting and Fed conditions"

The clinical portion of this study was conducted at Cetero Research in East Grand Forks, MN. The analytical portion was conducted at (b)(4). Although the clinical study was conducted at the East Grand Forks facility, study records and reserve samples were stored at (b)(4). Therefore, review of clinical study records and collection of reserve samples took place at (b)(4). A separate inspection was conducted at Cetero Research in East Grand Forks, MN to cover the clinical facility. Following this inspection (March 29, 2010), no significant findings were noted and no Form FDA-483 was issued. Following inspection of (b)(4) Form FDA-483 was issued (Attachment 1). DSI received (b)(4) response

to Form FDA-483 on April 15, 2010. Our evaluation of the Form FDA-483 observations and the firm's response follows:

Cetero Research, East Grand Forks, MN (Clinical)

No significant issues were found at this site.

(b) (4)

(Analytical)

The inspection included review of Method Validation #061.8 and Study R08-0838.

1. Failure to establish written procedures for the following:

- **assessment of instrumental carryover during chromatographic analysis of study samples**
- **criteria to determine re-processing of chromatographic data in analytical runs**

Although the firm did not have the aforementioned written procedures, the inspection found that neither carryover nor run re-processing significantly impact measured concentrations of quality controls (QCs) or run acceptance. Therefore, this did not significantly impact the measured metaxalone concentrations in study samples.

At the inspection close out, firm management acknowledged the findings and proposed to implement corrective actions. Their response to Form FDA-483 includes two SOPs that will become effective this month, one for carryover assessment and one for data re-processing. However, the SOP for data re-processing is not adequate as it does not set objective criteria for deciding when to reprocess a run.

DSI recommends that, although the firm should implement corrective actions, the above observations do not significantly affect data in study R08-0838. However, the SOP for data re-processing should be further revised to incorporate objective criteria for re-processing a run.

- 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 reasons for changing the parameters.**

Documentation issues are a repeat deficiency that must be corrected. Although the firm uses the MassLynx™ software audit trail to record changes to integration parameters, justification for such changes is not documented. However, the inspection found that changing integration parameters did not significantly affect the measured QC concentrations or run acceptance decisions. Therefore, study data were not significantly affected.

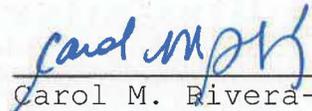
Firm management acknowledged this finding and proposed to implement corrective actions. In their response to the Form FDA-483, they claim they have re-trained their bioanalytical laboratory staff to document changes and reasons for such changes using their "Report for Reprocessed Run" form. However, this needs to be confirmed at the next inspection.

Conclusions:

Following the above inspections, the Division of Scientific Investigations recommends the following:

- Data from Study R08-0838 are acceptable for Agency review.
- [REDACTED] (b) (4) must document justifications of chromatogram re-integration and run re-processing for future studies.

After you have reviewed this transmittal memo, please append it to the original NDA submission.



Carol M. Rivera-Lopez, Ph.D.

Final Classifications:

NAI - Cetero Research, East Grand Forks, ND

FEI: 3004105783

VAI -

[REDACTED] (b) (4)
[REDACTED] (b) (4)

cc:

CDER DSI PM TRACK

DSI/GLPBB/Rivera-Lopez/Yau/Haidar/CF

HFD-170/Ramani Sista

HFR-CE300/Holaday

Draft: CRL 4/8,16/10

Edit: MFS 4/21/10, MKY 4/22/10

DSI file: 6015

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FACTS: [REDACTED] (b) (4)

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

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/s/

CAROL M RIVERA-LOPEZ

04/22/2010

Dr. Yau signed the paper copy on 4/22/2010. Original signed document is available in the DSI file.