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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

Application number: NDA 22-503
Supporting document/s: 16
Applicant's letter date: June 18, 2013
CDER stamp date: June 18, 2013
Product: Metaxalone tablets 640 mg
Indication: Adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions
Applicant: CorePharma, LLC
Review Division: Division of Pulmonary, Allergy and Rheumatologic Drug Products
Reviewer: Asoke Mukherjee, Ph.D
Supervisor/Team Leader: Timothy Robison, Ph.D.
Division Director: Badrul Chowdhury, M.D., Ph.D.
Project Manager: Carol Hill

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 22-503 are owned by CorePharma or are data for which CorePharma has obtained a written right of reference. Any information or data necessary for approval of Metaxalone 640 mg tablet that CorePharma does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 22-503.

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1 Executive Summary

1.1 Introduction:

The sponsor, CorePharma LLC, submitted the NDA for metaxalone 640 mg tablets as a 505(b) (2) application. The sponsor referenced Skelaxin 800 mg tablets marketed by King Pharmaceuticals as the FDA-approved reference listed drug. The Pharmacology and Toxicology Review dated April 20, 2010 recommended approval for the NDA. However, a complete response was issued by the Agency on June 11, 2010 due to deficiencies identified during a facility inspection. The sponsor submitted a Response to Complete Response for NDA 22-503 on June 18, 2013. However, the facilities re-inspection is pending at the time of this review.

The sponsor submitted the draft label incorporating revisions using the PLR format. This review evaluates the non-clinical portion of the draft label.

1.3 Recommendations:

1.3.1 Approvability:

The Pharmacology and Toxicology Review dated April 20, 2010 recommended approval for the NDA. No new nonclinical studies were provided in this resubmission. Recommendations for changes to the product label are shown below.

1.3.2 Additional Non-Clinical Recommendations:

None

1.3.3 Labeling:

Recommended labeling is listed below:

Recommended label (There is one deletion that is shown by strikeout of text):

8.1 Pregnancy

Pregnancy Category B. Reproduction studies in rats have not revealed evidence of impaired fertility or harm to the fetus due to metaxalone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing mothers

It is not known whether this drug is secreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when METAXALONE tablets, 640 mg are administered to a nursing woman.

10 OVERDOSAGE

Deaths by deliberate or accidental overdose have occurred with metaxalone, particularly in combination with antidepressants, and have been reported with this class of drug in combination with alcohol.

(b) (4)

Treatment – Gastric lavage and supportive therapy. Consultation with a regional poison control center is recommended.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of METAXALONE tablets, 640 mg has not been determined.

2 Drug Information

2.1 Drug:

Tradename: Not determined.

CAS Registry Number (Optional): 1665-48-1

Generic Name: Metaxalone 640 mg tablet

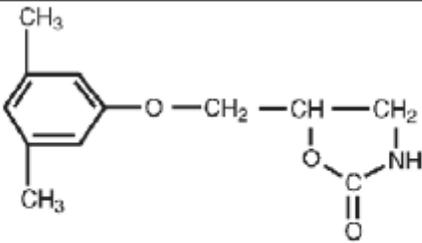
Code Name: RM 192, RM 523

Chemical Name: 5-(3, 5-dimethylphenoxy) methyl]-2-oxazolidone

Pharmacological Class: Skeletal muscle relaxant

Molecular Formula/Molecular Weight: 221.2^(b)₍₄₎ C₁₂H₁₅NO₃

Structure:

Structure	
Empirical formula	C ₁₂ H ₁₅ NO ₃
Molecular weight	221.2 ^(b) ₍₄₎

2.2 Relevant IND/s, NDA/s, and DMF/s

IND/NDA/DMF	drug/compound	sponsor	status
NDA 13-217	Skelaxin (metaxalone, 800 mg)	King Pharm., Inc.	Approved: August 1962
^(b) ₍₄₎			

2.3 Drug Formulation

Table 3.2.P.1.2-1: Composition of (b) (4) Tablets, 640 mg (Metaxalone Tablets, 640 mg)

Ingredient	Reference to Quality Standard	Function	Quantity per Tablet (mg)	IIG Limit*
Metaxalone (b) (4)	In-house	Active	(b) (4)	(b) (4)
Metaxalone	In-house	Active		
Lactose Monohydrate, NF (b) (4)	NF			
FD&C Yellow # 6, (b) (4)	In-house			
Propylene Glycol Alginate, NF (b) (4)	NF			
Alginic Acid, NF (b) (4)	NF			
Povidone, USP (b) (4)	USP			
Magnesium Stearate, NF	NF			

* Maximum allowable level of inactive ingredient for Solid oral dosage form, as listed in the FDA Inactive Ingredient Database.

2.6 Proposed Clinical Population and Dosing Regimen

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

3 Studies Submitted

3.1 Studies Reviewed

None

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

Pharmacology and Toxicology Review of NDA 22-503 by Dr. Jay Chang dated April 20, 2010

11 Integrated Summary and Safety Evaluation:

Corepharma LLC has submitted NDA 22-503 for (b) (4) Tablet 640 mg, which is a reformulation of metaxalone that is bioequivalent to the Reference Listed Drug (RLD) Skelaxin® 800 mg (NDA 13-217; King Pharmaceutical, Inc.) while administered at a lower dose. This application was submitted via the 505(b) (2) pathway with the proposed indication of adjunct to rest, physical therapy, and other measures for relief of discomforts associated with acute, painful musculoskeletal conditions, which is identical to the RLD. The Pharmacology and Toxicology Review dated April 20, 2010 recommended approval for the NDA. However, a complete response was issued by the Agency on June 11, 2010 due to deficiencies identified during a facility inspection. No new nonclinical studies were provided in this NDA resubmission. A labeling review that includes recommendations for changes to nonclinical portions of the product label is provided below.

Labeling Review:

The sponsor has submitted proposed labeling in general conformance with 21 CFR Parts 201, 314 and 601 Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products and with Guidance for Industry on the Content and Format of Labeling for Human Prescription Drug and Biological Products; Final Rule and Notices (January 24, 2006). The recommended nonclinical changes to product labeling are to conform to the most current CFR format (Sections 8.1, 8.3, 10, 12.1, and 13.1).

8.1 Pregnancy

Sponsor's Proposed Labeling:

8.1 Pregnancy

Pregnancy Category B. Reproduction studies in rats have not revealed evidence of impaired fertility or harm to the fetus due to metaxalone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Evaluation: The Sponsor's proposed labeling for Section 8.1 is acceptable.

8.3 Nursing Mothers

Sponsor's Proposed Labeling:

8.3 Nursing Mothers

It is not known whether this drug is secreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when METAXALONE tablets, (b) (4) are administered to a nursing woman.

Evaluation: The Sponsor's proposed labeling for Section 8.3 is acceptable.

10 OVERDOSE

Sponsor's proposed label:

Deaths by deliberate or accidental overdose have occurred with metaxalone, particularly in combination with antidepressants, and have been reported with this class of drug in combination with alcohol.

(b) (4)

Treatment – Gastric lavage and supportive therapy. Consultation with a regional poison control center is recommended.

Evaluation: Per current PharmTox labeling practices, non-clinical data are not required in the Overdosage section. Recommended labeling is shown below.

Recommend Labeling:

Deaths by deliberate or accidental overdose have occurred with metaxalone, particularly in combination with antidepressants, and have been reported with this class of drug in combination with alcohol.

Treatment – Gastric lavage and supportive therapy. Consultation with a regional poison control center is recommended.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of action

Sponsor's Proposed Labeling:

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

Evaluation: The Sponsor's proposed labeling for Section 12.1 is acceptable.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Sponsor's Proposed Labeling:

The carcinogenic potential of METAXALONE tablets, (b) (4) has not been determined.

Evaluation: The Sponsor's proposed labeling for Section 13.1 is acceptable.

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

/s/

ASOKE MUKHERJEE
10/21/2013

TIMOTHY W ROBISON
10/21/2013
I concur

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 22-503
Supporting document/s: 0000, 0003
Applicant's letter date: August 18, 2009
CDER stamp date: August 21, 2009
Product: TRADENAME (metaxalone) Tablets
Indication: Adjunct to rest, physical therapy, and other measures for relief of discomforts associated with acute, painful musculoskeletal conditions
Applicant: Corepharma LLC
Review Division: Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer: Jay H. Chang, PhD
Supervisor/Team Leader: Adam Wasserman, PhD
Division Director: Badrul Chowdhury, MD
Project Manager: Ramani Sista, PhD, RAC

Template Version: December 7, 2009

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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

This NDA may be approved from a pharmacology/toxicology perspective.

1.1.2 Additional Non Clinical Recommendations

There are no recommendations for nonclinical studies.

1.1.3 Labeling

The table below contains the draft labeling submitted by the Applicant, the proposed changes, and the rationale for the proposed changes. For the final version of the label, please refer to the Action Letter. Note: The recommended changes from the proposed labeling are in underlined red or strikeout font.

Table 1 TRADENAME (metaxalone) Labeling

Applicant's proposed labeling	Reviewer's proposed changes	Rationale for changes
<p>12.1. Mechanism of Action</p> <p>The mechanism of action of metaxalone in humans has not been established, but may be due to general central nervous system depression. Metaxalone has no direct action on the contractile mechanism of striated muscle, the motor end plate, or the nerve fiber.</p>	<p>No changes proposed. All language taken from the RLD.</p>	
<p>8.1. Pregnancy</p> <p>Reproduction studies in rats have not revealed evidence of impaired fertility or harm to the fetus due to metaxalone. (b) (4)</p> <p>[Redacted]</p>	<p>No changes proposed.</p> <p>[Redacted] (b) (4)</p>	

(b) (4)		
13.1. Carcinogenesis, mutagenesis, impairment of fertility The carcinogenic potential of metaxalone has not been determined.	No changes proposed. All language taken from the RLD.	

1.2 Brief Discussion of Nonclinical Findings

Corepharma LLC has submitted NDA 22-503 for (b) (4) Tablets via the 505(b)(2) pathway with the reference listed drug (RLD) as King Pharmaceutical's Skelaxin Tablets, 800 mg (NDA 13-217). Note that the applicant's proposed proprietary product name (b) (4) is under review and will herein be referred to as TRADENAME (metaxalone). TRADENAME (metaxalone) is a reformulation of metaxalone that is bioequivalent to the RLD while administered at a lower dose of 640 mg. The indication sought by the applicant is adjunct to rest, physical therapy, and other measures for relief of discomforts associated with acute, painful musculoskeletal conditions, which is identical to the RLD. Prior to the NDA submission, no INDs were submitted and no meetings were held with the Agency. Moreover, no nonclinical pharmacology or toxicology studies were submitted with the NDA. From the pharmacology/toxicology perspective, the NDA was considered fileable but potential review issues were raised in comments sent in the 74-day letter informing the NDA applicant that nonclinical data and/or additional information would be required to justify the total daily intake (TDI) of two excipients, which include propylene glycol alginate (PGA) and povidone (b) (4) resulting from consuming the maximum recommended daily dose (MRDD) of four TRADENAME (metaxalone) tablets. Note that both of these inactive ingredients are present in marketed drugs approved in the U.S. for oral use and are within the maximum concentrations listed in the FDA Inactive Ingredient Guide (IIG) when considering a single tablet. However, the two excipients are in excess of the IIG listed maximum concentrations when considering the MRDD of four tablets of TRADENAME (metaxalone). The NDA applicant subsequently submitted additional information, which did not include any new toxicity studies but rather a cover letter and literature to justify the levels of these two excipients. The literature included World Health Organization (WHO) Technical Reports which assigned a human "Acceptable Daily Intake" (ADI) of 70 mg/kg per body weight for PGA and an ADI of 50 mg/kg per body weight for povidone (specific K-grade not specified) based on a review of the available existing clinical literature and nonclinical toxicity study data. For an adult weighing 70 kg, the TDI of the excipients from the proposed MRDD of TRADENAME (metaxalone) tablets would translate to approximately (b) (4) % of the ADI set forth by the WHO for PGA and (b) (4) % of the ADI for povidone. Furthermore, this reviewer has determined that the TDI of both PGA and povidone (b) (4) from the consumption of 4 TRADENAME (metaxalone) tablets are exceeded in currently marketed FDA approved drugs when used as recommended by their respective labels, which indicates that the Agency has previously determined that such levels are acceptable. For example, the TDI of PGA in TRADENAME (metaxalone) tablets is exceeded by > (b) (4) by the level contained at the MRDD of the currently marketed drug Questran Light®, which contains cholestyramine,

a cholesterol lowering agent that is administered orally to bind bile acids for the treatment of hypercholesterolemia. In addition, the TDI of povidone from 4 TRADENAME (metaxalone) tablets is exceeded by > (b) (4) by the amount found at the MRDD of Colestid®, which is an approved nonabsorbable bile acid sequestrant indicated for the treatment of primary hypercholesterolemia. Taken together, the information above provides adequate qualification for the levels of the inactive ingredients contained in the MRDD of TRADENAME (metaxalone) tablets.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number (Optional)

1665-48-1

2.1.2 Generic Name

Metaxalone

2.1.3 Code Name

N/A

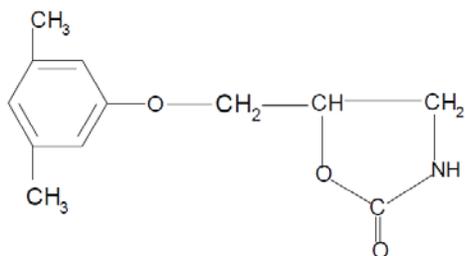
2.1.4 Chemical Name

5-(3,5-dimethylphenoxy)methyl]-2-oxazolidone

2.1.5 Molecular Formula/Molecular Weight

C₁₂H₁₅NO₃ / MW: 221.2 (b) (4)

2.1.6 Structure



2.1.7 Pharmacologic class

Skeletal muscle relaxant

2.2 Relevant IND/s, NDA/s, and DMF/s

Table 2 Relevant INDs, NDAs, and DMFs

<i>IND/NDA/DMF</i>	<i>drug/compound</i>	<i>sponsor</i>	<i>status</i>
NDA 13-217	Skelaxin (metaxalone, 800 mg)	King Pharm., Inc.	Approved: August 1962

(b) (4)

2.3 Clinical Formulation

2.3.1 Drug Formulation

All of the excipients in the TRADENAME (metaxalone) tablet formulation shown in the table below are present in drug products approved by the FDA at levels below the maximum potency listed in the FDA Inactive Ingredients Guide (IIG) when considering a single tablet. However, several excipients are above the IIG listed concentrations when considering the maximum recommended daily dose (MRDD) of four TRADENAME (metaxalone) tablets per day.

Table 3 Clinical formulation of TRADENAME (metaxalone) tablets

<i>Component</i>	<i>Function</i>	<i>Content (mg) per tablet</i>	<i>Content (mg) per 4 tablets</i>	<i>IIG Maximum Potency</i>
Metaxalone (b) (4)	Active pharmaceutical			(b) (4)
Metaxalone	Active pharmaceutical			(b) (4)
Lactose Monohydrate (b) (4) NF				
Alginate Acid (b) (4) NF				
Magnesium Stearate, NF				
Propylene Glycol Alginate (b) (4) NF				
Povidone (b) (4) USP				
FD&C Yellow #6, (b) (4)				
TOTAL WEIGHT		752.0		

* TDI from MRDD of TRADENAME (metaxalone) exceeds the maximum potency listed in the IIG

** IIG maximum potency not listed in weight.

Lactose monohydrate, alginic acid, magnesium stearate, and FD&C Yellow #6 are present in currently marketed drugs in the U.S. and are below the IIG Maximum listed concentrations for the oral route of administration even when considering four TRADENAME (metaxalone) tablets. However, the levels of both propylene glycol alginate and povidone (b) (4) are well above the IIG maximum listed concentrations/levels when considering the MRDD of TRADENAME (metaxalone). Therefore, these two excipients are considered potentially novel and require qualification according to the *ICH Guidance for Industry Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients (May 2005)*.

A request for additional information regarding the potential novel excipients was sent to the NDA applicant in the 74-day letter informing them that “based on the proposed maximum daily dose of four tablets of (b) (4) the inactive ingredients Propylene Glycol Alginate and Povidone (b) (4) appear to exceed the maximum potencies listed in the FDA Inactive Ingredients Guide. Your NDA must provide adequate justification for the safety of the proposed maximum daily exposure to the excipients. Note that any novel excipients must be adequately qualified for safety.” The NDA applicant subsequently submitted an amendment to the NDA that included a cover letter outlining a justification for the safety of the proposed maximum daily exposure to povidone (b) (4) and propylene glycol alginate. Although no new or additional toxicology studies were submitted with the NDA to qualify the level of excipients, the NDA applicant’s justification cited and included safety reports from an international risk assessment organization (references are listed below). A detailed discussion regarding the safety of povidone (b) (4) and propylene glycol alginate follow.

1. Toxicological Evaluation of Certain Food Additives and Contaminants. (1993) Monograph for Propylene Glycol Alginate. Forty-First Meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO Food Additives Series, No 32.
2. Evaluation of Certain Food Additives and Contaminants. (1987) Monograph of Polyvinylpyrrolidone. Thirtieth Report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series, 751.
3. PVP (Polyvinylpyrrolidone) Summary of Toxicity Information. (b) (4)

2.3.2 Comments on Novel Excipients

Propylene glycol alginate

Propylene glycol alginate (PGA) is a propylene glycol ester of alginic acid, which is derived from kelp. It is used as a stabilizing, suspending, gelling, and emulsifying agent in oral and topical pharmaceutical formulations and in cosmetic and food products. According to the Handbook of Pharmaceutical Excipients (Pharmaceutical Press London, UK, 2003), PGA is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may be harmful.

PGA is present in several drug products that have been approved by the FDA for oral use and are currently marketed in the US. The FDA IIG lists the maximum potency at 50.24%, but no total daily intake level in weight is listed. The total daily intake of PGA at the MRDD of four TRADENAME (metaxalone) tablets is (b) (4) mg. PGA is included in the clinical formulation of numerous approved drug products including several different formulations that contain the active pharmaceutical ingredient cholestyramine. These include Questran® (NDA 16-640), Questran Light® (NDA 19-669), and generic versions of Questran® and Questran Light® produced by Par Pharmaceutical Co. (ANDA 77-203; ANDA 77-204) and Sandoz (ANDA 74-557; ANDA 74-558). Cholestyramine is a cholesterol lowering polymeric resin administered orally to bind bile acids for the treatment of hypercholesterolemia, especially elevated LDL cholesterol (type IIa and IIb hyperlipoproteinemia), and for pruritus associated with biliary stasis. According to the Questran Light® label, the initial dose of cholestyramine for adults is 4 g 1–2 times/day, the maintenance dose is 4–16 g/day divided into two doses, and the MRDD is 24 g/day divided into 1–6 doses. Questran Light® contains (b) (4) mg of PGA per 4 g scoop/packet of cholestyramine and the generic version from Par Pharmaceutical Co. contains up to (b) (4) mg per 4 g scoop/packet. Therefore, the total daily intake of PGA is (b) (4) mg when the MRDD of Questran Light® is consumed. This exceeds the TDI of PGA in 4 (b) (4) tablets by > (b) (4)

The acceptable daily human intake of PGA was evaluated in a 1993 report by the Joint FAO/WHO (Food and Agriculture Organization of the United Nations/World Health Organization) Expert Committee on Food Additives (JEFCA) (41st Meeting), which summarized the committee's review of published and unpublished nonclinical toxicological studies that tested PGA in acute toxicity studies, short term toxicity studies, long term carcinogenicity studies, reproduction studies, genotoxicity studies and teratogenicity studies conducted on different animal species. According to the report, a long term repeat-dose oral toxicity study in which dogs were fed a diet containing up to 15% PGA for one year showed no effects on food consumption, weight gain, hematological parameters, organ weights, and histopathology. Rats fed 5, 15, or 25% PGA in the diet for two years exhibited slightly reduced lifespan, decreased food consumption, and loose stool at doses levels of 15 and 25% PGA, but histopathology of major tissues did not reveal lesions or other abnormalities. Embryofetal development reproductive toxicity studies in rats given 0, 7, 33, 155, or 720 mg PGA/kg body weight per day by oral gavage did not result in increased abnormalities in either soft or skeletal tissues relative to controls. Moreover, genotoxicity assays, which included Ames tests, *in vitro* chromosomal aberrations tests, and *in vivo* rat bone marrow micronucleus assays, all concluded that PGA was negative for genotoxic potential according to the limits of the assays. The report also described a study in healthy human volunteers that received 175 mg PGA/kg body weight per day orally for 7 days followed by 200 mg/kg per day for an additional 16 days. The study reported no allergic reactions, no significant effects on fecal parameters, and no significant changes in hematological, biochemical, and urinary parameters. Based on this information, JEFCA allocated an ADI of 70 mg/kg per body weight to PGA, which translates to 4900 mg for a 70 kg adult. Therefore the amount of PGA in the MRDD of TRADENAME (metaxalone) tablets (b) (4)

mg) accounts for approximately (b) (4) or (b) (4)% of the ADI set forth by the WHO for human use.

In summary, PGA is considered by this reviewer to be reasonably safe at the levels present in four TRADENAME (metaxalone) tablets. The TDI of PGA from the recommended use of an FDA approved drug (Questran Light®) exceeds the levels that result from taking the MRDD of TRADENAME (metaxalone). Moreover, an evaluation conducted by the internationally recognized WHO program JEFCA assigned an acceptable human daily intake that is > (b) (4) higher, which strongly argues that toxic effects resulting from PGA consumption of TRADENAME (metaxalone) tablets are highly unlikely.

Povidone (b) (4)

Povidone also referred to as polyvinylpyrrolidone (PVP) is a synthetic polymer consisting mainly of linear (b) (4) groups. Its solubility in water, physiological compatibility, non-toxic, temperature-resistant, pH-stable, non-ionic, colorless, and essentially chemically inert nature all contribute to its wide use in pharmaceuticals and cosmetics. Povidone is available in various grades that reflect their degree of PVP polymerization and consequently their mean molecular weights (MW). The different grades are indicated by K-values, which correspond to the viscosities of the polymers in aqueous solution relative to that of water. According to the Handbook of Pharmaceutical Excipients (Pharmaceutical Press London, UK, 2003), povidone can be produced with an approximate MW of 2500 (grade K-12) to 3,000,000 (grade K-120). (b) (4)

(b) (4)
Notably, povidone (b) (4) comprise polymers of approximately the same range of MWs between (b) (4)

Povidone (b) (4) is present in numerous marketed drug products approved in the US for oral, sublingual, transdermal and vaginal administration with a maximum listed potency of 75.0 mg for the oral route according to the FDA IIG. Although one tablet of TRADENAME (metaxalone) contains only (b) (4) mg of povidone (b) (4) the total daily intake resulting from the MRDD of four tablets results in (b) (4) mg, which exceeds the maximum listed level by > (b) (4). The approved drug containing (b) (4) mg of povidone (b) (4) was identified as fexofenadine hydrochloride 180 mg tablets (ANDA 76-191), which is a generic formulation of Allegra®. The MRDD of fexofenadine HCl 180 mg is one tablet per day. Therefore, the safety of povidone (b) (4) in (b) (4) tablets is not supported by the Agency's previous determination of safety of this approved drug.

Povidone (b) (4) which is closely related to (b) (4) in regards to chemical profile, is also present in numerous marketed drug products. The maximum potency listed in the FDA IIG for oral administration is 80.0 mg. This reviewer identified the approved drug product containing (b) (4) mg of povidone (b) (4) to be a generic formulation of metformin hydrochloride (ANDA 79-148; Indicus Pharma), which is an oral antihyperglycemic agent used for the treatment of type 2 diabetes. The RLD is Glucophage® (NDA 20-

357; Bristol Myers Squibb), which comes in 500, 850, and 1000 mg strengths. According to the Glucophage® label, the MRDD of metformin HCl is 2550 mg in adults. Each 850 mg tablet of metformin HCl contains (b) (4) mg of povidone (b) (4). Therefore, at the MRDD of metformin HCl, the TDI of povidone (b) (4) is (b) (4) mg, which exceeds the (b) (4) mg contained in four tablets of TRADENAME (metaxalone).

Additionally, Colestid® (NDA 20-222; July 19, 1994), which is a nonabsorbable bile acid sequestrant indicated for the treatment of primary hypercholesterolemia, was identified by this reviewer to contain (b) (4) mg of povidone (b) (4) per 1 g tablet. For adults, the recommended initial dose of Colestid® is 5 g PO 1-2 times daily and the MRDD is up to 30 g/day PO given in 2-4 divided doses. Therefore, when the MRDD of Colestid® is administered the TDI of povidone (b) (4) is (b) (4) mg, which exceeds the amount in four TRADENAME (metaxalone) tablets by > (b) (4).

A toxicological evaluation of PVP was conducted by JEFCA (WHO Food Additive Series 15) in 1980. In their report, the committee reviewed a range of nonclinical toxicology studies that included acute toxicity, long term carcinogenicity, teratogenicity, and genotoxicity studies with the goal of determining an acceptable daily intake (ADI) of PVP for man. In a chronic toxicity study in which rats were fed diets of 0, 50,000, or 100,000 ppm povidone K-25, no toxic effects or histological changes were noted and the appearance of benign and malignant tumors were within normal limits for the strains of mice used. Two teratogenicity studies in which rats were fed 10% povidone K-25 in one study and 10% povidone K-90 in another showed that both grades of povidone at these levels were well tolerated by pregnant animals. Moreover, no clinically recognizable symptoms and no malformations were observed in the progeny in either study. The report also summarized the results of *in vitro* genetic toxicity studies that demonstrated that PVP did not cause significant mutagenic effects or transformation in mouse cells (e.g., lymphoma L5178Y, TK+/-BUDR, and Balb/3T3) treated with PVP at concentrations of 0.5%, 1.0%, 5.0% and 10%. While the only biological effect attributed to oral administration of povidone was stool softening or diarrhea, studies involving parenteral administration, primarily intravenous or intraperitoneal, indicated that povidone may accumulate in the reticuloendothelial system (RES), giving rise to a vacuolated appearance associated with foam cells. Notably, the higher MW molecules appeared to be retained the longest. Based on the sum of such information, JEFCA deferred the establishment of an ADI pending a further review of PVP. PVP was reviewed again by JEFCA in 1985 and the committee maintained a temporary ADI of up to 25 mg/kg of body weight based on additional information on PVP. In 1987, JEFCA revisited issues regarding PVP and changed the ADI to up to 50 mg/kg of body weight, which translates to 3500 mg for a 70 kg adult. Therefore the amount of povidone in the MRDD of TRADENAME (metaxalone) tablets ((b) (4) mg) accounts for approximately (b) (4) or (b) (4) % of the ADI set forth by the WHO for human use.

In summary, povidone (b) (4) is considered by this reviewer to be reasonably safe at the levels present in four TRADENAME (metaxalone) tablets. The TDIs of povidone (b) (4) resulting from the recommended use of several FDA approved drugs (e.g.,

Colestid® and Metformin HCl) exceed the levels that result from taking the MRDD of TRADENAME (metaxalone). Moreover, an evaluation conducted by JEFCA established an acceptable human daily intake that is > (b) (4) higher than the levels found in the MRDD of TRADENAME (metaxalone), which strongly argues that toxic effects resulting from the consumption of povidone in TRADENAME (metaxalone) are highly unlikely.

2.3.3 Comments on Impurities/Degradants of Concern

Drug Substance

According to the *Guidance for Industry ICH Q3A (R2) Impurities in New Drug Substances* for a maximum daily dose (MDD) of ≥ 2 g/day, the qualification threshold for identified impurities is 0.05%. One impurity, which is presented in the table below, has been detected in the (b) (4) metaxalone drug substance. The NDA applicant has set the specification of NMT 0.05% for 3,5-dimethylphenol, which is adequate to remain within the ICH limit. (*Reviewer's note*: 3,5-dimethylphenol was evaluated by CDER/OPS/SRS/ICSAS (CompTox consultation) for rodent carcinogenicity and genetic toxicity and was predicted to be negative for both rat and mouse carcinogenicity and negative for genetic toxicity.) The specification for unknown impurities has been set to NMT 0.05%, which is within the identification threshold recommended by the *ICH Q3A* document.

Table 4 Impurity Specifications for Metaxalone and Metaxalone (b) (4)

Impurity	Impurity Structure	Origin of Impurity	Specification limit	Acceptable
3,5-Dimethylphenol (3,5-DMP)	(b) (4)	(b) (4)	NMT 0.05%	Yes
Individual Unspecified Unidentified impurity			NMT 0.05%	Yes
Total impurities			NMT 0.5%	Yes

According to the Residual Solvent Statement included with the NDA, only two solvents (b) (4) metaxalone drug substance and these include (b) (4). Both of these solvents are listed in the *Guidance for Industry Q3C Impurities: Residual Solvents (1997)* companion document *Q3C Tables and Lists*. Moreover, the specifications limits set by the NDA Applicant are within the levels recommended in the *ICH Q3C* document as presented in the table below.

Table 5 Metaxalone and Metaxalone (b) (4) Residual Solvents

Solvent	Class	Specification limit	Acceptable
(b) (4)	(b) (4)	NMT (b) (4) ppm	Yes
(b) (4)	(b) (4)	NMT (b) (4) ppm	Yes

Drug Product

According to the *Guidance for Industry Q3B (R2) Impurities in New Drug Products*, the qualification threshold for impurities/degradants in the drug product for an MDD of > 2 g is 0.10% and the identification threshold is 0.15%. As shown in the table below, the proposed specifications for the identified impurity (b) (4) and unidentified impurities are within the levels recommended in the *ICH Q3B* document.

Table 6 Impurity Specifications for the TRADENAME (metaxalone) Drug Product

Impurity	Impurity Structure	Origin of Impurity	Specification limit	Acceptable
(b) (4)				
Individual Unspecified Unidentified impurity			NMT 0.10%	Yes
Total impurities			NMT 0.5%	Yes

2.4 Proposed Clinical Population and Dosing Regimen

According to the proposed labeling, TRADENAME (metaxalone) is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The recommended dose for adults and children over 12 years of age is one 640 mg tablet three to four times a day. This information is consistent with the labeling of the RLD Skelaxin® 800 mg.

2.5 Regulatory Background

Metaxalone originally approved in the US in August 1962 (NDA 13-217, Skelaxin®), and subsequently determined to be effective under the DESI program (Aug 15, 1974, 39 FR 29396) as an adjunct to rest, physical therapy and other measures for relief of discomforts associated with acute, painful musculoskeletal conditions. It is approved as a 400 mg and 800 mg tablets, however, only the 800 mg tablet is currently marketed. The recommended dose for adults and children older than 12 years is 800 mg three to four times a day, with no restriction on the length of therapy.

CorePharma received tentative approval for a generic metaxalone product (ANDA 40-486) in June 2003 but has not marketed this product.

Prior to this NDA submission, no INDs were submitted and no meetings were held between CorePharma LLC and the Agency to discuss TRADENAME (metaxalone).

3 Studies Submitted

3.1 Studies Reviewed

No pharmacology or toxicology studies were conducted or submitted with this NDA.

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

N/A

4 Pharmacology

4.1 Primary Pharmacology

No pharmacology studies were conducted or submitted with the NDA. According to the RLD Skelaxin® label, “the mechanism of action of metaxalone in humans has not been established, but may be due to general central nervous system depression. Metaxalone has no direct action on the contractile mechanism of striated muscle, the motor end plate, or the nerve fiber.”

4.2 Secondary Pharmacology

N/A

4.3 Safety Pharmacology

No nonclinical safety pharmacology studies were submitted with the NDA.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No nonclinical pharmacokinetic, ADME, or toxicokinetic studies were submitted with this NDA.

5.2 Toxicokinetics

N/A

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose toxicity studies were submitted with this NDA.

6.2 Repeat-Dose Toxicity

No repeat-dose toxicity studies were submitted with this NDA.

7 Genetic Toxicology

No genetic toxicity studies were submitted with this NDA.

8 Carcinogenicity

No carcinogenicity studies were submitted with this NDA. According to the RLD Skelaxin® label, “the carcinogenic potential of metaxalone has not been determined.”

9 Reproductive and Developmental Toxicology

No reproductive toxicology studies were submitted with this NDA. According to the RLD Skelaxin® label, “Reproduction studies in rats have not revealed evidence of impaired fertility or harm to the fetus due to metaxalone. Post marketing experience has not revealed evidence of fetal injury, but such experience cannot exclude the possibility of infrequent or subtle damage to the human fetus. Safe use of metaxalone has not been established with regard to possible adverse effects upon fetal development. Therefore, metaxalone tablets should not be used in women who are or may become pregnant and particularly during early pregnancy unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.”

10 Special Toxicology Studies

No special toxicology studies were submitted with this NDA.

11 Integrated Summary and Safety Evaluation

Corepharma LLC has submitted NDA 22-503 for (b) (4) Tablet 640 mg, which is a reformulation of metaxalone that is bioequivalent to the Reference Listed Drug (RLD) Skelaxin® 800 mg (NDA 13-217; King Pharmaceutical, Inc.) while administered at a lower dose. Note that the proprietary name (b) (4) is under review at the Agency and has been referred to as TRADENAME (metaxalone) in this review. This application was submitted via the 505(b)(2) pathway with the proposed indication of adjunct to rest,

physical therapy, and other measures for relief of discomforts associated with acute, painful musculoskeletal conditions, which is identical to the RLD.

No nonclinical pharmacology or toxicology studies were submitted with the NDA as CorePharma LLC is relying on the FDA's prior judgment of safety, as described in the most current approved labeling for the RLD. Although the NDA was filed, potential review issues were raised in comments sent in the 74-day letter informing the NDA applicant that nonclinical data and/or additional information would be required to justify the total daily intake (TDI) of two excipients, which include propylene glycol alginate (PGA) and povidone (b) (4) resulting from consuming the maximum recommended daily dose (MRDD) of four TRADENAME (metaxalone) tablets. Note that these inactive ingredients are both present in marketed drugs approved in the U.S. for oral use and within the maximum concentrations listed in the FDA Inactive Ingredient Guide (IIG) when considering a single tablet. However, the two excipients are in excess of the IIG listed maximum concentrations when considering the MRDD of TRADENAME (metaxalone). The NDA applicant subsequently submitted additional information, which did not include any new toxicity studies but rather a cover letter and literature to justify the levels of these two excipients. The literature included World Health Organization (WHO) Technical Reports, which established human "Acceptable Daily Intake" (ADI) values of 70 mg/kg per body weight for PGA and an ADI of 50 mg/kg per body weight for povidone (specific K-grade not specified). For an adult weighing 70 kg, the TDI of the two excipients from the proposed MRDD of 4 (b) (4) tablets would translate to approximately (b) (4) % of the ADI for PGA and (b) (4) % of the ADI for povidone. In addition, this reviewer has determined that the TDI of both PGA and povidone (b) (4) from the consumption of four TRADENAME (metaxalone) tablets are exceeded in currently marketed FDA approved drugs when used as recommended by their respective labels, which indicates that the Agency has previously determined that such levels were acceptable. For example, the TDI of PGA in TRADENAME (metaxalone) tablets is exceeded by > (b) (4) by the level contained at the MRDD of the currently marketed drug Questran Light®, which contains cholestyramine, a cholesterol lowering agent that is administered orally to bind bile acids for the treatment of hypercholesterolemia. In addition, the TDI of povidone from four TRADENAME (metaxalone) tablets is exceeded by > (b) (4) by the amount found at the MRDD of Colestid®, which is an approved nonabsorbable bile acid sequestrant indicated for the treatment of primary hypercholesterolemia. Taken together, the information above provides adequate information to demonstrate that the levels of the inactive ingredients contained in the MRDD of TRADENAME (metaxalone) tablets are safe.

12 Appendix/Attachments

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/

JAY H CHANG
04/20/2010

ADAM M WASSERMAN
04/20/2010

I concur the drug may be approved from the Pharmacology/Toxicology perspective.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: NDA 22-503

Applicant: CorePharma LLC

Stamp Date: August 21, 2009

Drug Name: (b) (4)

NDA/BLA Type: 505(b)(2)

On **initial** overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			<i>Not applicable.</i> No pharmacology/toxicology section (Module 4) was submitted with the NDA.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			<i>Not applicable.</i> No pharmacology/toxicology section (Module 4) was submitted with the NDA.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			<i>Not applicable.</i> No pharmacology/toxicology section (Module 4) was submitted with the NDA.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			<i>Not applicable.</i>
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			<i>Not applicable.</i> No toxicology studies were conducted or submitted. However, we have comments to sponsor for the 74-day letter regarding adequate justification for the safety of the proposed maximum daily exposure of two excipients in (b) (4)
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			<i>Not applicable.</i> No toxicology studies were conducted or submitted.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			<i>Not applicable.</i> No toxicology studies were conducted or submitted.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			<i>Not applicable.</i> No pre-submission discussions were held.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		Language is taken from the RLD.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		The proposed specifications for impurities in the drug substance and drug product are within those recommended in the Guidances for Industry Q3A and Q3B.
11	Has the applicant addressed any abuse potential issues in the submission?		X	
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			<i>Not applicable.</i>

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Please forward the following comment to Sponsor:

Based on the proposed maximum daily dose of 4 tablets of (b) (4) the inactive ingredients Propylene Glycol Alginate and Povidone (b) (4) appear to exceed the maximum daily potencies listed in the FDA Inactive Ingredient's Guide. Your NDA must provide adequate justification for the safety of the proposed maximum daily exposure to the excipients. Note that any novel excipients must be adequately qualified for safety.

Refer to the Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005) which is available on the FDA web page at the following <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079250.pdf>, which states that new excipients means any ingredients that are intentionally added to therapeutic and diagnostic products, but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage, although they may act to improve product delivery (e.g., enhance absorption or control release of the drug substance); and (2) ***are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration.*** (emphasis added)

Jay H. Chang, PhD	October 22, 2009
Reviewing Pharmacologist	Date
Adam Wasserman, PhD	October 22, 2009
Team Leader/Supervisor	Date

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22503

ORIG-1

COREPHARMA
LLC

(b) (4)
640MG
(METAXALONE)

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

/s/

JAY H CHANG
04/20/2010

ADAM M WASSERMAN
04/20/2010