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APPLICATION NUMBER:

022503Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW Office of New Drug Products			
Application No.:	NDA 022503 (supporting document # 0019)	Reviewer: Haritha Mandula, Ph.D.	
Submission Date:	December 15, 2014		
Division:	Division of Pulmonary, Allergy and Rheumatology Products	Acting Biopharmaceutics Lead: Kelly M. Kitchens, Ph.D.	
Applicant:	CorePharma LLC	Acting Supervisor: Tapash Ghosh, Ph.D.	
Trade Name:	N/A	Date Assigned:	January 29, 2015
Established Name:	Metaxalone Tablets	Date of Review:	April 7, 2015
Indication:	Metaxalone is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions.	Type of Submission: Resubmission/Class 2; Original (Type 3-New Dosage Form).	
Formulation/strengths	Tablets, 640 mg		
Route of Administration	Oral		
Type of Review:	Revision to the dissolution specification at 30 minutes		
<u>SUMMARY:</u>			
<p>Background: CorePharma submitted an Original NDA Submission on 08/18/2009 (Sequence 0000) with a proposed dissolution specification of “NLT ^{(b) (4)}% (Q) of the labeled amount dissolved in 90 minutes” for both release and stability. On April 20, 2010, CorePharma received an email from FDA requesting a revision to the dissolution specification at 90 minutes from “NLT ^{(b) (4)}% (Q)” to “Q = ^{(b) (4)}%” and recommended that a dissolution specification at 30 minutes be established at “No more than ^{(b) (4)}%”. In CorePharma’s correspondence title “CMC Amendment” dated April 27, 2010 (Sequence 0008), CorePharma accepted the FDA’s recommended dissolution specifications of “30 min: no more than ^{(b) (4)}%” and at “90 min: Q = ^{(b) (4)}%”.</p>			
<p>Submission: CorePharma agrees with the FDA and would like to retain the dissolution specification at “90 min: Q = ^{(b) (4)}%” as previously communicated. The current stability data at controlled room temperature conditions (up to 36 months) which is provided in Module 3.2.P.8.3 met the dissolution specifications at 30 minutes and 90 minutes for the exhibit batches.</p>			
The drug substance is a BCS Class II drug (High Permeability, Low Solubility) and as			

stated in the August 1997, Guidance for Industry– Dissolution Testing of Immediate Release (IR) Solid Dosage Forms, for slowly dissolving or poorly water soluble drugs (BCS Class II); a two-point dissolution specification should be established. The first time point should reflect a dissolution range (a dissolution window) and at a later time point to ensure 85% dissolution, is recommended to characterize the quality of the product.

CorePharma reviewed the USP monograph of another BCS Class II drug product (Carbamazepine Immediate Release Tablets. It was determined that the first time point dissolution specification is a range and it is recommended in the product monograph to use Acceptance Table 2 in the USP General Chapter (USP <711>).

Based on the above, CorePharma is proposing the (b) (4) of the dissolution specification at 30 minutes from “30 mins: Not More Than (b) (4)%” to “30 mins: (b) (4)% to (b) (4)% and in accordance with Acceptance Table 2 in the USP General Chapter for Dissolution (USP <711>)”. CorePharma is not requesting a change in the dissolution specification at 90 minutes. The previously filed dissolution specifications and the proposed specifications are provided below

Filed Specifications (Sequence 0008)	Proposed Specifications
NMT (b) (4)% Dissolved in 30 minutes	30 min: L ₁ = (b) (4)% to (b) (4)% I ₂ = Average of 12 units: (b) (4)% to (b) (4)%; None is more than (b) (4)% of stated ranges: (b) (4)% to (b) (4)% L ₃ = Average of 24 units: (b) (4)% to (b) (4)%; NMT 2 units out of 24 units: (b) (4)% to (b) (4)%; No unit is greater than (b) (4)%
NLT (b) (4)% (Q) Dissolved in 90 minutes	90 min: L ₁ = (b) (4)% (Q) to (b) (4)% L ₂ = Average of 12 units: (b) (4)% (Q); No unit is less than (b) (4)% (Q) I ₃ = Average of 24 units: (b) (4)% (Q); NMT 2 units less than (b) (4)% (Q); No unit is less than (b) (4)% (Q)
% Dissolved in 60 Minutes (For Information purpose only)	Not proposed

As noted in the FDA’s April 20, 2010 email, the earlier time point (30 minutes) was recommended due to low solubility nature of drug substance and taking consideration of particle size of the API being a critical variable for dissolution. Therefore a dissolution range of (b) (4)% - (b) (4)% is proposed for release and stability. The range at 30 minutes is also proposed to low for CorePharma to proceed through the standard 3 stages/levels of dissolution acceptance.

Review: The Biopharmaceutics review is focused on the evaluation and acceptability of the sponsor’s proposed specifications with respect to the dissolution data. The sponsor proposed a specification of:

30 min: (b) (4)%
90 min: Q = (b) (4)%

Based on the dissolution data provided in the original submission and release data submitted in the amendment, the reviewer recommends the following specifications:

30 min: (b) (4) %
90 min: Q= (b) (4) %

On 03/17/2015, the applicant was asked to acknowledge their acceptance of the recommended dissolution specifications. On 03/19/2015, the applicant acknowledged and accepted the agency's recommended dissolution specifications.

On 03/26/2015, the applicant was requested to update and submit drug product specifications per the applicant's acceptance of the agency's recommended dissolution specifications. On 03/30/2015, the applicant responded that the drug product specifications and master stability protocol were revised to reflect the recommended dissolution specifications in Modules 3.2.P.5.1 and 3.2.P.8.2, respectively.

RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 22503 for Metaxalone Tablets, 640 mg, is recommended for approval.

Signature

Haritha
Mandula -A

Digitally signed by Haritha Mandula -A
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ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300422580,
cn=Haritha Mandula -A
Date: 2015.04.07 19:18:45 -04'00'

Haritha Mandula, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Products

Signature

Kelly M.
Kitchens -S

Digitally signed by Kelly M. Kitchens -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=200033657
4, cn=Kelly M. Kitchens -S
Date: 2015.04.08 10:13:12 -04'00'

Kelly M. Kitchens, Ph.D.
Acting Biopharmaceutics Lead
Office of New Drug Products

cc. TGhosh; PSeo.

BIOPHARMACEUTICS ASSESSMENT

Introduction:

Metaxalone, an oxazolidinone derivative, is a central nervous system depressant that has sedative and skeletal muscle relaxant effects. When administered orally, its skeletal muscle relaxant effects are minimal and are probably related to its sedative effect. A single, oral 800-mg dose of metaxalone produces a mean peak level of 296 ng/mL in 2 hours. The onset of action is usually within 1 hour and the duration of action is about 4-6 hours. The drug has a plasma half-life of 2-3 hours.

Solubility:

The calculated pKa for metaxalone is 12.3 ± 0.4 . Metaxalone has very low solubility across the pH range evaluated. The aqueous solubility of Metaxalone as a function of pH was studied in-house and the results obtained are as follows:

Solvent	Solubility
Water	Insoluble
Ethanol	Soluble

Solvent Media	Solubility (mg/mL)				Dose Solubility Volume*
	Trial # 1	Trial # 2	Trial # 3	Average	
0.1N HCl (pH 1.0)	0	0	0.3	0.3	2667

	3	3			
pH 3.0 Acetate Buffer	0.3	0.4	0.5	0.4	2000
pH 4.5 Acetate Buffer	0.3	0.3	0.3	0.3	2667
pH 7.5 Phosphate Buffer	0.3	0.3	0.3	0.3	2667

*Based upon highest available strength of 800 mg.

Dissolution

The proposed dissolution method and specification for the product are as follows:

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



Figure 1. Dissolution profiles of Skelaxin tablets 800 mg (RLD; batch ES807358A) and metaxalone tablets 640 mg (Test Product) (batch CR0820).

Table 3. Dissolution Profiles of Test Product in Comparison with those of Reference Product

	Reference Listed Drug Skelaxin® Tablets 800 mg Lot # ES807358A Exp: 11/2010	Test Product Metaxalone Tablets 640 mg				
		CR0820	CR0904	CR0905		
15 Minutes Average (%) Range (%) RSD (%)	(b) (4)					
30 Minutes Average (%) Range (%) RSD (%)						
45 Minutes Average (%) Range (%) RSD (%)						
60 Minutes Average (%) Range (%) RSD (%)						
90 Minutes Average (%) Range (%) RSD (%)						
120 Minutes Average (%) Range (%) RSD (%)						
F2 Value				Lot # CR0820 is evaluated for bio-study F2 = 64 for Lot # CR0820 (up to 90 minutes) compared to Skelaxin 800 mg F2 = 65 for Lot # CR0904 (up to 90 minutes) compared to Skelaxin 800 mg F2 = 61 for Lot # CR0905 (up to 90 minutes) compared to Skelaxin 800 mg F2 = 91 for Lot # CR0904 (up to 120 minutes) compared to Lot # CR0820 F2 = 83 for Lot # CR0905 (up to 120 minutes) compared to Lot # CR0820		

Originally the sponsor submitted the NDA with a proposed dissolution specification of “NLT (b) (4) % (Q) of the labeled amount dissolved in 90 minutes” for both release and stability. FDA requested a revision to the dissolution specification at 90 minutes from “NLT (b) (4) % (Q)” TO “Q= (b) (4) %” and recommended a dissolution specification at 30 minutes be established at “No more than (b) (4) %”. The sponsor agreed to the FDA’s recommended dissolution specification of “30 min: no more than (b) (4) %” and at “90 min: Q= (b) (4) %”.

The sponsor submitted additional stability data at controlled room temperature conditions (up to 36 months) which met the interim dissolution specifications at 30 min and 90 minutes for the exhibit batches.

However, the sponsor is requesting to propose a range at 30 min of (b) (4) % and 90 min: Q= (b) (4) % to better characterize and control the quality of the drug product.

Comments on proposed change in specifications:

- The reviewer agrees with the sponsor that metaxalone is a poorly soluble drug and data was provided showing that the change in media and pH does have a great impact on dissolution (for more details please refer to the original biopharmaceutics NDA review by Dr. Sandra Suarez Sharp, dated April 16, 2010).

- Per the Guidance for Industry: Dissolution testing of Immediate Release (IR) Solid Dosage Forms, for slowly dissolving or poorly water soluble drugs (BCS class II); a two point dissolution specification should be established. The first time point should reflect a dissolution range, and a later time point to ensure 85% dissolution is recommended to characterize the quality of the product.
- The reviewer verified the USP monograph for other slowly dissolving drug products like carbamazepine tablets and found that a dissolution range (~20) has been recommended at the initial time point.
- At this time, a USP monograph does not exist for metaxalone tablets.
- The sponsor proposed a specification of:

30 min: (b) (4) %
 90 min: Q (b) (4) %

- Based on the dissolution data provided in the original submission and release data submitted in the amendment, the reviewer recommends the following specifications:

30 min: (b) (4) %
 90 min: Q= (b) (4) %

- On 03/17/2015, the applicant was asked to acknowledge their acceptance of the recommended dissolution specifications.
- On 03/19/2015, the applicant acknowledged and accepted the agency's recommended dissolution specifications.
- On 03/26/2015, the applicant was requested to update and submit drug product specifications per the applicant's acceptance of the agency's recommended dissolution specifications.
- On 03/30/2015, the applicant responded that the drug product specifications and master stability protocol were revised to reflect the recommended dissolution specifications in Modules 3.2.P.5.1 and 3.2.P.8.2, respectively.

Recommendation:

From the Biopharmaceutics perspective, NDA 22503 for Metaxalone Tablets, 640 mg, is recommended for approval.

CLINICAL PHARMACOLOGY REVIEW FOR METAXALONE TABLETS 640 MG

<i>NDA</i>	22-503 Resubmission Class 2 (SDN # 16)	<i>Submission Date(s)</i>	06/18/2013
<i>Proposed Brand Name</i>	Metaxalone Tablets 640 mg		
<i>Generic Name</i>	Metaxalone Tablets 640 mg		
<i>Reviewer</i>	Sheetal Agarwal, Ph.D.		
<i>Team Leaders</i>	Satjit Brar, Pharm.D., Ph.D.		
<i>OCP Division</i>	Division of Clinical Pharmacology-2		
<i>OND Divisions</i>	Division of Pulmonary, Allergy and Rheumatology Products		
<i>Sponsor</i>	Core Pharma		
<i>Submission Type</i>	Re-submission (in response to a CR action) for a 505(b)(2) NDA referencing NDA 13-217 for Skelaxin Tablets 800 mg (King Pharma)		
<i>Formulation; Strength(s)</i>	Oral Tablets; 640 mg		
<i>Proposed Indication(s)</i>	Adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions		
<i>Proposed Dosing Regimen</i>	In adults and children over 12 years of age one tablet (640 mg) three or four times a day. The safety and efficacy in children under 12 years of age have not been established.		

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1.0 Executive Summary

1.1 Recommendation:

Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 has reviewed Core Pharma's re-submitted NDA 22-503 requesting approval of Metaxalone Tablets 640 mg, for the proposed indication of adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions and finds the proposed drug product acceptable from a clinical pharmacology perspective.

1.2 Phase 4 commitments:

From a clinical pharmacology perspective, no Phase 4 commitment is applicable to this NDA.

1.3 Summary of important clinical pharmacology findings:

Metaxalone tablet has been marketed since the early 1960s based on Drug Efficacy Study and Implementation (DESI) regulation of 1962. Originally, Skelaxin® 400 mg tablet strength was approved for marketing on August 13, 1962 and Skelaxin® 800 mg scored tablet strength was approved on August 30, 2002 under NDA # 13-217. In 2004, the 400 mg strength was discontinued. The Skelaxin® 800 mg tablet, marketed by King Pharma, is currently listed as the Reference Listed Drug (RLD) in the Orange Book.

Core Pharma submitted their original NDA for a new tablet formulation of 640 mg strength of metaxalone on 08/18/2009. This application received a complete response action (letter in DARRTS dated 6/11/2010) due to deficiencies in their manufacturing facility in Middlesex, NJ. In the original NDA, 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 C_{max} and AUC were within the 80% to 125% bioequivalence limits in fasted state). No new clinical efficacy and safety data was submitted in the original NDA. At the time, clinical pharmacology reviewer Dr. Sayed Al Habet found the NDA acceptable from a clinical pharmacology perspective (review in DARRTS dated 04/21/2010).

In this re-submission, the sponsor has not submitted any new clinical pharmacology or clinical data. However, at the time of writing this review, it was conveyed to the review team that the manufacturing deficiencies identified in the first cycle of the review (in 2010) still existed. The proposed labeling submitted by the sponsor in the resubmission includes edits conveyed to the sponsor by the review team during the first review cycle. However it will be re-reviewed and any additional comments, if any, will be incorporated in this review for the next review team to consider. The NDA is acceptable from a clinical pharmacology perspective.

2. Labeling Recommendations

A list of suggested edits to the sponsor's proposed label is provided below along with the rationale for the proposed change, for the future review team to consider. The labeling modifications were not discussed with the sponsor during the current review cycle due to the fact that the NDA will most likely receive a CR action again.

- i. Delete from Highlights: [REDACTED] (b) (4)

Rationale: There is no compelling reason to include cautionary statements in Highlights.

- ii. Add to Section 2, Dosage and Administration: METAXALONE tablets, 640 mg yields similar systemic exposure of metaxalone as that from Skelaxin (metaxalone) 800 mg tablets. [See *CLINICAL PHARMACOLOGY (12.3)*]

Rationale: The nominal dose of metaxalone is different in this product (640 mg) from that of the currently marketed metaxalone product (800 mg). It is important that prescribers and patients know that both the products lead to similar systemic exposure of metaxalone, irrespective of the differences in the nominal dose, and that they should not try and match the nominal dose of metaxalone to achieve similar therapeutic benefits, which could lead to an overdose situation.

- iii. Delete from Section 5.2, [REDACTED] (b) (4)

Rationale: No PK data supporting this information was provided by the sponsor.

The current approved label for metaxalone (NDA 13-217), which is not in PLR format, indicates that metaxalone is metabolized by the liver and excreted in the urine as unidentified metabolites. It includes the following information related to hepatic and renal impairment: *'The impact of hepatic and renal disease on the pharmacokinetics of metaxalone has not been determined. In the absence of such information, SKELAXIN should be used with caution in patients with hepatic and/or renal impairment.'* (Clinical Pharmacology); and *'Significantly impaired renal or hepatic function.'* (Contraindications)

Pending discussion with the clinical review team, it does not seem justifiable to contraindicate the product in severe hepatic impairment subjects only. It is possible that the drug may have a less beneficial therapeutic profile in 'significantly impaired hepatic impairment' subjects as indicated in the reference product label which could include both moderate and severe hepatic impairment subjects as well as subjects undergoing dialysis. However, if 'significantly impaired hepatic function' is interpreted as severe hepatic impairment by the healthcare community (as interpreted by the sponsor), and if there are significant safety concerns with this product due to its narrow therapeutic index profile, it may be justifiable to leave this contraindication as is.

- iv. Delete Section [REDACTED] (b) (4)

Rationale:

(b) (4)

- v. Delete from section 8.6, Hepatic Impairment: METAXALONE tablets, 640 mg are contraindicated in patients with severe hepatic impairment.

Rationale: Refer to rationale under point iii.

- vi. Delete from section 8.7, Renal Impairment: METAXALONE tablets, 640 mg are contraindicated in patients with severe renal impairment.

Rationale: Refer to rationale under point iii for hepatic impairment. The same rationale applies to contraindicating this product in severe renal impairment.

- vii. Edits to section 12.3, Pharmacokinetics as shown below:

Proposed by the sponsor:

(b) (4)

Recommended by this reviewer: In a relative bioavailability study in healthy adult volunteers, the peak plasma concentration (C_{max}) and extent of absorption (AUC) of metaxalone from METAXALONE tablets 640 mg were found to be similar to that of metaxalone from Skelaxin (metaxalone) 800 mg tablets. After a single dose of METAXALONE tablets, 640 mg, under fasted conditions mean C_{max} and AUC values were 2 ng/mL and 16 ng.h/mL respectively. The time-to-peak plasma concentration (T_{max}) occurred at 3 h (range 1.5-12 h). Compared to fasted condition, the presence of a high fat meal resulted in 23% increase in C_{max} with no change in AUC and a T_{max} of 8 h (range 3.5-16 h).

Rationale: Make the label less wordy and more accurate with complete information.

- viii. Edits to section 12.3, Pharmacokinetics, Special Populations, Age:

Proposed by the sponsor:

(b) (4)

(b) (4)

Recommended by this reviewer: The effects of age on the pharmacokinetics of METAXALONE tablets 640 mg have not been evaluated.

Rationale:

(b) (4)

ix. Edits to section 12.3, Pharmacokinetics, Special Populations, Gender:

Proposed by the sponsor:

(b) (4)

Recommended by this reviewer: Females exhibited higher systemic exposure compared to males following administration of METAXALONE tablets, 640 mg under fasted state in healthy volunteers. The C_{max} and AUC of metaxalone were found to be ~40% greater in females compared to males.

Rationale: The effect of gender on metaxalone PK can be adequately described under fasted conditions,

(b) (4)

x. Delete from section 14, Clinical Studies:

(b) (4)

Rationale: Section 14 is included in label to include a description of the clinical studies,

(b) (4)

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/s/

SHEETAL S AGARWAL
11/20/2013

SATJIT S BRAR
11/20/2013

Final Version (April 21, 2010) Clinical Pharmacology Review

NDA: 22-503	Dates of Submission: August 18, 2009
Generic Name	Metaxalone
Brand Name:	(b) (4) (initially proposed, but final TBD)
Formulation:	Tablet
Strengths:	640 mg
OCP Division OND Division	Division of Clinical Pharmacology II Division of Pulmonary, Allergy, and Rheumatology Products
Route of Administration:	Oral
Indication:	Adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions
Dosage and Administration:	In adults and children over 12 years of age one tablet (640 mg) three or four times a day. The safety and efficacy in children under 12 years of age have not been established.
Type of Submission:	Original NDA (505(b)(2))
Sponsor:	CorePharma LLC, Middlesex, NJ
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.

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1.0 Executive Summary

1.1 Recommendation:

From the Clinical Pharmacology perspective, this NDA is acceptable provided that (a) a mutually acceptable agreement regarding the labeling language can be reached between the Agency and the Applicant and (b) DSI inspection is satisfactory.

1.2 Phase 4 Commitment

From the Clinical Pharmacology perspective, no phase 4 commitment is applicable to this NDA.

1.3 Summary of Important Clinical Pharmacology Findings:

Metaxalone tablet has been marketed since the early 1960s based on Drug Efficacy Study and Implementation (DESI) regulation of 1962. Originally, Skelaxin® 400 mg tablet strength was approved for marketing on August 13, 1962 and Skelaxin® 800 mg scored tablet strength was approved on August 30, 2002 under NDA # 13-217. In 2004, the 400 mg strength was discontinued. The Skelaxin® 800 mg tablet, marketed by King Pharma, is currently listed as the Reference Listed Drug (RLD) in the Orange Book.

The current NDA is submitted by Core Pharma under 505(b)(2) provision for a new tablet formulation of 640 mg strength of metaxalone. The initial proposed trade name for this strength was (b) (4). However, during the review cycle, upon the Agency's request, the name, (b) (4) was withdrawn (T-con dated December 7, 2009). At the time of writing this review no new trade name has been submitted by the sponsor.

In support of the 505(b)(2) application the sponsor submitted data from a 4-way crossover relative bioavailability study (R08-0838). No new clinical efficacy and safety data was submitted in this NDA.

In Study R08-0838, sponsor assessed equivalency in terms of C_{max} and AUC of metaxalone 640 mg tablets to Skelaxin® 800 mg tablets under fasted and fed conditions. The study was conducted in 47 healthy subjects in fasted and fed conditions after administration of 640 mg strength (test product, 640 mg metaxalone tablet) and 800 mg Skelaxin® (RLD) as follows:

Treatment A (Fasted, Test): Single dose of 640 mg metaxalone tablets after an over night fast

Treatment B (Fed, Test): Single dose of 640 mg metaxalone tablets 30 min after a high-fat breakfast

Treatment C (Fasted, RLD): Single dose of 800 mg Skelaxin® tablets after an over night fast

Treatment D (Fed, RLD): Single dose of 800 mg of Skelaxin® tablets 30 min after a high-fat breakfast

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

Summary of Results:

- The plasma concentration-time profiles of metaxalone were comparable following 640 mg metaxalone and 800 mg Skelaxin® tablets under **fasted condition** (Figure 1.3.1).
- The 90% CI for both C_{max} and AUC were within the 80% to 125% BE limits in **fasted state** (Table 1.3.1).

Figure 1.3.1. Mean (SD) Plasma Concentration-Time Profiles of Metaxalone Following 640 mg Metaxalone Tablet and 800 mg Skelaxin® Tablet in Fasted Healthy Subjects (n=47).

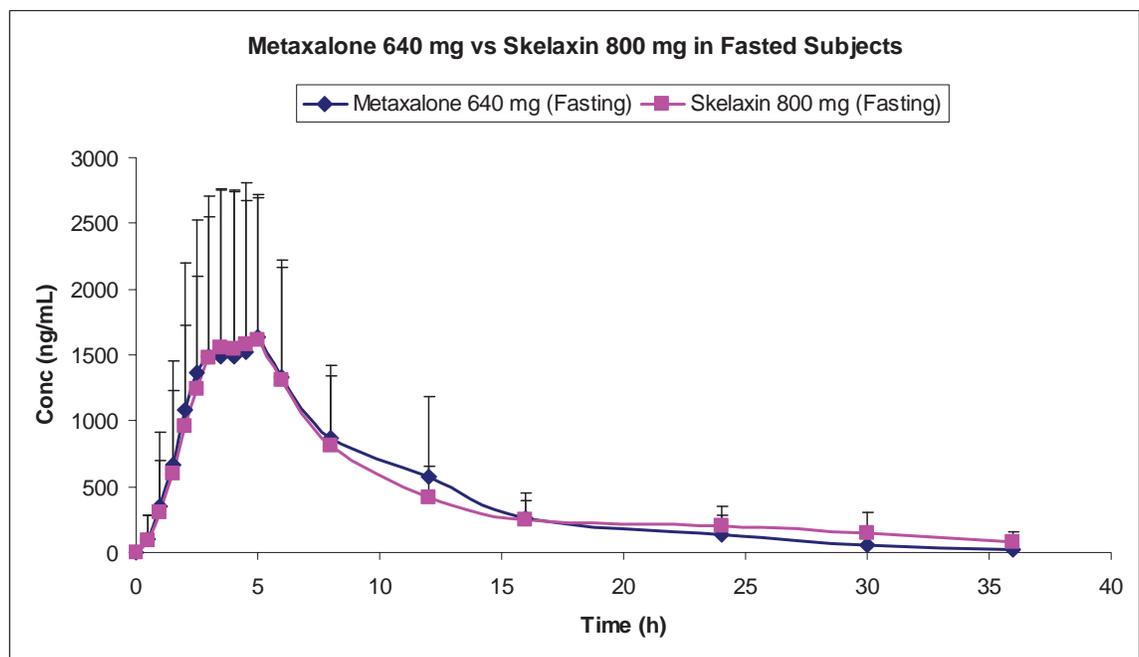


Table 1.3.1. Geometric Mean Metaxalone PK Parameters, Ratio of Geometric Means and 90% CI Following Metaxalone 640 mg and 800 mg Skelaxin® Tablets in all Fasted Subjects.

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

- However in fed conditions, the plasma concentration-time profile of metaxalone following 640 mg metaxalone tablets was significantly lower than after 800 mg Skelaxin® tablet (**Figure 1.3.2**).
- The C_{max} and AUC in fed state were approximately 28% and 25% lower after 640 mg metaxalone tablets compared to 800 mg Skelaxin® tablet, respectively (**Table 1.3.2**).
- The 90% CI for both C_{max} and AUC were outside the 80% to 125% BE limits.

Figure 1.3.2. Mean (SD) Plasma Concentration-Time Profiles of Metaxalone Following 640 mg Metaxalone Tablet and 800 mg Skelaxin Tablet in Fed Healthy Subjects (n=47).

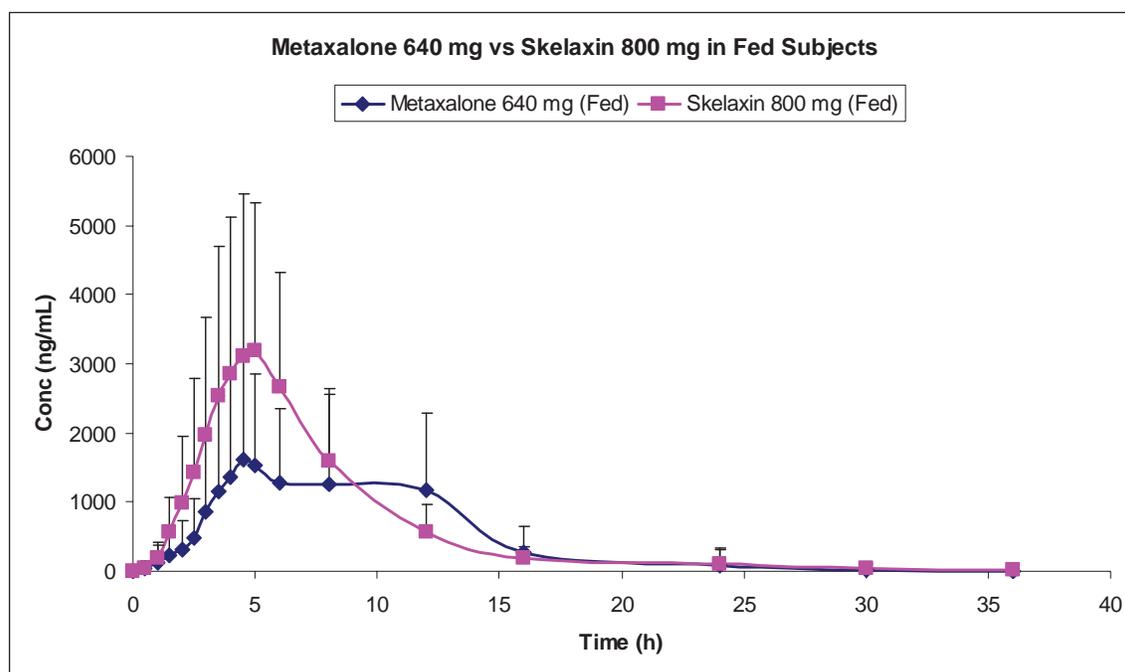


Table 1.3.2. Geometric Mean Metaxalone PK Parameters, Ratio of Geometric Means, and 90% CI Following 640 mg Metaxalone and 800 mg Skelaxin® Tablets in all Fed Subjects.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	SKELAXIN® Tablets (800 mg) Fed	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	14600.21	19359.95	75.41	(69.53, 81.80)
AUC _{0-inf} (ng·hr/mL)	14840.39	19624.22	75.62	(70.02, 81.67)
C _{max} (ng/mL)	2207.56	3046.51	72.46	(61.96, 84.75)

In contrast to the 640 mg metaxalone tablet, food substantially increased the absorption of metaxalone following 800 mg Skelaxin® tablet (**Figure 1.3.3**). The C_{max} and AUC were approximately 75% and 30% higher in fed state than in fasted state, respectively (**Table 1.3.3**). Food effect is already documented in the currently approved label for Skelaxin® 800 mg tablet and food effect data from current submission is consistent with what is already known.

Figure 1.3.3. Mean (SD) Plasma Concentration-Time Profiles of Metaxalone Following 800 mg Skelaxin Tablet in Fed and Fasted Healthy Subjects (n=47).

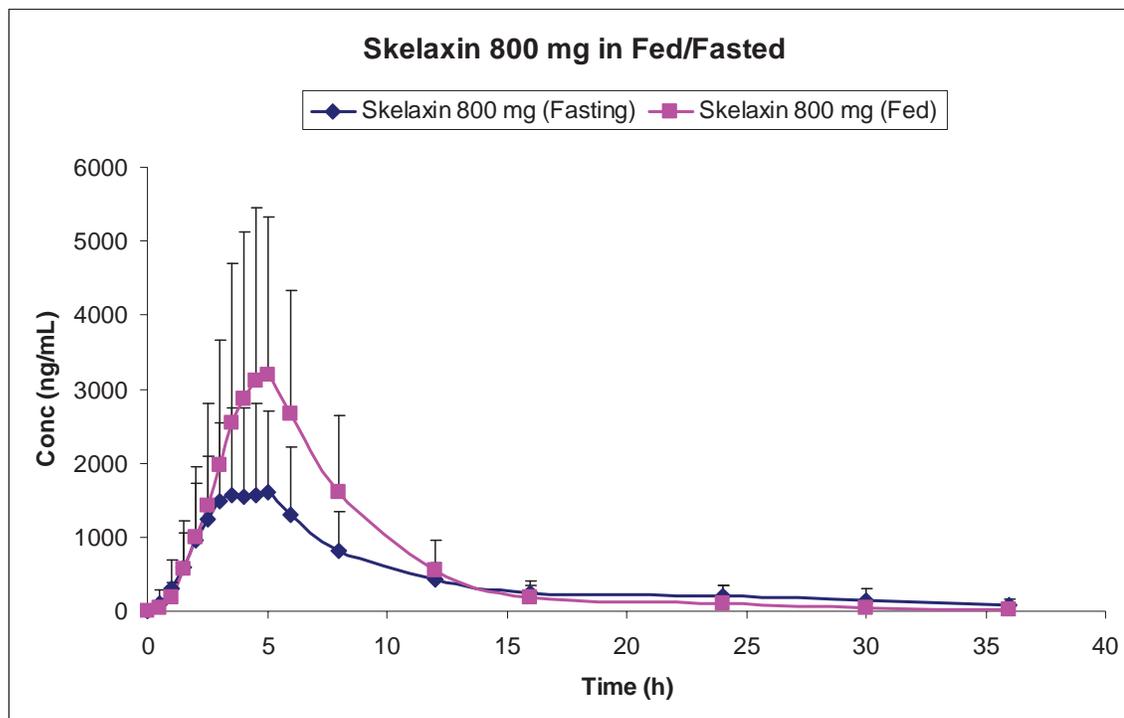
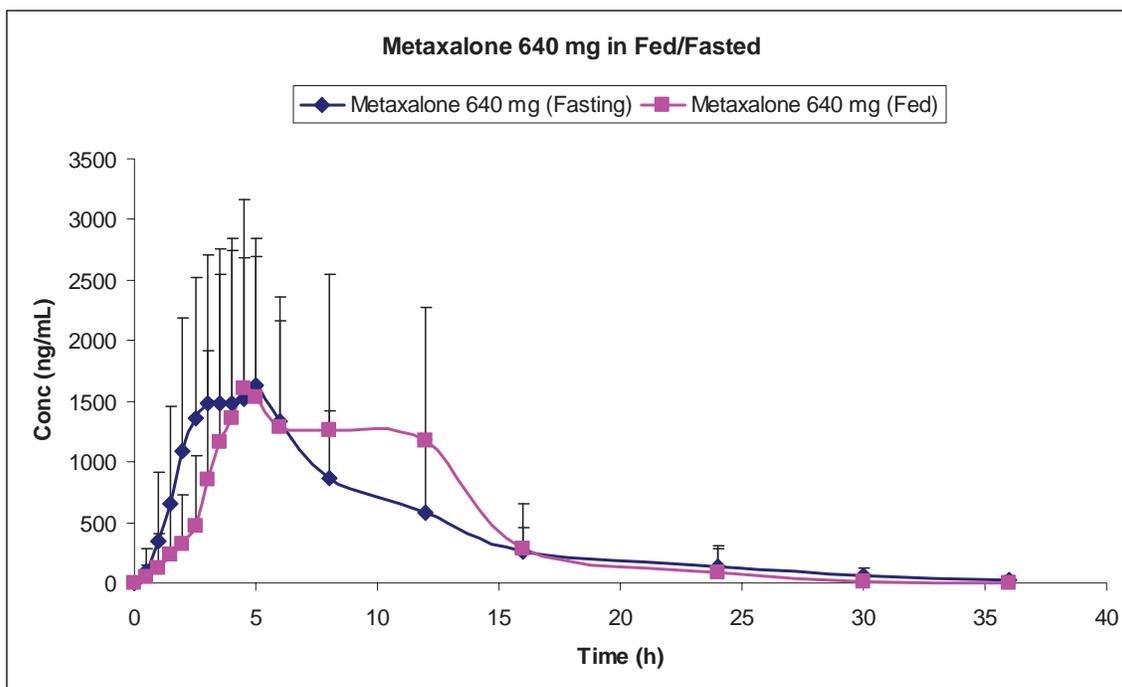


Table 1.3.3. Geometric Mean Metaxalone PK Parameters, Ratio of Geometric Means, and 90% CI Following 800 mg Skelaxin® Tablet in all Fed and Fasted Subjects.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	SKELAXIN® Tablets (800 mg) Fed	SKELAXIN® Tablets (800 mg) Fasting	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	19359.95	13907.27	139.21	(128.35, 150.99)
AUC _{0-inf} (ng·hr/mL)	19624.22	14866.84	132.00	(122.22, 142.56)
C _{max} (ng/mL)	3046.51	1735.28	175.56	(150.11, 205.33)

- When 640 mg metaxalone tablet was given with food, the absorption phase seems to be extended (Figure 1.3.4). However, the T_{max} in fasted and fed conditions appears to occur at the same time.

Figure 1.3.4. Mean (SD) Plasma Concentration-Time Profiles of Metaxalone Following 640 mg Metaxalone Tablet in Fed and Fasted Healthy Subjects (n=47).



- The AUCs were similar in fed and fasted conditions with the 90% CI falling within 80% and 125% (**Table 1.3.4**). The 90% CI for the C_{max} is outside the 80% and 125% and the C_{max} under fed conditions is higher by about 23% than that after fasted condition.

Table 1.3.4. Geometric Mean Metaxalone PK Parameters and 90% CI Following 640 mg Metaxalone Tablet (Test) in all Fed and Fasted Subjects.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	Metaxalone Tablets (640 mg) Fasting	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	14600.21	13686.84	106.67	(98.35, 115.70)
AUC _{0-inf} (ng·hr/mL)	14840.39	13988.59	106.09	(98.23, 114.57)
C _{max} (ng/mL)	2207.56	1798.83	122.72	(104.93, 143.53)

Gender difference in the PK of metaxalone is historically known. According to the currently approved label dated November 24, 2006 for Skelaxin® it was stated that “The bioavailability of metaxalone was significantly higher in females compared to males as evidenced by C_{max} (2115 ng/mL *versus* 1335 ng/mL) and AUC_∞ (17884 ng·h/mL *versus* 10328 ng·h/mL)”.

Gender differences in PK were also observed in this study. Overall, the plasma concentration-time profiles of metaxalone are consistently higher in females than in males in fasted and in fed conditions irrespective of product being administered (**Figures 1.3.4 and 1.3.5**).

Figure 1.3.4. Gender Differences in Metaxalone AUC in Fed and Fasted Subjects After the Administration of 640 mg Metaxalone and 800 mg Skelaxin® Tablets

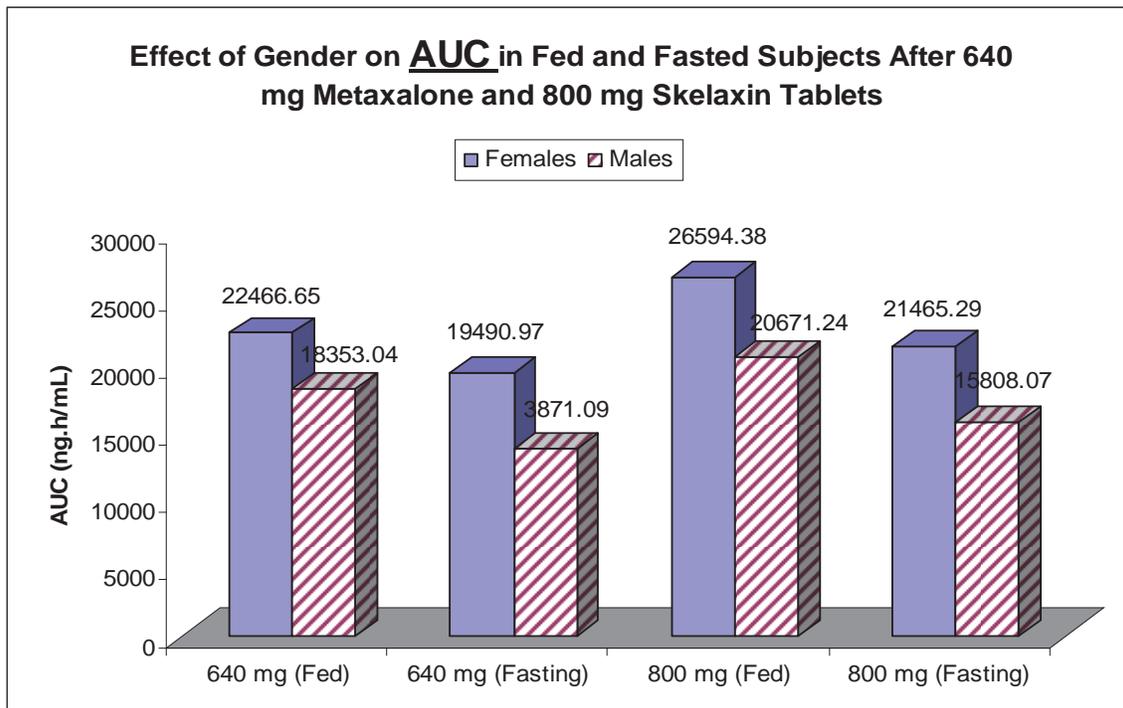
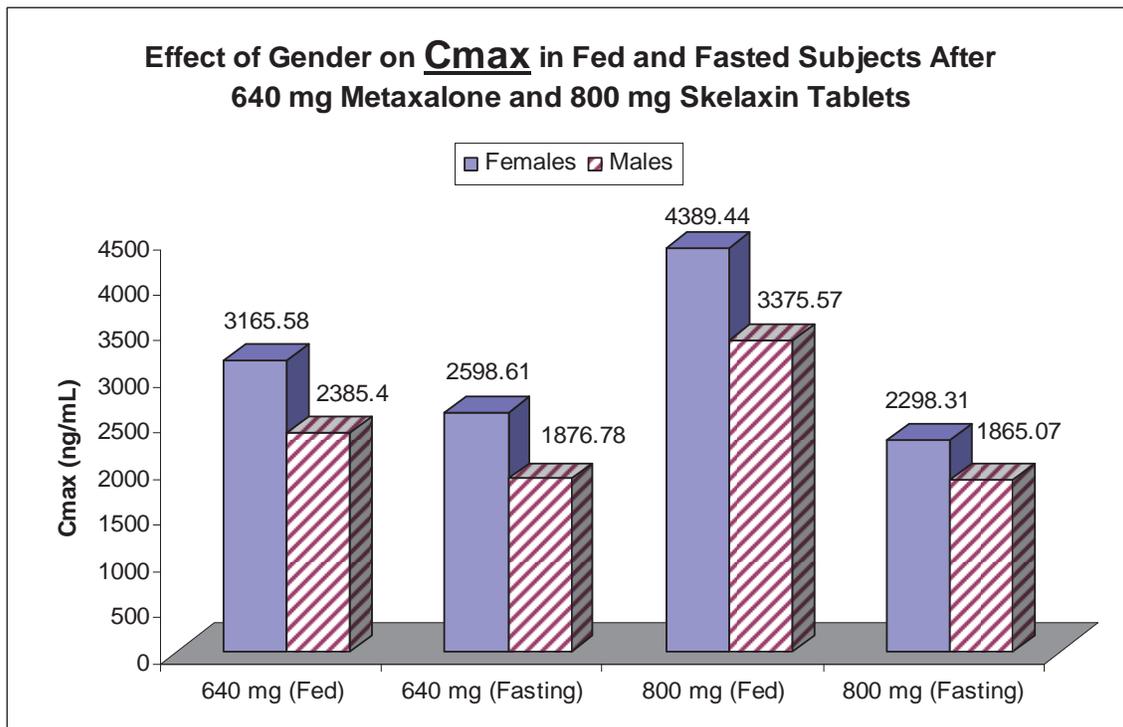


Figure 1.3.5. Gender Differences in Metaxalone C_{max} in Fed and Fasted Subjects After the Administration of 640 mg Metaxalone and 800 mg Skelaxin®



Based on the statistical analysis and the 90% CI, the two products are not bioequivalent in either females or males when administered under fasted or fed conditions. However, it is not required that the products have to be equivalent in the sub-groups of males and females. The general BA/BE guidance for industry recommends that if a product is intended for use in both sexes, sponsor should attempt to include similar proportions of males and females in the study. However, the guidance also acknowledges that there may not be sufficient power for BE demonstration in each subgroup and explicitly states that statistical analysis of subgroups is not recommended.

(b) (4)

The sponsor is proposing to use the trade name (b) (4) 640 mg tablet which is (b) (4) In addition, the recommended dose of (b) (4) is 640 mg tablet whereas (b) (4) (b) (4)

In the “Dosage and Administration” section of the proposed label and other appropriate sections the differences between 800 mg and 640 mg tablets in terms of substitution should be stated.

On December 7, 2009 the Division of Medication Error Prevention and Analysis held a T-con with the sponsor to discuss name issues. The sponsor was informed to withdraw the name and propose a new name as soon as possible. At the time of writing this review, no new name has been submitted by the sponsor.

Pediatric Indication:

Skelaxin 800 mg tablet is indicated for adults and children over 12 years of age. Based on this, 640 mg metaxalone is also indicated for adults and children over 12 years of age. However, the sponsor is requesting waiver for children <12 years of age. The rationale for the waiver submitted by the sponsor is as follows:

- The drug does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients.
- The mechanism of action of metaxalone is not well known.
- The musculokeletal injuries are not common in children ages 6 to 11 years of age.
- Other analgesics are proven efficacious in children 6-17 years of age.
- Studies are impractical. Studies in children under 6 years of age are not likely to be interpretable in the case of muscle relaxants. The response is also difficult to quantify.

Based on internal discussion within the review team, this proposal appears reasonable.

Overall Summary:

- Based on this study, the new 640 mg metaxalone tablet is equivalent to 800 mg Skelaxin® only under fasted condition and not under fed conditions.
- Food increased the C_{max} after 640 mg tablet by approximately 23% with no change in AUC compared to that after fasted condition. Food increased the C_{max} and AUC of metaxalone following administration of Skelaxin® tablet by approximately 75% and 30%, respectively. The data from this study is in general consistent with the food effect in the currently approved label for Skelaxin® Tablet.
- Consistent with the gender related PK differences already reported in the currently approved label for Skelaxin®, the exposure of metaxalone in females appears to be consistently higher in females compared to males irrespective of feeding conditions and the products being administered.
- The two products are not bioequivalent when administered in either females or males alone under fed or fasted conditions. Nevertheless, this is not an issue as the FDA BA/BE guidance discourages stratification of the bioequivalence data by gender. The relative bioavailability and bioequivalence studies are normally required to be conducted in males and females healthy subjects. Hence, the combined data from all fasted subjects (n=47) is considered adequate to conclude that the two products exhibit equivalent systemic exposure only under fasted condition.
- Labeling language in reference to substitution issues between 800 mg Skelaxin® and 640 mg metaxalone tablets need to be addressed in the package insert as appropriate in light of different nominal doses between the two products.

Conclusion:

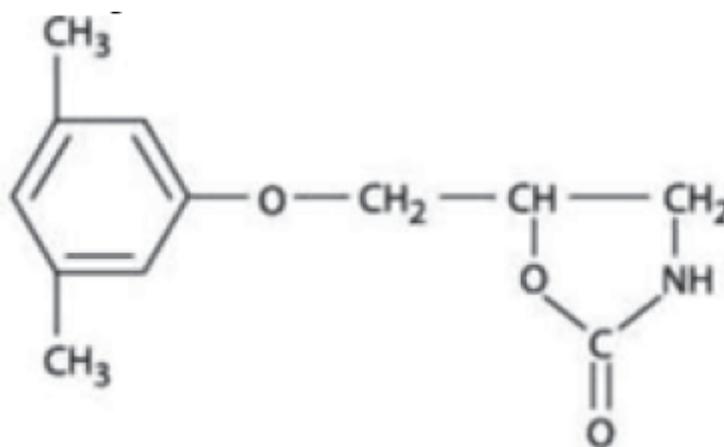
From the clinical pharmacology perspective, overall adequate clinical pharmacology information has been provided in the application.

2. Question Based Review

2.1 General Attributes/Background:

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

Metaxalone will be available as (b) (4) tablet in only 640 mg strength. Its chemical name is: 5-[(3,5- dimethylphenoxy) methyl]-2-oxazolidinone with a molecular weight of 221.25. Its empirical formula is C₁₂H₁₅NO₃. Its structural formula is as follows:



Metaxalone is freely soluble in chloroform, soluble in methanol and in 96% ethanol, but practically insoluble in ether or water.

Overview of Regulatory Issues:

This is a 505(b)(2) application for metaxalone 640 mg tablets. The sponsor referenced NDA 13-217 held by King Pharmaceuticals for Skelaxin® tablets 800 mg (RLD). The NDA is supported by a relative bioavailability study showing **equivalent** C_{max} and AUC **under fasted conditions** between the test and reference products. **Under fed conditions**, the two products were **not equivalent**. The new tablet has higher bioavailability (about 20% higher) and if it was developed at 800 mg strength, it would have failed bioequivalence test against the RLD 800 mg tablet. Therefore, the sponsor developed 640 mg tablet that would provide equivalent exposure to RLD. The indications and other labeling language are essentially similar to the currently approved label for RLD.

The draft 505(b)(2) guidance under Bioequivalence bullet (page5) states "Generally, an application for a pharmaceutically equivalent drug product must be submitted under section 505(j) of the Act and the proposed product must be shown to be bioequivalent to the reference listed drug (21 CFR 314.101 (d)(9)). Applications for proposed drug products where the rate (21CFR314.54(b)(2)) and/or extent (21 CFR 314.54 (b)(1)) of absorption exceed, or otherwise different from, the 505 (j) standards for bioequivalence compared to a listed drug may be submitted pursuant to section 505(b)(2) of the Act. Such a proposed product may require additional clinical studies to document safety and

efficacy at the different rate and extent of delivery. Generally, the difference in rate and extent of absorption should be reflected in the labeling of the 505(b)(2) product. The proposed product does not need to be shown to be clinically better than the previously approved product; however 505(b)(2) should not be used as a route of approval for poorly bioavailable generic drug products unable to meet the 505(j) standards for bioequivalence. If the proposed product is a duplicate of an already approved product, it should not be submitted as a 505(b)(2) application (21 CFR 314.101 (d)(9))."

The above issues were shared with Regulatory Project Management Staff in the Office of New Drugs (OND) on October 1, 2009 via e-mail for feedback. On October 14, 2009 Ms. Kim Quaintance responded with the following statement:

"According to the regulations, we can refuse to file an application for a drug product that differs from the referenced product if it is *less* bioavailable. Given that this product is more bioavailable in the fed state, we can review this (it can be filed) as a (b)(2). Of course whether the data support approval is a totally different matter!"

Based on this feedback, the NDA was filed.

Labeling Issues:

1) Effect of Food Issue:

The two products were not equivalent under fed conditions. However, no language appeared in either the currently approved label or the proposed labels in reference to the effect of food. The "Dosage and Administration" section of the proposed label is similar to that of the currently approved label which states the following:

"The recommended dose for adults and children over 12 years of age is one 640 mg tablet three to four times a day".

The rationale for not having any restriction for administration with respect to food is that there is no adequate exposure-response information available for metaxalone. The lack of restriction in administration of metaxalone with reference to food allows individual prescriber to make their own decision based on patient's responses to treatment (OCP review dated February 3, 2004).

2) Product Substitution Issue:

The RLD strength is 800 mg and the proposed new strength is 640 mg. During prescribing there is potential for confusion in reference to substitution between the two products.

3) Product Name Issue:

The name of (b) (4) 640 mg tablet (b) (4) Agency communicated to the sponsor that this name is not acceptable during a Teleconference on December 7, 2009. At the time of writing this review the Agency is awaiting the submission of the new trade name.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action:

The mechanism of action of metaxalone is unknown. However, it appears to be related 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.

Proposed Indications:

Proposed indications are the same as the RLD. According to the currently approved label for Skelaxin, 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 mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Metaxalone does not directly relax tense skeletal muscles in man.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The recommended dose for adults and children over 12 years of age is one 640 mg tablet three to four times a day.

This recommendation is similar to that currently approved for Skelaxin® 800 mg. However, the only difference is in the nominal dose (i.e., 640 mg instead of 800 mg for Skelaxin®). Sponsor established equivalent exposure (in terms of C_{max} and AUC) between metaxalone 640 mg tablet and Skelaxin® 800 mg tablet under fasted conditions.

2.1.4 What are the Core Studies Submitted in this NDA?

The sponsor conducted a four way relative bioavailability study in fed and fasted healthy subjects comparing 640 mg test product (b) (4) and RLD, 800 mg Skelaxin® (Study # R08-0838). This study is described below briefly and the detailed description can be found in Section 4.2 (Individual Study Review):

Objective:

The primary objective of this study was to determine the relative bioavailability of 640 mg metaxalone tablet to that of 800 mg Skelaxin® Tablet following a single dose in healthy adult subjects when administered under fasted and fed conditions.

Study Design:

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

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

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

Results:

- The plasma concentration-time profiles of metaxalone were comparable following 640 mg metaxalone tablets and 800 mg Skelaxin® tablets under **fasted conditions** (Figure 2.1.4.1).
- The 90% CI for both C_{max} and AUC were within the 80% to 125% BE limits in **fasted state** (Table 2.1.4.1).

Figure 2.1.4.1. Mean (SD) Plasma Concentration-Time Profiles of Metaxalone Following 640 mg Metaxalone Tablets and 800 mg Skelaxin Tablet in All Fasted Subjects (n=47).

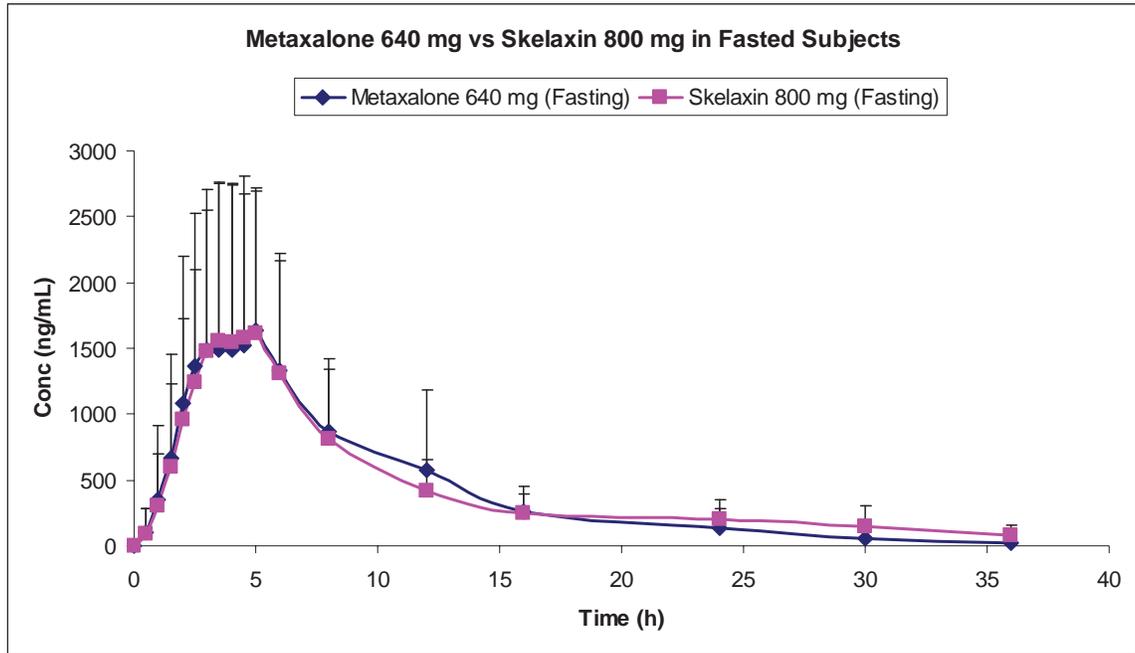


Table 2.1.4.1. Geometric Mean Metaxalone PK Parameters, Ratio of Geometric Means, and 90% CI Following Metaxalone 640 mg tablets and 800 mg Skelaxin® Tablets in All Fasted Subjects.

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

- However in fed subjects, the plasma concentration-time profile of metaxalone following 640 mg Metaxalone tablets was remarkably lower than after 800 mg Skelaxin® tablet (**Figure 2.1.4.2**).
- The C_{max} and AUC in fed state were approximately 28% and 25% lower after 640 mg metaxalone tablets compared to 800 mg Skelaxin® tablet, respectively (**Table 2.1.4.2**). Also, the 90% CI for both C_{max} and AUC were outside 80% to 125%.

Figure 2.1.4.2. Mean Plasma Concentration-Time Profiles of Metaxalone Following 640 mg Metaxalone Tablets and 800 mg Skelaxin® Tablets in All Fed Healthy Subjects (n=47).

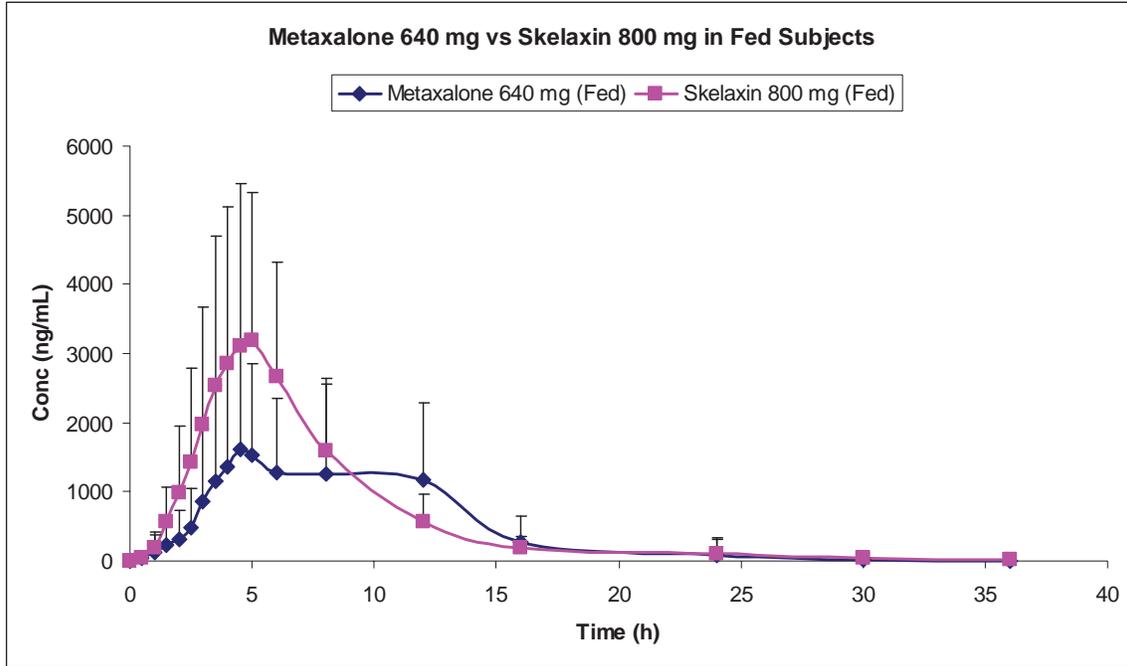


Table 2.1.4.2. Geometric Mean Metaxalone PK Parameters, Ratio of Geometric Means, and 90% CI Following (b) (4) (640 mg) and 800 mg Skelaxin® Tablets in all Fed Subjects.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	SKELAXIN® Tablets (800 mg) Fed	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	14600.21	19359.95	75.41	(69.53, 81.80)
AUC _{0-inf} (ng·hr/mL)	14840.39	19624.22	75.62	(70.02, 81.67)
C _{max} (ng/mL)	2207.56	3046.51	72.46	(61.96, 84.75)

- In sharp contrast to 640 mg metaxalone tablet, food increased the C_{max} and AUC by approximately 75% and 30% following 800 mg Skelaxin® tablet, respectively (Figure 2.1.4.3 and Table 2.1.4.3). Food effect is already documented in the currently approved label for Skelaxin® 800 mg tablet.

Figure 2.1.4.3. Mean Plasma Concentration-Time Profiles of Metaxalone Following 800 mg Skelaxin Tablet in All Fed and Fasted Healthy Subjects (n=47).

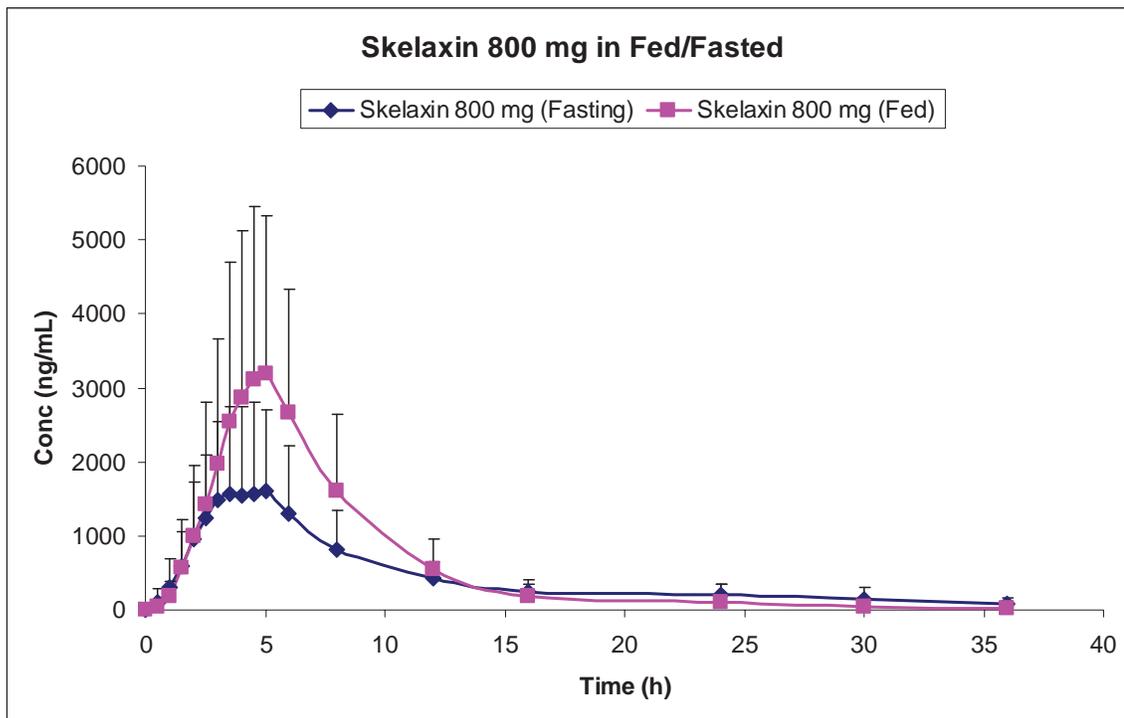
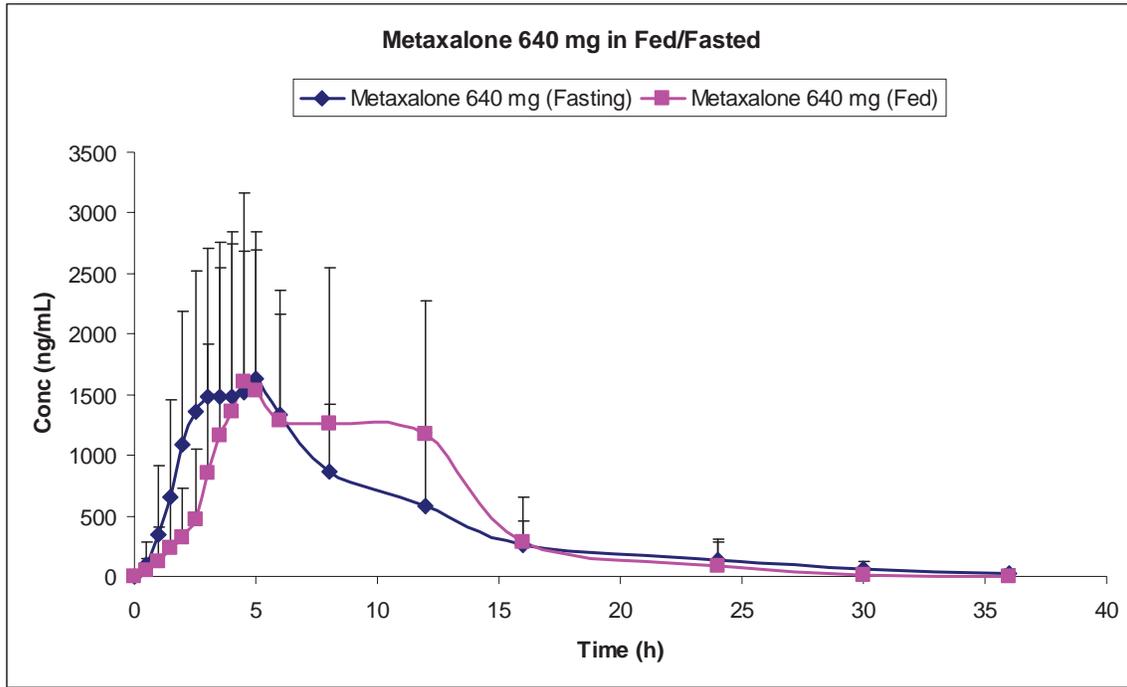


Table 2.1.4.3. Geometric Mean Metaxalone PK Parameters, Ratio of Geometric Means, and 90% CI Following 800 mg Skelaxin® Tablet in all Fed and Fasted Subjects.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	SKELAXIN® Tablets (800 mg) Fed	SKELAXIN® Tablets (800 mg) Fasting	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	19359.95	13907.27	139.21	(128.35, 150.99)
AUC _{0-inf} (ng·hr/mL)	19624.22	14866.84	132.00	(122.22, 142.56)
C _{max} (ng/mL)	3046.51	1735.28	175.56	(150.11, 205.33)

- When 640 mg metaxalone tablet was given with food, the absorption phase seems to be extended but the T_{max} appears to occur at the same time as that of the fasted state. (Figure 2.1.4.4).

Figure 2.1.4.4. Mean Plasma Concentration-Time Profiles of Metaxalone Following 640 mg Metaxalone Tablet in All Fed and Fasted Healthy Subjects (n=47).



- The AUCs appears to be comparable in fed and fasted conditions (Table 2.1.4.4). The 90% CI for the AUC is within 80% to 125% limits. However, for C_{max} the 90% CI is outside the 80% to 125% limits C_{max} under mean conditions being about 23% higher in fasted condition.

Table 2.1.4.2.4. Geometric Mean Metaxalone PK Parameters, Geometric Mean Ratios, and 90% CI Following 640 mg (b) (4) (Test) Tablet in all Fed and Fasted Subjects

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	Metaxalone Tablets (640 mg) Fasting	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	14600.21	13686.84	106.67	(98.35, 115.70)
AUC _{0-inf} (ng·hr/mL)	14840.39	13988.59	106.09	(98.23, 114.57)
C _{max} (ng/mL)	2207.56	1798.83	122.72	(104.93, 143.53)

In light with what is already known, there are clear gender differences in this study in the PK of metaxalone in fed and fasted subjects. The plasma concentration-time profiles of metaxalone are consistently higher in females than in males in fasted and in fed conditions and irrespective of product being administered. This will be discussed later in more detail in Section 2.3 (Intrinsic Factors).

Reviewer's Comments and Summary:

- Based on this study, the 640 mg tablet of Metaxalone is equivalent to 800 mg Skelaxin® only under fasted condition.
- Food had a smaller effect on the exposure after 640 mg Metaxalone tablet compared to that after Skelaxin® 800 mg tablet and the two formulations are not equivalent under fed state.
- In general, the data from this study is consistent with that in the currently approved label with respect to the effect of food on Skelaxin®. Food markedly increases the absorption of metaxalone following Skelaxin® tablet. Skelaxin® tablet, inspite of the substantial food effect can be taken with or without food. Since the effect of food on metaxalone 640 mg tablet is smaller compared to Skelaxin® tablet, metaxalone 640 mg tablet can also be administered without restriction to food.
- In light with previous observations on females having higher exposures than males, the exposure to metaxalone in this study in females appears to be consistently higher by approximately 25% than in males irrespective of feeding conditions and the products being administered. The gender based PK differences for metaxalone following the administration of Skelaxin® 800 mg tablet was the subject of several reviews (OCP reviews dated October 6, 2004, April 22, 2005, and October 21, 2005). The existing language in the current label of Skelaxin® tablet is based on these reviews.
- The two products **are not bioequivalent** when administered in either females or males alone under fed or fasted conditions (see Section 2.3). However, the BA/BE guidance requires pooled data analysis and discourages stratification of the data based on gender. The relative bioavailability and bioequivalence studies are normally required to be conducted in healthy subjects of both genders. Therefore, the combined data from all fasted subjects (n=47) is considered adequate to conclude that the two products are equivalent only under fasted condition.

2.2 General Clinical Pharmacology

2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

The submission does not have any clinical safety and efficacy data. All data in this NDA were presented as comparative PK.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The sponsor determined the plasma concentration of the parent drug, metaxalone in this study. From the clinical pharmacology perspective this is acceptable to determine the relative bioavailability to the reference product.

2.2.3 Exposure Response

2.2.3.1 What are the characteristics of the exposure-response relationships for efficacy?

No formal PK/PD study was conducted in this NDA to establish the relationship between exposure and response/efficacy. In addition, being a DESI's drug (i.e., marketed based on Drug Efficacy Study and Implementation regulation of 1962), no adequate PK/PD information and/or dose-response relationship are adequately established and/or available in the literature.

The focus of this NDA was to assess the comparative bioavailability between the test product (640 mg tablet) and the reference 800 mg Skelaxin®. Therefore, no PK/PD analysis was performed in this submission to establish the relationship between metaxalone dose and efficacy.

2.2.3.2 What are the characteristics of the exposure-response relationships for safety?

No formal PK/PD study was conducted in this NDA to establish the relationship between exposure and safety.

2.2.3.3 Does this Drug Prolong the QT or QTc Interval?

No formal QTc study was conducted in this NDA to establish the effect of metaxalone on QTc.

2.2.4 What are the PK characteristics of the drug?

2.2.4.1 What are the single and multiple dose PK parameters of metaxalone and its metabolites? How do the PK parameters change with time following chronic dosing?

Not applicable.

2.2.4.2 Are the PK of metaxalone and its metabolites linear and dose-proportional?

The sponsor did not provide any information in reference to dose proportionality. However, according to the currently approved label for Skelaxin® the increase in dose from 400 mg to 800 mg results in a “roughly proportional increase in metaxalone exposure as indicated by peak plasma concentrations (C_{max}) and area under the curve (AUC). Dose proportionality at doses above 800 mg has not been studied.”

2.2.4.3 What is the Extent of Systemic Exposure after Metaxalone Administration?

As stated previously, only one study was conducted in this NDA to establish the PK and relative bioavailability after the test and reference product (see Section 2.4.1).

2.3 Intrinsic factors

2.3.1 Does age, weight, race, gender, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

No formal special population studies were conducted in this NDA. However, as previously known, there is gender difference in the PK characteristics of metaxalone following either the test or the reference product under fed and fasted conditions in study R08-0838.

The relative bioavailability study was conducted in 47 subjects (18 females and 29 males) in a four-way crossover design in fed and fasted healthy subjects as described earlier in section 2.1.4.

From this study, it appears that there were clear gender differences in the PK of metaxalone in fed and fasted subjects. The plasma concentration-time profiles of metaxalone are consistently higher in females than in males under fasted and fed conditions and irrespective of product being administered (**Figures 2.3.1.1 to 2.3.1.6**).

Figure 2.3.1.1. Gender Differences in Mean Plasma Concentration-Time Profiles of Metaxalone Following 640 mg Metaxalone Tablets in Fasted Females (n=18) and Males (n=29).

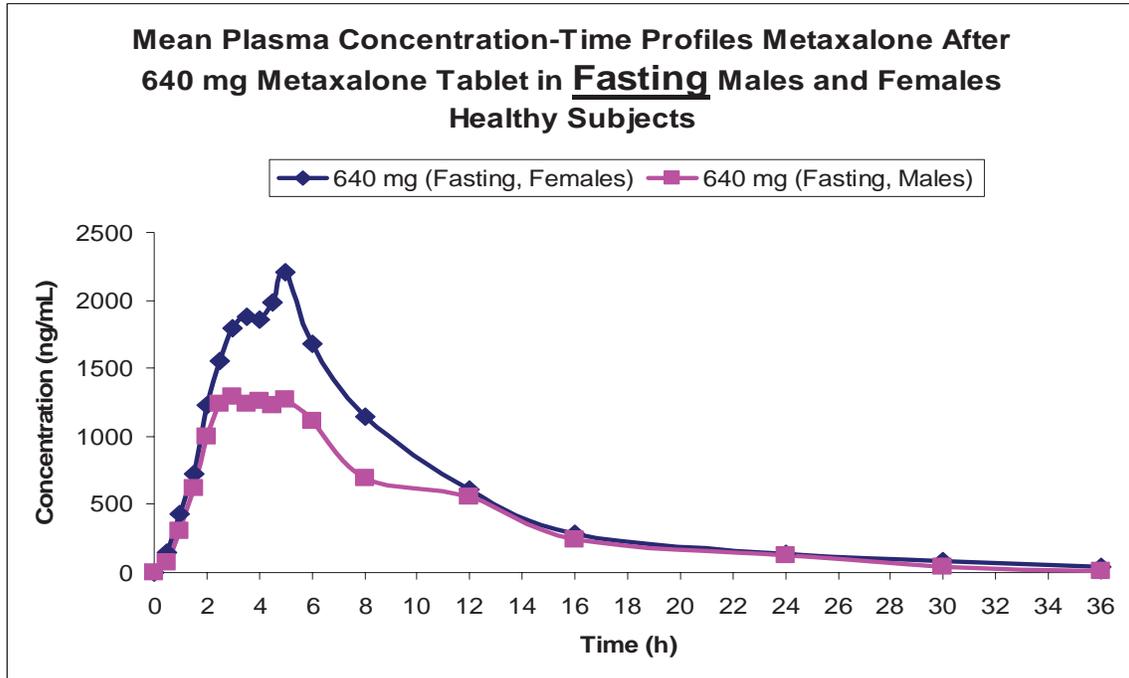


Figure 2.3.1.2. Gender Differences in Mean Plasma Concentration-Time Profiles of Metaxalone Following 640 mg Metaxalone Tablets in Fed Females (n=18) and Males (n=29).

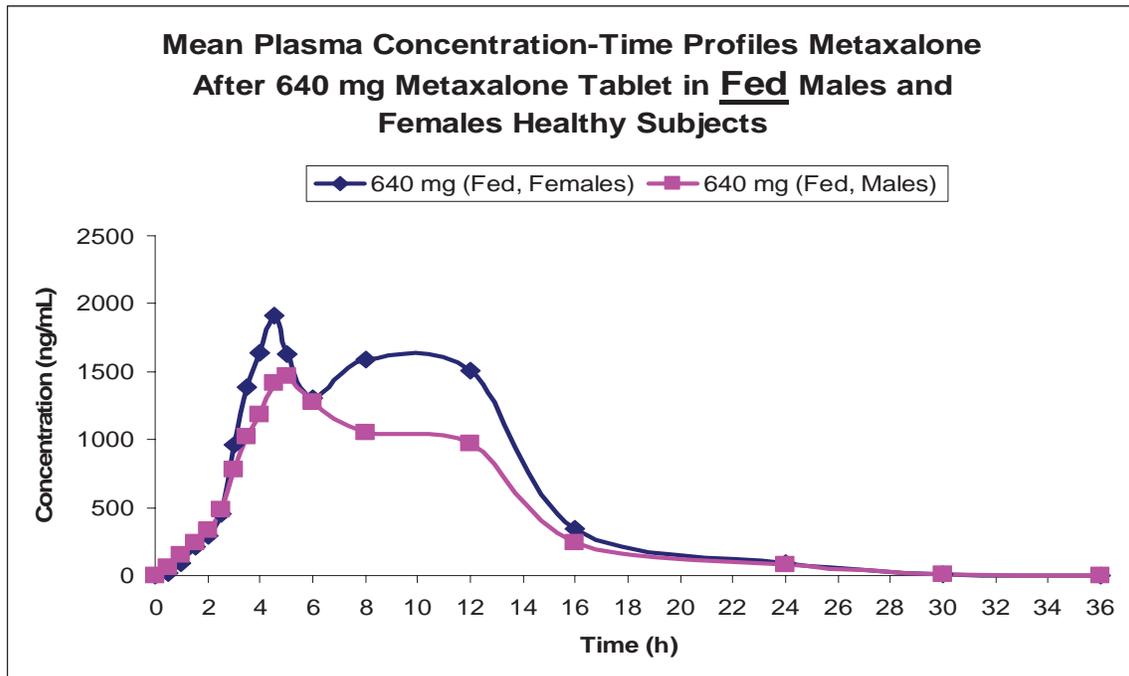


Figure 2.3.1.3. Gender Differences in Mean Plasma Concentration-Time Profiles of Metaxalone Following 800 mg Skelaxin® Fasted Females (n=18) and Males (n=29).

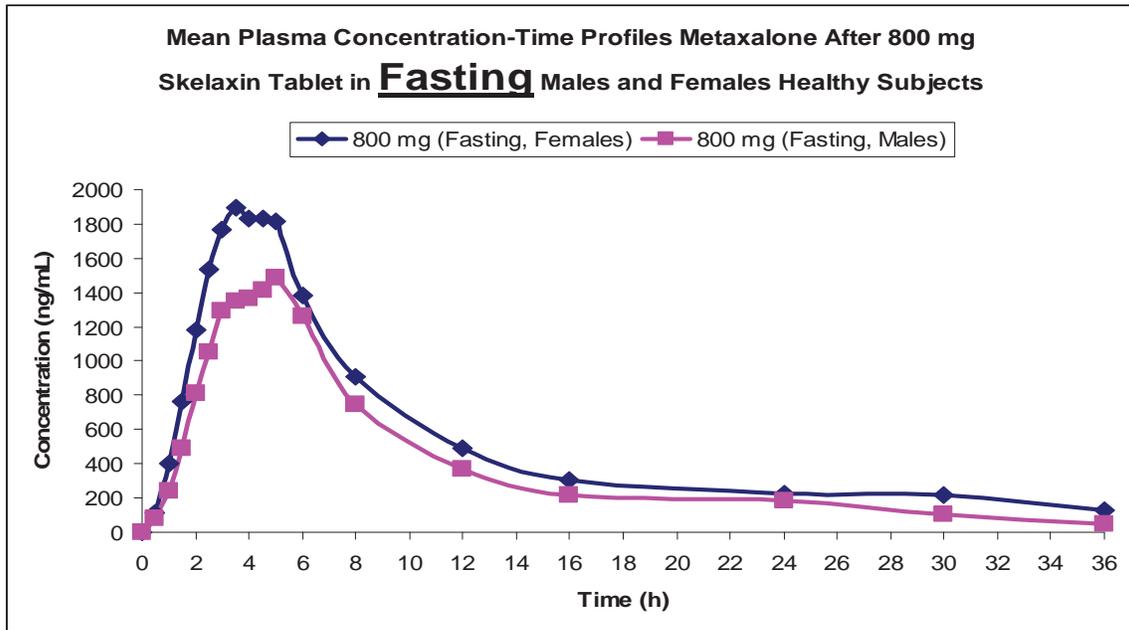


Figure 2.3.1.4. Gender Differences in Mean Plasma Concentration-Time Profiles of Metaxalone Following 800 mg Skelaxin® Fed Females (n=18) and Males (n=29).

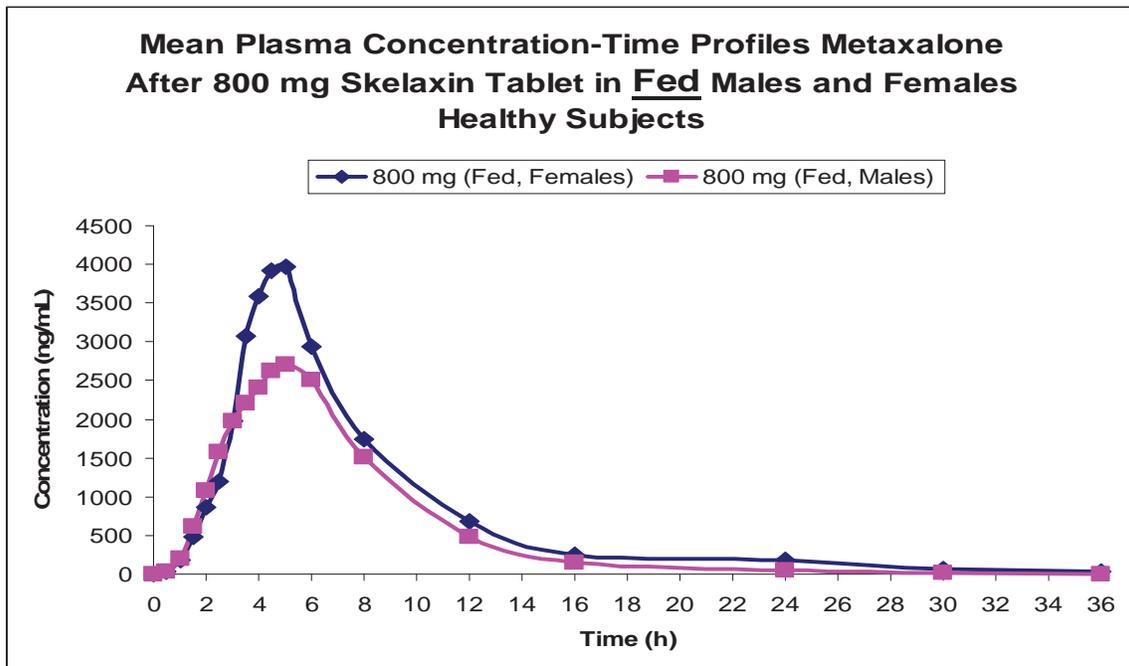


Figure 2.3.1.5. Gender Differences in Metaxalone AUC in Fed and Fasted Subjects After the Administration of 640 mg Metaxalone Tablets and 800 mg Skelaxin®

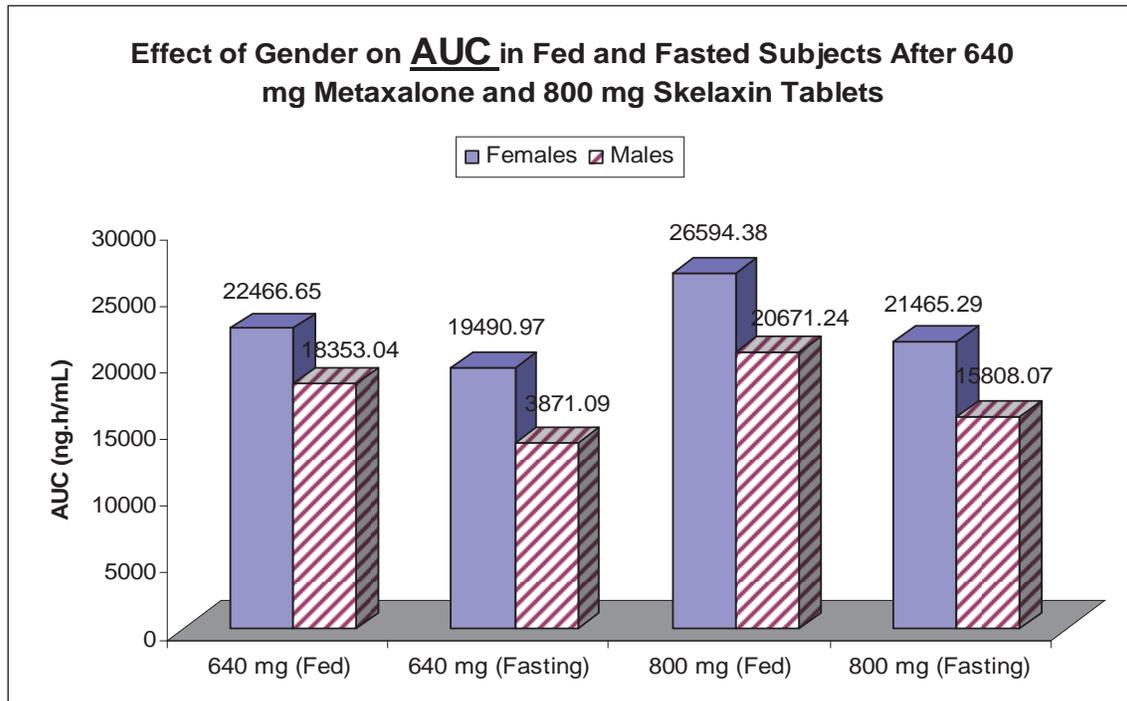
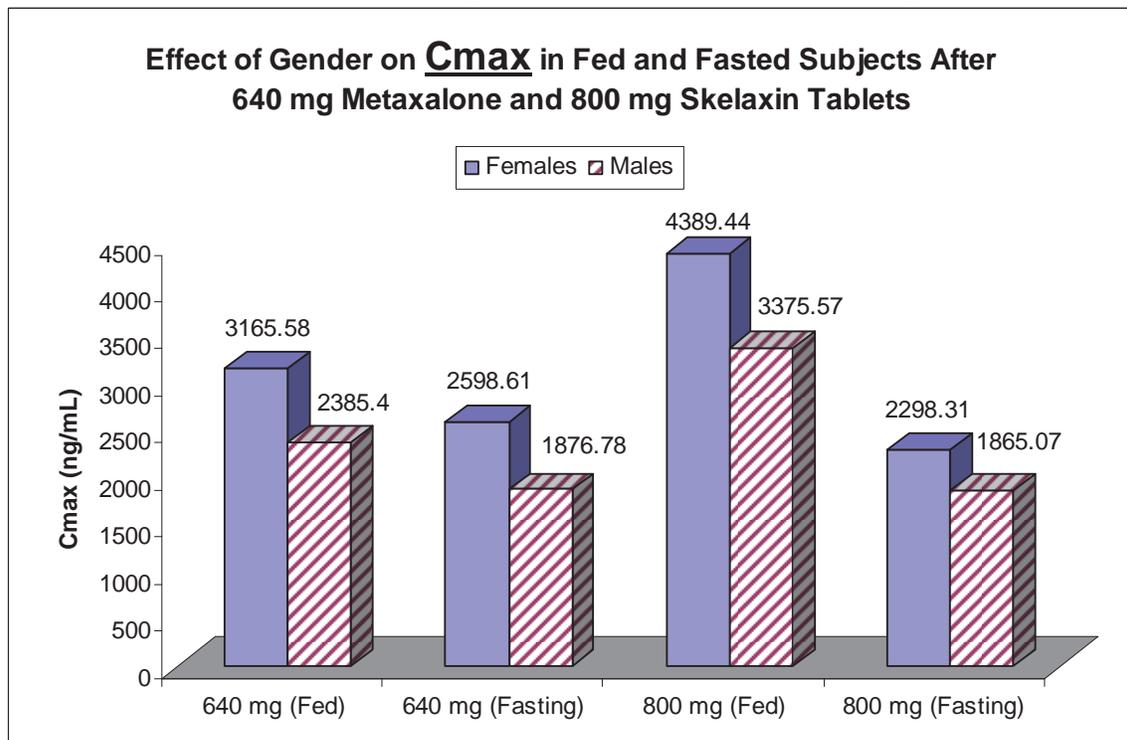


Figure 2.3.1.6. Gender Differences in Metaxalone C_{max} in Fed and Fasted Subjects After the Administration of 640 mg Metaxalone Tablets and 800 mg Skelaxin®



The 90% CI for AUC after 640 mg and 800 mg products is within 80% to 125% in fasted females and males, but not for the C_{max}. The 90% CI for C_{max} in females was between 82.79% and 133.85% and for males it was between 83.34% and 127.12%. Under fed conditions, however, none of the PK parameters were within 80% to 125% in females or males following either product.

Furthermore, within the same product the C_{max} and AUC were outside the 80% to 125% BE limits under fasted or fed conditions in both genders after 640 mg metaxalone tablets and 800 mg Skelaxin® tablets. In other words, food affects the bioavailability of the metaxalone, irrespective of formulation. For details on statistical analysis and the 90% CI limits for each gender see **Section 4.2, individual study review**. The effect of food is also discussed in **Section 2.5.2**.

Reviewer's Comments:

In general, the data from this study is in agreement in terms of higher exposure of metaxalone in females that was previously known with Skelaxin®. The currently approved label dated November 24, 2006 states that “the bioavailability of metaxalone was significantly higher in females compared to males as evidenced by C_{max} (2115 ng/mL *versus* 1335 ng/mL) and AUC_∞ (17884 ng·h/mL *versus* 10328 ng·h/mL)”.

2.4 Extrinsic factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of herbal products, diet, smoking and alcohol on metaxalone use were not evaluated. No specific studies were conducted to investigate the effect of extrinsic factors on the disposition of metaxalone.

2.5 General Biopharmaceutics

DSI Inspection was requested at the time of filing the NDA. At the time of writing this review, DSI inspection report has not been issued.

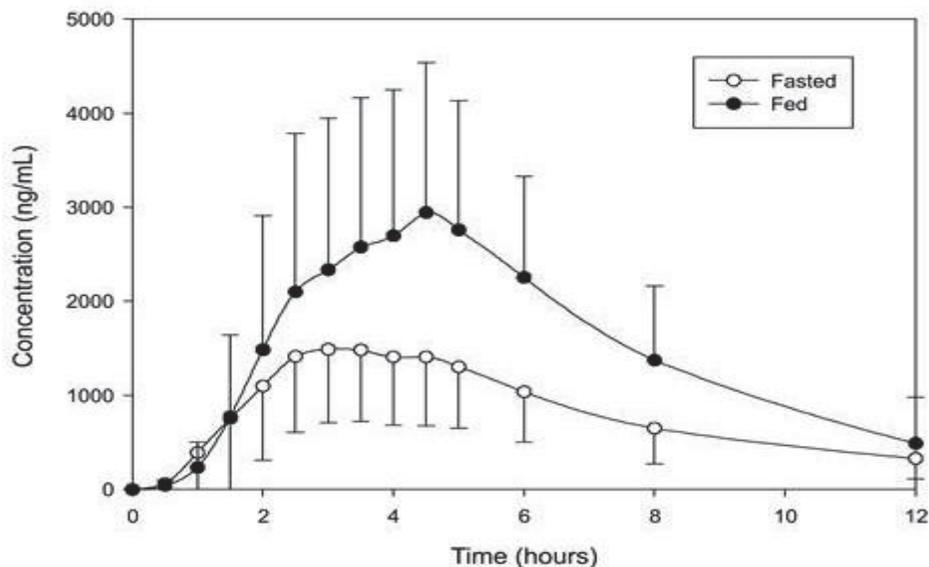
2.5.1 What is the BCS classification for Metaxalone?

This information was not provided by the sponsor in this NDA.

2.5.2 What is the effect of food on the BA of Metaxalone?

According to the currently approved label for Skelaxin® 800 mg tablet food increases the C_{max} and AUC of metaxalone (**Figure 2.5.2.1**).

Figure 2.5.2.1. Effect of Food on Skelaxin® 800 mg Tablet (Extracted from the currently approved label)



In spite of the substantial effect, the currently approved label does not recommend dosage adjustment with respect to food consumption. In the “Dosage and Administration” section of the Skelaxin® label states the following: “The recommended dose for adults and children over 12 years of age is one 800 mg tablet three to four times a day”. However, in the “precaution” section of the label the following statement is made in reference to food intake in elderly patients: “Taking Skelaxin with food may enhance general CNS depression; elderly patients may be especially susceptible to this CNS effect ...”

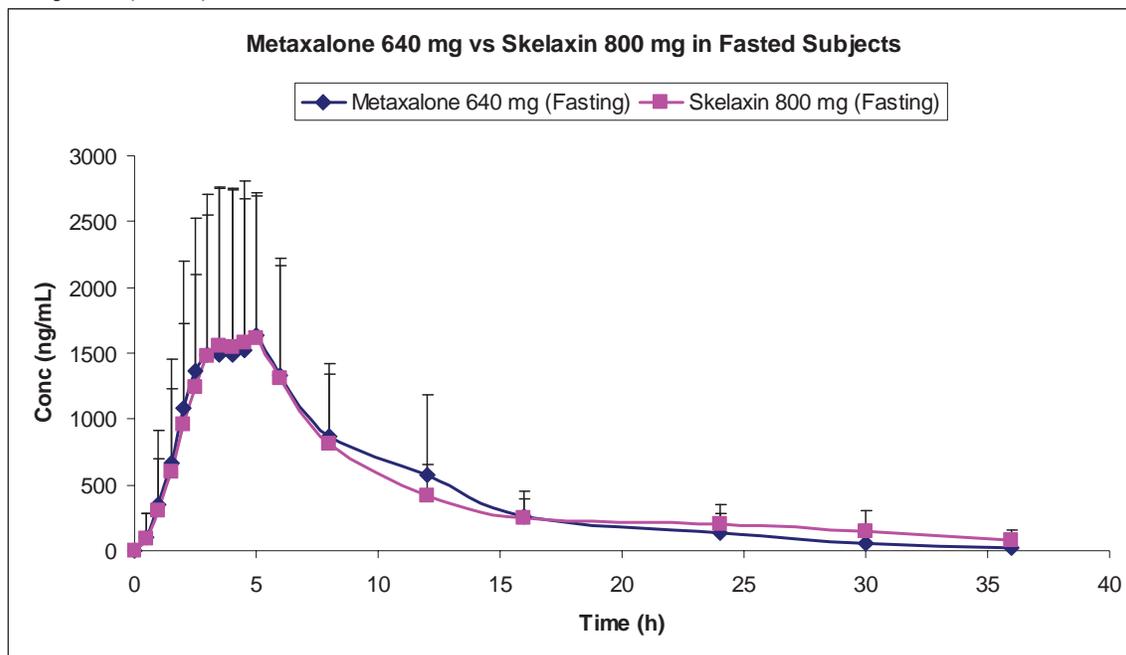
The issue of effect of food was previously addressed in several Office of Clinical Pharmacology Reviews (dated February 3, 2004, October 6, 2004, April 22, 2005, and October 21, 2005). However, due to lack of information on exposure-response relationships of metaxalone for both efficacy and/or safety and lack of data relating to administration of Skelaxin 800 mg tablet with food and its effect on efficacy and/or

safety, no dosage adjustment was recommended with respect to food. It was felt that the lack of restriction taking the medication with or without food would allow the prescriber to determine the dosage based on individual patient's response.

In the current NDA, the sponsor investigated the effect of food on metaxalone in 47 healthy subjects. The primary objective of this study was to determine the relative bioavailability of 640 mg Metaxalone Tablets to that of 800 mg Skelaxin® Tablet following a single dose in healthy adult subjects when administered under fasted and fed conditions. The study design was described earlier in Section 2.1.2 and additional details can be found in Section 4.2 (Individual Study Review).

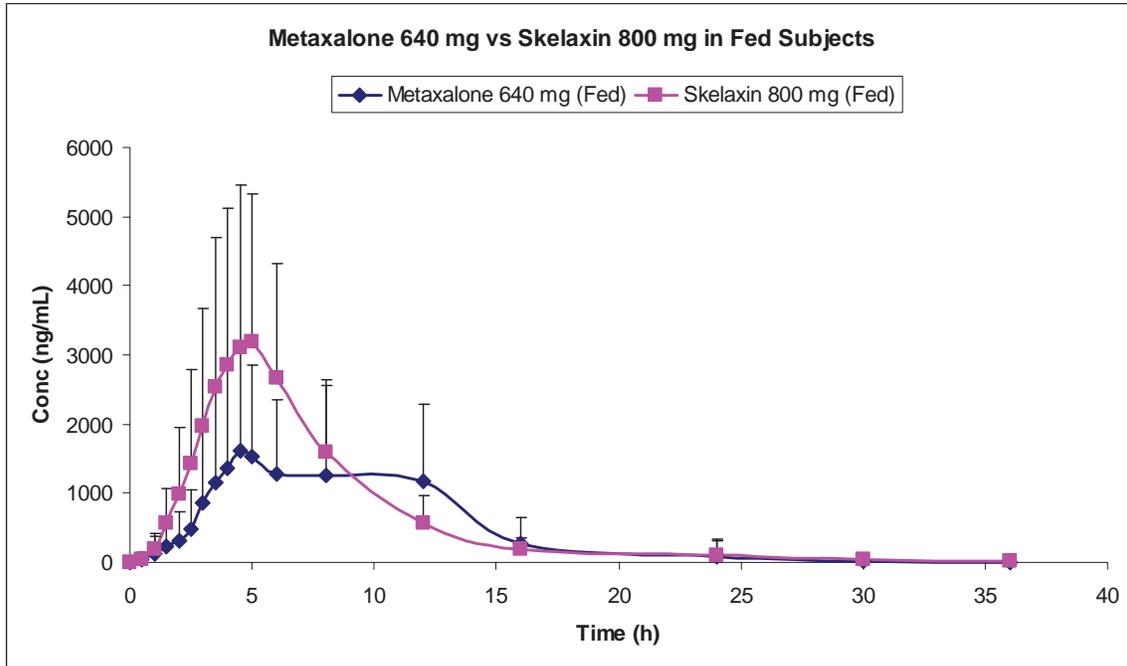
In all subjects, the plasma concentration-time profiles of metaxalone were comparable following 640 mg metaxalone and 800 mg Skelaxin® tablets under **fasted condition** (Figure 2.5.2.2).

Figure 2.5.2.2. Mean (SD) Plasma Concentration-Time Profiles of Metaxalone Following 640 mg Metaxalone Tablets and 800 mg Skelaxin Tablet in All Fasted Subjects (n=47).



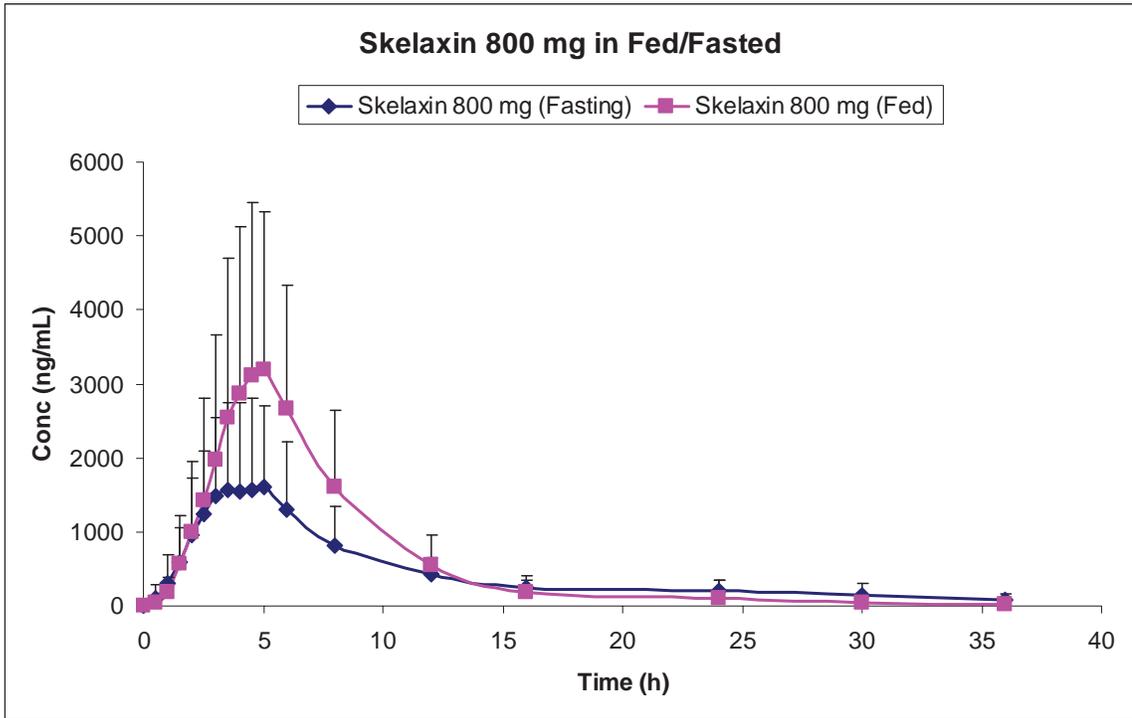
- However in fed subjects, the plasma concentration-time profile of metaxalone following 640 mg metaxalone tablets was remarkably lower than after 800 mg Skelaxin® tablet (Figure 2.5.2.3).

Figure 2.5.2.3. Mean (SD) Plasma Concentration-Time Profiles of Metaxalone Following 640 mg Metaxalone Tablets and 800 mg Skelaxin Tablet in All Fed Healthy Subjects (n=47).



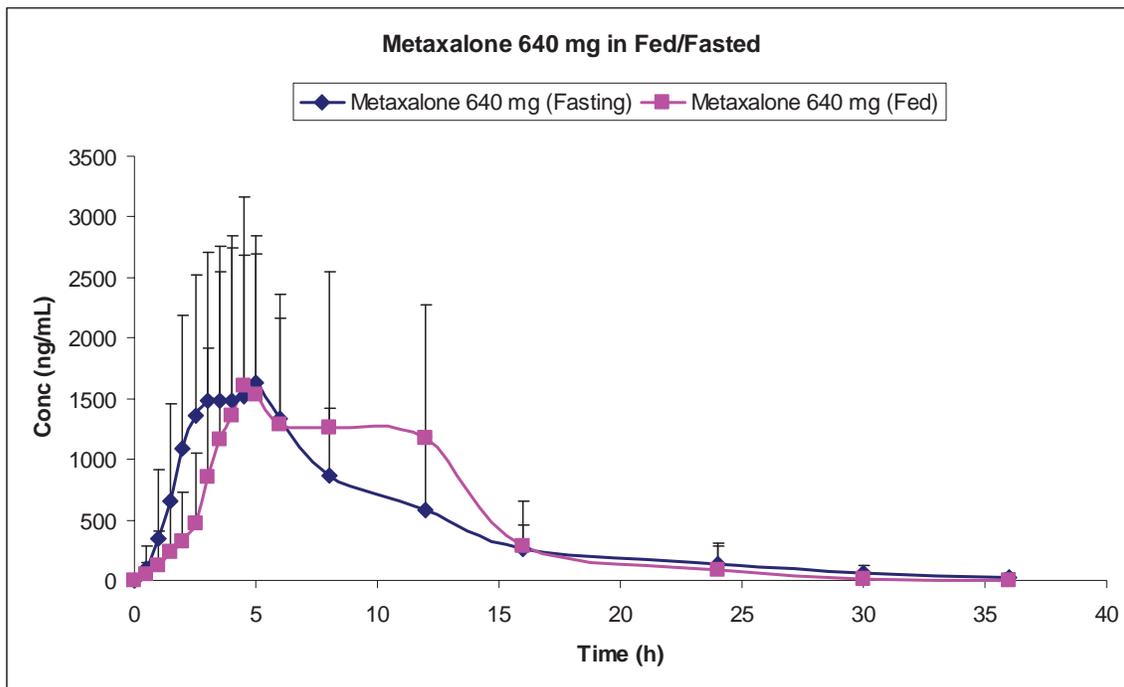
The C_{max} and AUC in fed state were approximately 28% and 25% lower after 640 mg metaxalone tablet compared to 800 mg Skelaxin® tablet, respectively. In contrast to 640 mg tablet, food markedly increased the absorption of metaxalone following 800 mg Skelaxin® tablet (**Figure 2.5.2.4**). The C_{max} and AUC were approximately 75% and 30% higher in fed state than in fasted state, respectively. As stated earlier, the food effect is already documented in the currently approved label for Skelaxin® 800 mg tablet.

Figure 2.5.2.4. Mean Plasma Concentration-Time Profiles of Metaxalone Following 800 mg Skelaxin Tablet in All Fed and Fasted Healthy Subjects (n=47).



- When the new 640 mg metaxalone tablet was given with food, the absorption phase seems to be extended relatively speaking (**Figure 2.5.2.5**). However, the T_{max} appears to occur at the same time as that of the fasted state.

Figure 2.5.2.5. Mean Plasma Concentration-Time Profiles of Metaxalone Following 640 mg Metaxalone Tablet in All Fed and Fasted Healthy Subjects (n=47).



Conclusions:

Based on this data, the 640 mg tablet should be given irrespective of food, similar to that of the reference product, Skelaxin® tablet. As discussed in various sections of this review, this recommendation is consistent with that made in the previous clinical pharmacology reviews of NDA 13-217.

2.5.3 Was the to-be-marketed formulation used in the PK/Clinical trials?

Yes.

2.5.4 What is the Formulation Composition of the Products?

The composition of the proposed product for 640 mg strength is quite different from the currently marketed 800 mg Skelaxin® (Tables 2.5.4.1 and 2.5.4.2). The new product contains (b) (4). This may enhance the absorption and bioavailability of metaxalone. Hence, the dose/strength is lower than the marketed 800 mg strength for Skelaxin®. For additional details on the composition and manufacturing process, see ONDQA review.

Table 2.5.4.1. Skelaxin® Formulation Composition.

Components	Composition	
	400 mg. Tablets	800 mg Tablets
Metaxalone	400.0 mg	800 mg
Ammonium Calcium Alginate (b) (4)	(b) (4)	(b) (4)
Alginic Acid NF		
Corn Starch NF (b) (4)		
B Rose Liquid		

Components	Composition	
	400 mg. Tablets	800 mg Tablets
(b) (4)	(b) (4)	(b) (4)
Magnesium Stearate NF		
Total Weight		924.7 mg

Source of Table: Chemistry review dated July 9, 2009 by Vispi Bhavnagri, NDA 13-217, submitted March 8, 2002.

Table 2.5.4.2. Metaxalone 640 mg Formulation Composition:

Ingredient	Reference to Quality Standard	Function	Quantity/Tablet (mg)	Amount (%) / Tablet
Metaxalone (b) (4)	In-House	Active	(b) (4)	(b) (4)
Metaxalone	In-House	Active		
Lactose Monohydrate (b) (4)	NF	(b) (4)		
FD&C Yellow # 6, (b) (4)	In-House			
Propylene Glycol Alginate (b) (4)	NF			
Alginic Acid (b) (4)	NF			
Povidone (b) (4)	USP			
(b) (4)				
Magnesium Stearate	NF			
Total Weight				
(b) (4)				

2.5.5 Are the proposed dissolution method and dissolution specifications supported by the data provided by the sponsor?

For detailed discussion and final assessment related to dissolution specs and method acceptability see ONDQA review.

The dissolution conditions used by the sponsor (#QCM 642) for metaxalone Tablets is summarized in **Table 2.5.5.1**. The specification for dissolution NLT (b) (4) % (Q) of the labeled amount dissolved in 90 minutes is based on six months stability data of Metaxalone Tablets, 640 mg.

Table . 2.5.5.1. *In vitro* Dissolution Method (GCM 642):

Component	Description
Sample Preparation	Standard and Sample solution concentration is about 71 µg/mL
System Suitability	The %RSD of two standard absorbance readings is Not More Than 3.0.
Apparatus	II (Paddles)
Medium	0.5% Sodium Lauryl Sulfate
Volume	900 mL
Speed	100 RPM
Temperature	37°C ± 0.5°C
Time Points:	Single Point: 90 minutes Profile: 15, 30, 45, 60, 90 and 120 minutes
Sample Volume	10 mL for Manual sampling and 7 mL for Auto sampling
Tolerance	NLT ^(b) ₍₄₎ % (Q) of the labeled amount dissolved in 90 minutes

The *in vitro* dissolution profiles for 640 mg and 800 mg strengths are shown in **Figure 2.5.5.1** and **Tables 2.5.5.2 and 2.5.5.3**. The similarity factor (F_2) was above 50 for the two products indicating that the *in vitro* dissolution of the two products is similar (**Table 2.5.5.4**)

Figure 2.5.5.1. *In Vitro* Dissolution profiles of 800 mg Skelaxin (Lot # ES807358A) and 640 mg Metaxalone Tablet (Lot # CR0820 used in PK study)



Table 2.5.5.2. *In vitro* Dissolution Data for 640 mg Metaxalone Tablet (Method QCM-642)

Tablet #	% Drug Dissolved in					
	15 Minutes	30 Minutes	45 Minutes	60 Minutes	90 Minutes	120 Minutes
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Average (%)						
Range (%)						
RSD (%)						

Table 2.5.5.3. *In vitro* Dissolution Data for 800 mg Skelaxin® (Method QCM-468)

Tablet #	% Drug Dissolved in				
	15 Minutes	30 Minutes	45 Minutes	60 Minutes	90 Minutes
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average (%)	(b) (4)				
Range (%)					
RSD (%)					

Table 2.5.5.4. Similarity Factor (F₂) For Skelaxin 800 mg and Metaxalone 640 mg Tablets.

Dissolution Comparison	F2 value
Skelaxin® Tablets, 800 mg (lot # ES807358A) vs. Corepharma's (b) (4) Tablets, 640 mg (lot # CR0820)	<u>64</u>
Skelaxin® Tablets, 800 mg (lot # ES807358A) vs. Corepharma's (b) (4) Tablets, 640 mg # CR0904)	<u>65</u>
Skelaxin® Tablets, 800 mg (lot # ES807358A) vs. Corepharma's (b) (4) Tablets, 640 mg (lot # CR0905)	<u>61</u>
Corepharma's (b) (4) Tablets, 640 mg (lot # CR0820) vs. Corepharma's (b) (4) Tablets, 640 mg (lot # CR0904)	<u>91</u>
Corepharma's (b) (4) Tablets, 640 mg (lot # CR0820) vs. Corepharma's (b) (4) Tablets, 640 mg (lot # CR0905)	<u>83</u>

2.6 Analytical Section

The plasma concentrations of metaxalone was determined by a validated LC-MS-MS method (Table 2.6.1)

Table 2.6.1 . Summary of LC-MS/MS Assay for Metaxalone Method in Plasma

Information Requested	Data
Bioanalytical method validation report location	Provide the volume(s) and page(s)
Analyte	Metaxalone
Internal standard (IS)	Metaxalone-d ₆
Method description	Liquid-liquid extraction
Limit of quantitation	10.00 ng/mL
Average recovery of drug (%)	72.56%
Average recovery of IS (%)	62.48%
Standard curve concentrations (ng/mL)	10.00, 20.00, 50.00, 100.00, 500.00, 1000.00, 2500.00, 5000.00, 7500.00 ng/mL
QC concentrations (ng/mL)	30.00, 750.00, 2000.00, 6000.00 ng/mL
QC Intraday precision range (%)	1.23% - 1.54%
QC Intraday accuracy range (%)	101.19% - 104.89%
QC Interday precision range (%)	3.38% - 5.35%
QC Interday accuracy range (%)	98.34% - 98.70%
Bench-top stability (hrs:mins)	23:54 hours-minutes @ room temperature
Stock stability (hrs:mins)	717:19 hours-minutes @ room temperature; 717:19 hours-minutes @ 4°C
Processed stability (hrs:mins)	672:31 hours-minutes @ room temperature; 96:20 hours-minutes @ 4°C
Freeze-thaw stability (cycles)	5 cycles
Long-term storage stability (days)	163 days @ -20°C
Dilution integrity	9000.00 ng/mL 1:9 / 3:1
Selectivity	No interfering peaks noted in eight blank plasma samples

The limit of quantitation of the assay is 10 ng/mL. The assay precision (% CV) was <6%. The standard curve concentrations ranged from 10.00 ng/mL to 7500 ng/mL. The between batch accuracy of QCs was between 98.34% and 98.70%. The within-batch accuracy ranged from 101.19% to 104.89%. Overall, the assay validation data are satisfactory (Tables 2.6.1 and 2.6.2).

Table 2.6.1. Between Assay (batch) Accuracy and Precision (% CV)

Concentration (ng/mL)	10.00	20.00	50.00	100.00	500.00	1000.00	2500.00	5000.00	7500.00	Intercept	x Coefficient	x ² Coefficient	r ²
V0618B02	9.81 9.89	19.47 19.92	50.29 50.13	102.44 {No data}	487.65 494.90	1033.18 1063.34	2453.07 2489.04	4868.46 5013.63	7529.66 7569.85	0.00094	0.00120	-2.44356E-08	0.9997
V0618B03	8.83 9.75	19.63 19.44	51.68 51.24	106.09 107.21	496.94 500.24	1006.96 1011.89	2431.34 2518.16	4926.49 5088.54	7581.61 7425.09	0.00102	0.00123	-2.04389E-08	0.9998
L0618B04	11.22 11.09	19.32 20.27	46.71 47.10	99.37 101.38	456.95 480.02	982.21 1020.31	2499.58 2551.76	5003.35 5099.34	7693.23 7216.96	-0.00032	0.00111	-1.97973E-08	0.9994
L0618B06	8.88 9.68	18.57 19.21	51.76 50.79	106.34 99.30	529.86 521.68	1041.50 1048.93	2545.71 2470.98	4736.92 4785.03	7606.62 7715.65	0.00234	0.00106	-1.42715E-08	0.9989
Mean	9.89	19.48	49.96	103.16	496.03	1026.04	2494.96	4940.22	7542.33	0.00099	0.00115	-1.97358E-08	0.9994
SD	0.8801	0.5026	1.9787	3.3677	22.9160	25.9764	42.7179	134.9313	159.9176	0.00109	0.00008	4.18110E-09	0.0004
CV	8.90%	2.58%	3.96%	3.26%	4.62%	2.53%	1.71%	2.73%	2.12%				
Accuracy	98.94%	97.39%	99.93%	103.16%	99.21%	102.60%	99.80%	98.80%	100.56%				

Table 2.6.1. Within Assay (batch) Accuracy and Precision (% CV)

Concentration (ng/mL)	Test Samples		
	LOW 30.00	MID 2000.00	HIGH 6000.00
1	30.10	1999.41	6295.07
2	31.07	1997.71	6197.07
3	30.83	2007.98	6289.01
4	30.49	2051.89	6176.74
5	31.11	2036.99	6390.92
6	30.41	2048.57	6412.86
Mean	30.67	2023.76	6293.61
SD	0.4010	24.9094	96.6350
CV	1.31%	1.23%	1.54%
Accuracy	102.23%	101.19%	104.89%

3.0 Detailed Labeling Recommendations

The draft/preliminary labeling of the pertinent clinical pharmacology related changes is shown below (Additions indicated by underline and deletions by strikethrough).

The labeling comments will be incorporated directly into the sponsor's proposed label after discussion with the review team. Here is the highlight of the ***PRELIMINARY*** labeling comments which are subject to change at the time of approval of the NDA:

2. DOSAGE AND ADMINISTRATION

The recommended dose for adults and children over 12 years of age is one 640 mg tablet three to four times a day.

3. DOSAGE FORMS AND STRENGTHS

(b) (4) metaxalone) is available as a 640mg oval, (b) (4) peach tablet, debossed on one side with "cor (b) (4) 324" (b) (4) and plain on the other side. Available in bottles of 100 (64720-324-10) (b) (4)

(b) (4)

4. CONTRAINDICATIONS

(b) (4) Known tendency to drug induced, hemolytic, or other anemias. (b) (4) impaired renal or hepatic function.

5. WARNINGS AND PRECAUTIONS

(b) (4) may enhance the effects of alcohol and other CNS depressants. (b) (4)

(b) (4)

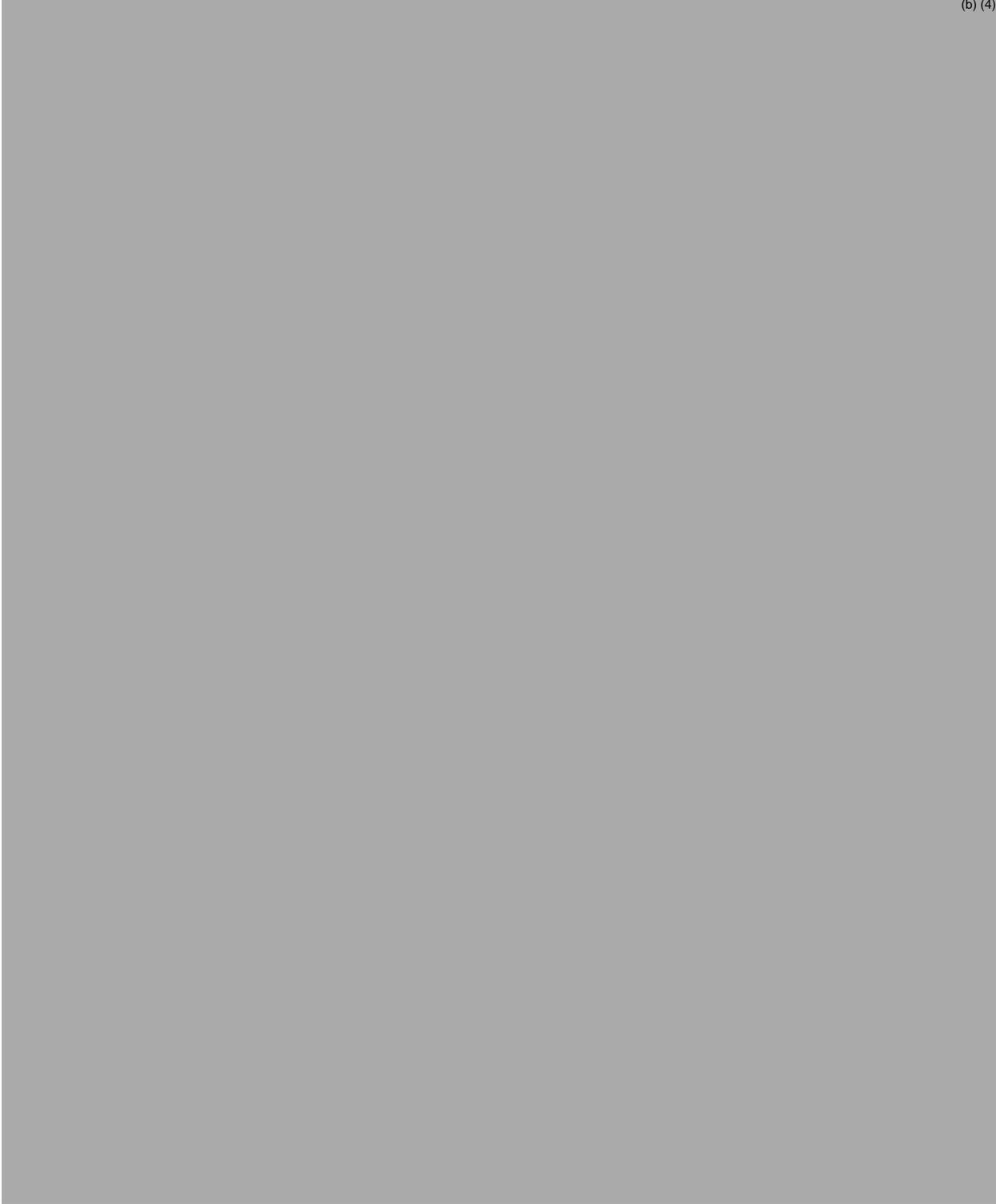
(b) (4)

(b) (4) (b) (4) may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle, especially when used with alcohol or other CNS depressants.

8.3. Pediatric use

Safety and effectiveness in children 12 years of age and below have not been established.

12. CLINICAL PHARMACOLOGY



(b) (4)

(b) (4)

(b) (4)

Note to the sponsor: replace the above paragraph with the new data from study number R08-0838 in females (n=18) and males (n=29).

(b) (4)

4.2 Individual Study Review:

Study # R08-0838 (Relative BA):

Objective:

The primary objective of this study was to determine the relative bioavailability of 640 mg Metaxalone Tablets to that of 800 mg Skelaxin® Tablet (a Reference Listed Dugs-RLD) following a single dose in healthy adult subjects when administered under fasted and fed conditions.

Study Design:

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

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

Products Administration:

Tablets were administered under standard fasted conditions or following the consumption of a standard high-fat breakfast. The study was initiated with 48 healthy subjects. All were dosed and studied as a single cohort. Each subject received either:

- 1) A single oral dose of 640 mg tablet of metaxalone following an overnight fast of at least 10 hours, or 30 minutes following a high-fat breakfast; or
- 2) A single oral dose of 800 mg tablet of the reference product, Skelaxin® Tablets following an overnight fast of at least 10 hours, or 30 minutes following a high-fat breakfast. Treatments were administered in randomly assigned sequence. A washout period of 7 days was allowed between each treatment period.

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

Subjects Demographics:

A total of 48 healthy subjects composed of 30 men and 18 women were enrolled (47 completed). A detailed listing of demographic data for these subjects is shown in **Table 4.2.1**.

Table 4.2.1. Summary of Mean (Range) Demographic Data

Parameters	All Subjects (N=48)	Males (N=30)	Females (N=18)
Age	34.9 (18-69)	31.8 (18-69)	40.1 (18-62)
Weight (lbs)	166.5 (118-241)	176.4 (119-241)	150.1 (118-195)
Height (in.)	68.0 (62-77)	69.9 (63-77)	64.8 (62-69)
BMI	25.3 (18.1-31.7)	25.3 (18.1-31.7)	25.2 (19.4-31.6)
Race ¹			
African American:	2 (4.17%)	2 (6.67%)	0.00%
Asian:	1 (2.08%)	1 (3.33%)	0.00%
Caucasian:	42 (87.5%)	26 (86.67%)	16 (88.89%)
Hispanic:	2 (4.17%)	1 (3.33%)	1 (5.56%)
American Indian or Alaskan Native:	4 (8.33%)	1 (3.33%)	3 (16.67%)
Native Hawaiian	1 (2.08%)	1 (3.33%)	0.00%

Subject 33 reported race as White and Native Hawaiian or Other Pacific Islander

Subject 34 reported race as White and American Indian or Alaskan Native

¹Mean (percentage)

Results:

- In all subjects, the plasma concentration-time profiles of metaxalone were comparable following 640 mg metaxalone and 800 mg Skelaxin® tablets under **fasted condition** (Figure 4.2.1).
- The 90% CI for both C_{max} and AUC were within 80% to 125% in **fasted state** (Table 4.2.2).

Figure 4.2.1. Mean (SD) Plasma Concentration-Time Profiles of Metaxalone Following 640 mg Metaxalone Tablets and 800 mg Skelaxin Tablet in All Fasted Subjects (n=47).

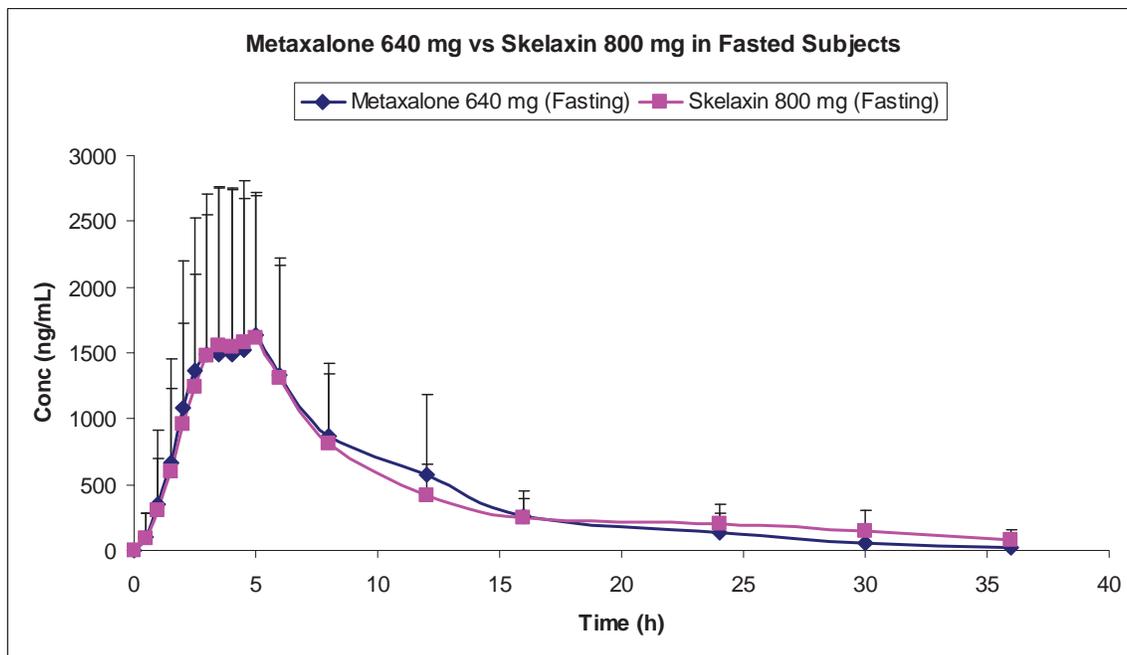


Table 4.2.2. Geometric Mean Metaxalone PK Parameters, Geometric Mean Ratios, and 90% CI Following Metaxalone Tablets (640 mg) and 800 mg Skelaxin® Tablets in All Fasted Subjects.

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

- However in fed subjects, the plasma concentration-time profile of metaxalone following 640 mg metaxalone tablets was remarkably lower than after 800 mg Skelaxin® tablet (**Figure 4.2.2**).
- The 90% CI for both C_{max} and AUC were outside 80% to 125% limits and the C_{max} and AUC in fed state were approximately 28% and 25% lower after metaxalone tablet compared to 800 mg Skelaxin® tablet, respectively (**Table 4.2.3**). This shows that the effect of food on the systemic exposure of 640 mg metaxalone tablet is smaller than that observed with Skelaxin 800 mg tablet.

Figure 4.2.2. Mean (SD) Plasma Concentration-Time Profiles of Metaxalone Following 640 mg Metaxalone Tablets and 800 mg Skelaxin Tablet in All Fed Healthy Subjects (n=47).

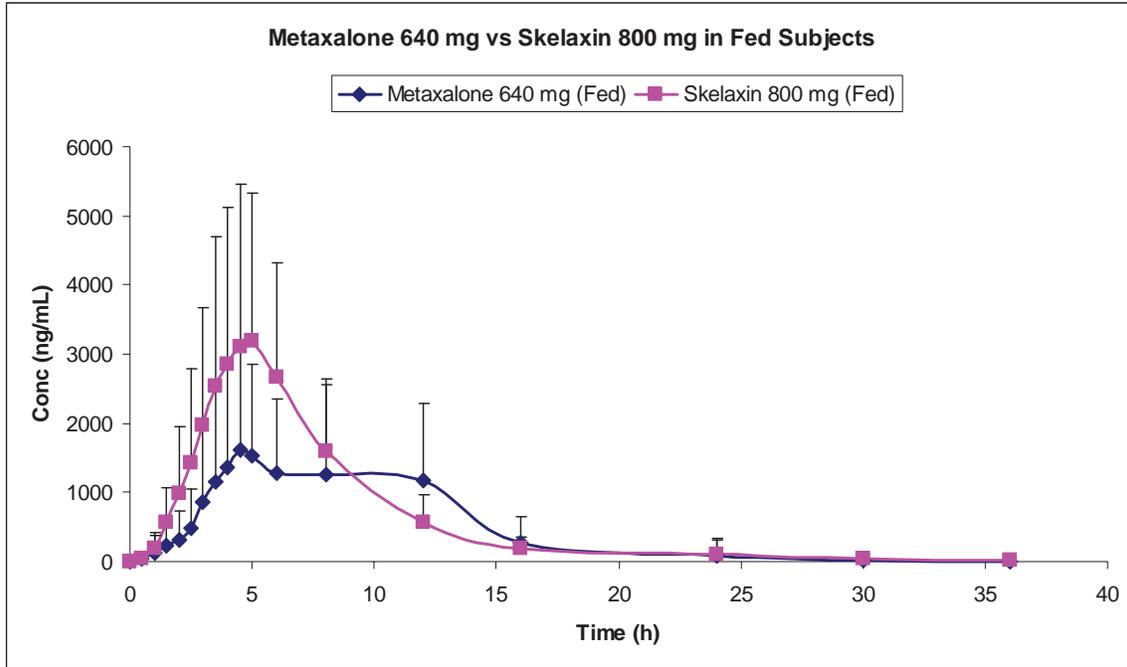


Table 4.2.4. Geometric Mean Metaxalone PK Parameters, Geometric Mean Ratios, and 90% CI Following Metaxalone Tablets (640 mg) and 800 mg Skelaxin® Tablets in all Fed Subjects.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	SKELAXIN® Tablets (800 mg) Fed	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	14600.21	19359.95	75.41	(69.53, 81.80)
AUC _{0-inf} (ng·hr/mL)	14840.39	19624.22	75.62	(70.02, 81.67)
C _{max} (ng/mL)	2207.56	3046.51	72.46	(61.96, 84.75)

- In contrast to 640 mg tablet, food increased C_{max} and AUC of metaxalone by approximately 75% and 30% following 800 mg Skelaxin® tablet, respectively (Figure 4.2.3 and table 4.2.4). The food effect on Skelaxin® tablet is already documented in the currently approved label for Skelaxin® 800 mg tablet. In addition, effect of food on Skelaxin® tablet from multiple studies was reviewed and its implications were addressed in several clinical pharmacology reviews dated February 3, 2004, October 6, 2004, April 22, 2005, and October 21, 2005.

Figure 4.2.3. Mean (SD) Plasma Concentration-Time Profiles of Metaxalone Following 800 mg Skelaxin Tablet in All Fed and Fasted Healthy Subjects (n=47).

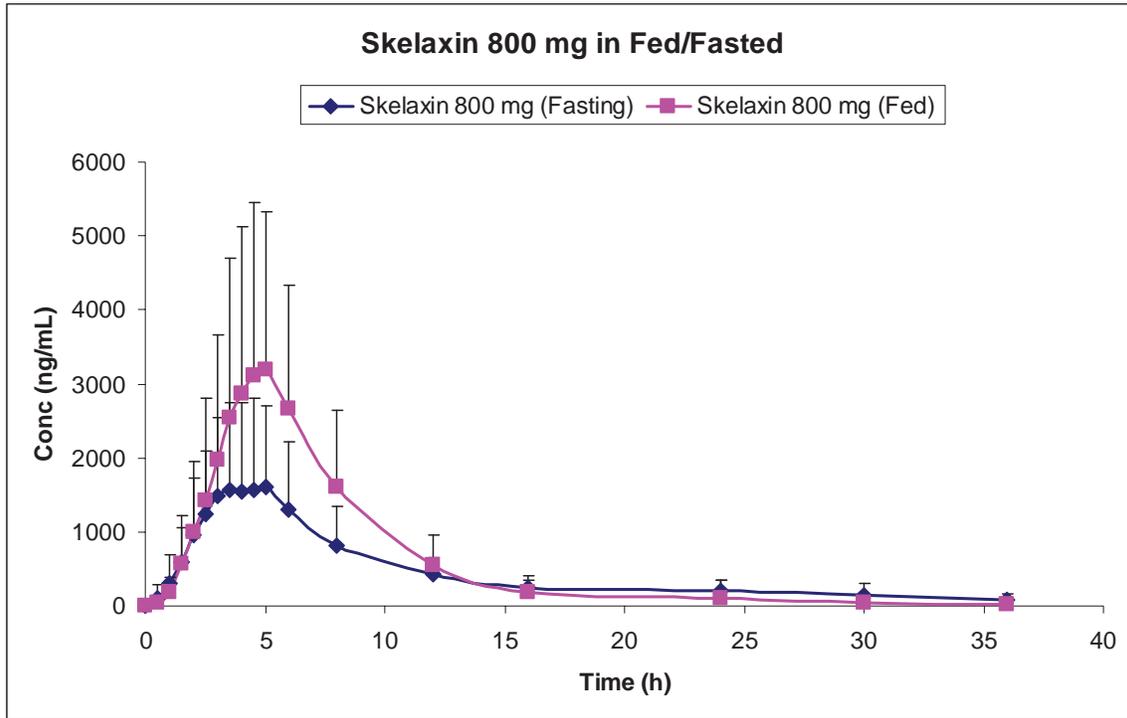
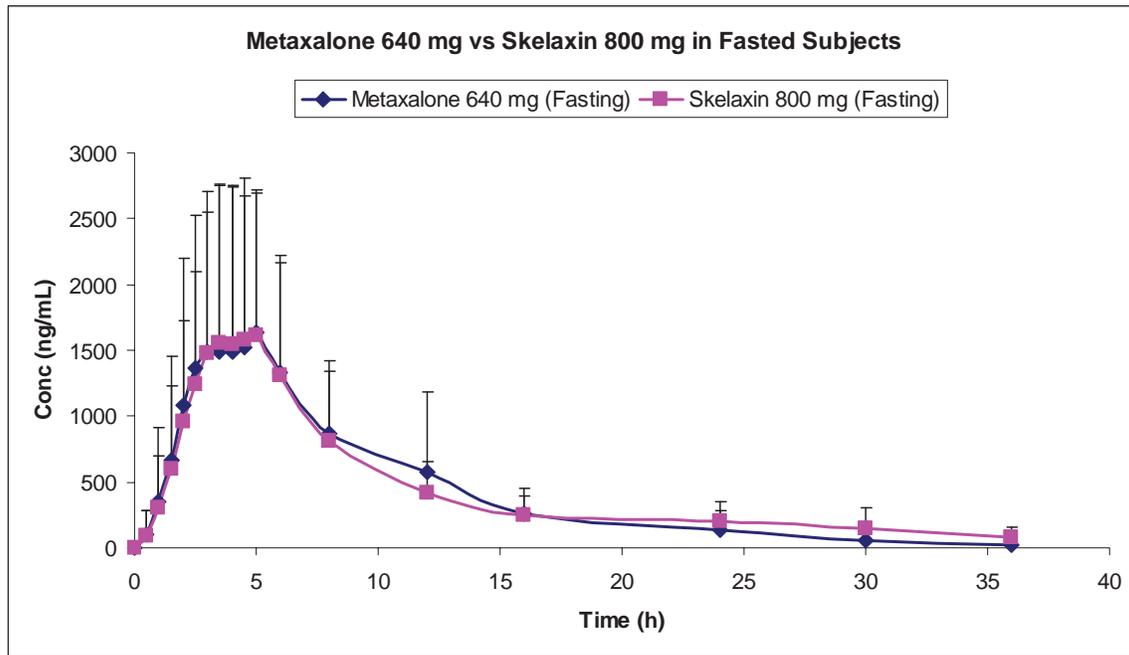


Table 4.2.4. Geometric Mean Metaxalone PK Parameters, Geometric Mean Ratios, and 90% CI Following 800 mg Skelaxin® Tablet in all Fed and Fasted Subjects.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	SKELAXIN® Tablets (800 mg) Fed	SKELAXIN® Tablets (800 mg) Fasting	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	19359.95	13907.27	139.21	(128.35, 150.99)
AUC _{0-inf} (ng·hr/mL)	19624.22	14866.84	132.00	(122.22, 142.56)
C _{max} (ng/mL)	3046.51	1735.28	175.56	(150.11, 205.33)

- When 640 mg metaxalone tablet was given with food, the absorption phase seems to be extended relatively speaking (Figure 4.2.4). Although, the absorption profile seems to have prolonged after food, the peak concentration appears to occur at the same time as that of the fasted state.

Figure 4.2.4. Mean Plasma Concentration-Time Profiles of Metaxalone Following 640 mg Metaxalone Tablet in All Fed and Fasted Healthy Subjects (n=47).



- AUCs appears to be comparable in fed and fasted conditions with 90% confidence intervals falling within the 80% to 125% limits (Table 4.2.5). The 90% CI for the C_{max} is outside the 80% and 125% limits with C_{max} under fed conditions being about 23% higher.

Table 4.2.5. Geometric Mean Metaxalone PK Parameters, Geometric Mean Ratios, and 90% CI Following 640 mg Metaxalone Tablets (Test) Tablet in all Fed and Fasted Subjects.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	Metaxalone Tablets (640 mg) Fasting	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	14600.21	13686.84	106.67	(98.35, 115.70)
AUC _{0-inf} (ng·hr/mL)	14840.39	13988.59	106.09	(98.23, 114.57)
C _{max} (ng/mL)	2207.56	1798.83	122.72	(104.93, 143.53)

It is already well documented that Skelaxin® tablets exhibits PK differences between males and females. The data from this study also show clear gender differences in the PK of metaxalone in fed and fasted subjects. The plasma concentration-time profiles of metaxalone are consistently higher in females than in males in fasted and in fed conditions and irrespective of product being administered (Figures 4.2.5 to 4.2.8).

Figure 4.2.5. Gender Differences in Mean Plasma Concentration-Time Profiles of Metaxalone Following 640 mg Metaxalone Tablets Fasted Females (n=18) and Males (n=29).

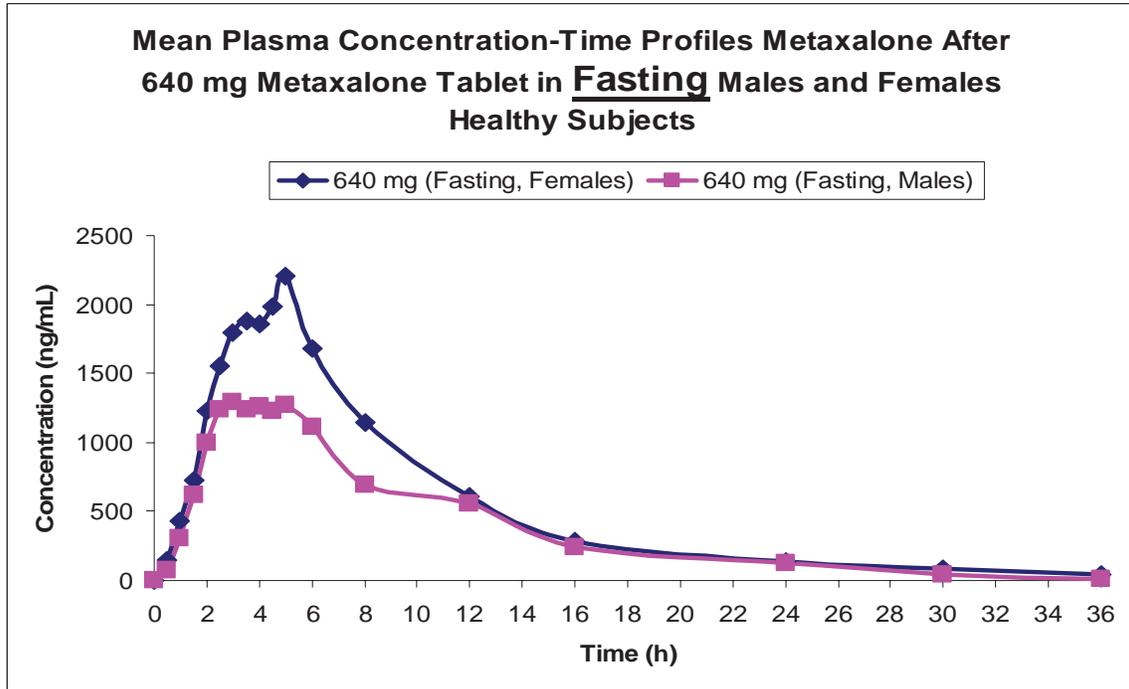


Figure 4.2.6. Gender Differences in Mean Plasma Concentration-Time Profiles of Metaxalone Following 640 mg Metaxalone Tablets Fed Females (n=18) and Males (n=29).

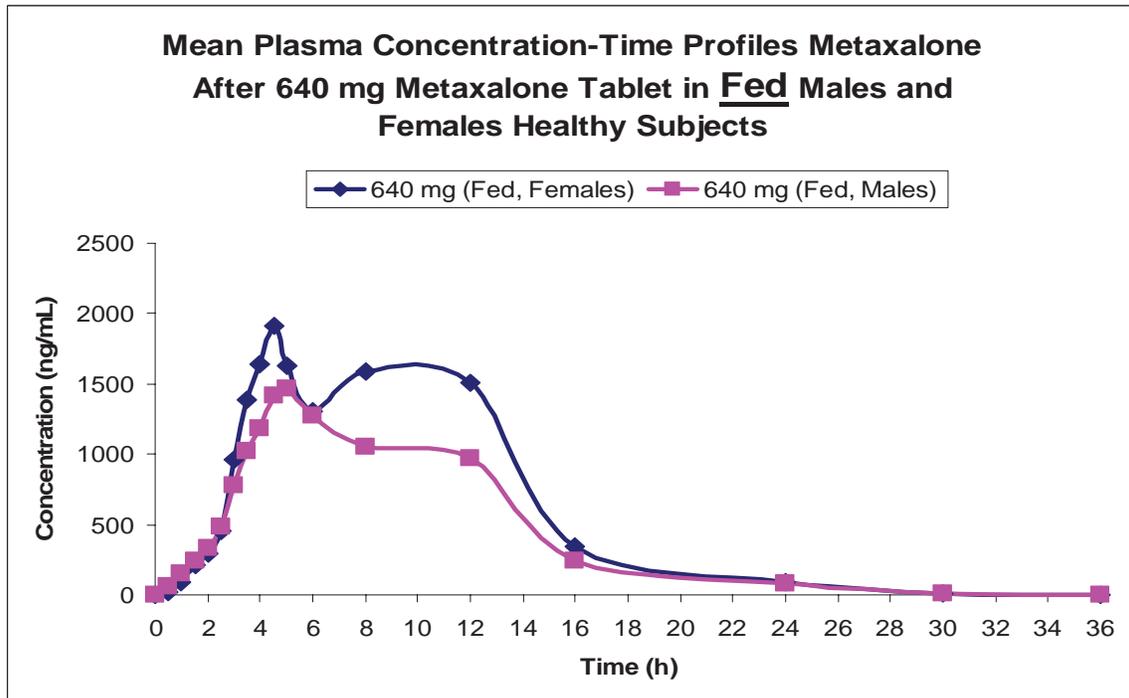


Figure 4.2.7. Gender Differences in Mean Plasma Concentration-Time Profiles of Metaxalone Following 800 mg Skelaxin® Fasted Females (n=18) and Males (n=29).

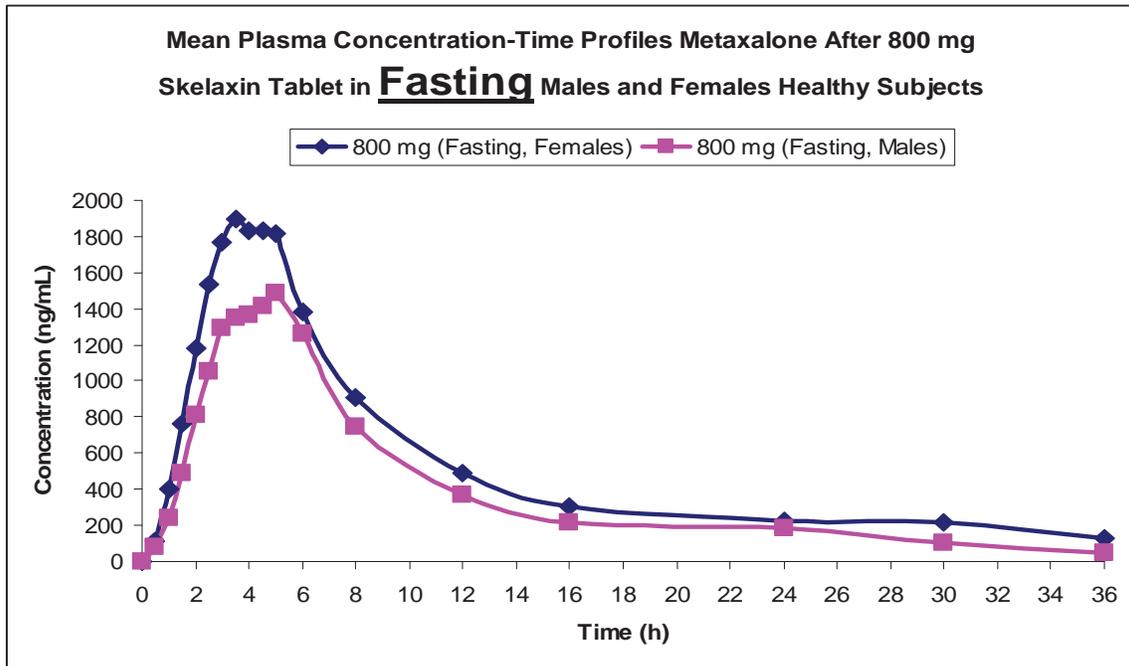
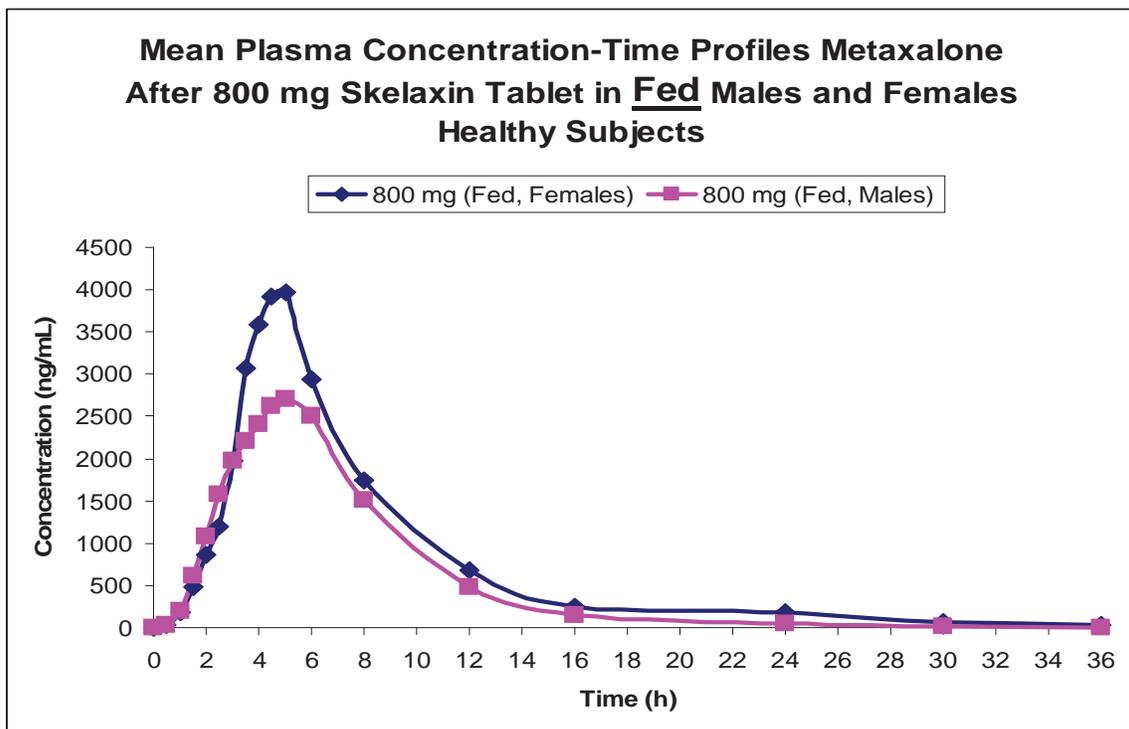


Figure 4.2.8. Gender Differences in Mean Plasma Concentration-Time Profiles of Metaxalone Following 800 mg Skelaxin® Fed Females (n=18) and Males (n=29).



From the bar graphs and summary PK tables it can be clearly observed that the C_{max} and AUC in females are consistently higher than in males after all treatments **Figures 4.2.9 and 4.2.10 and Tables 4.2.6 and 4.2.7).**

Figure 4.2.9. Gender Differences in Metaxalone AUC in Fed and Fasted Subjects After the Administration of 640 mg Metaxalone Tablets and 800 mg Skelaxin®

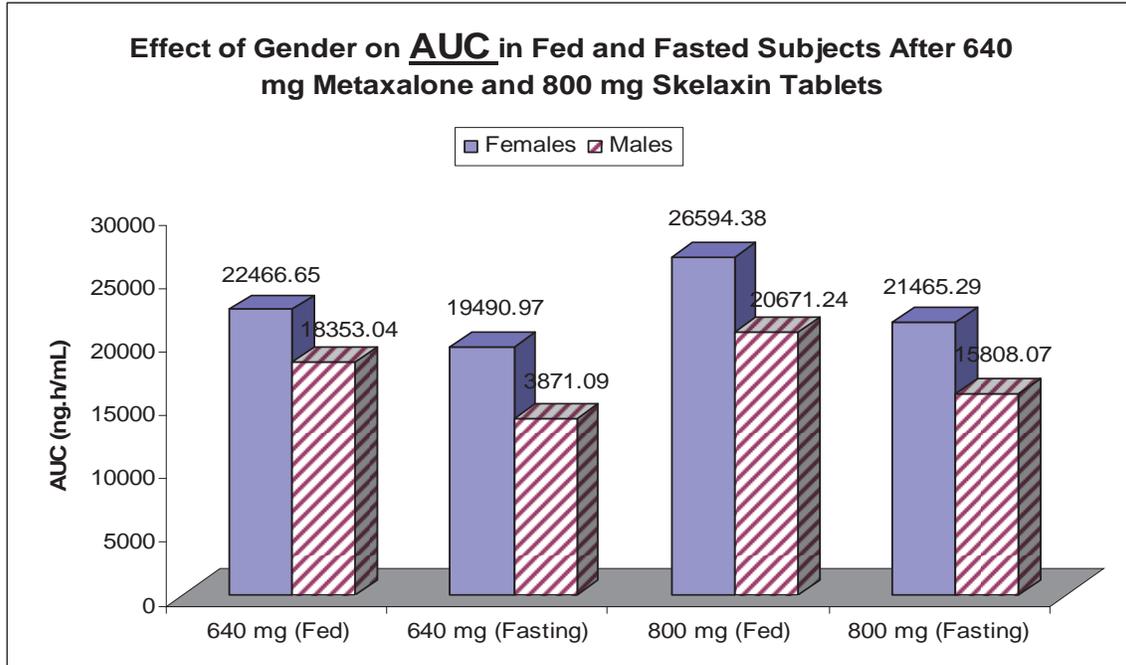


Figure 4.2.10. Gender Differences in Metaxalone C_{max} in Fed and Fasted Subjects After the Administration of 640 mg Metaxalone Tablets and 800 mg Skelaxin®

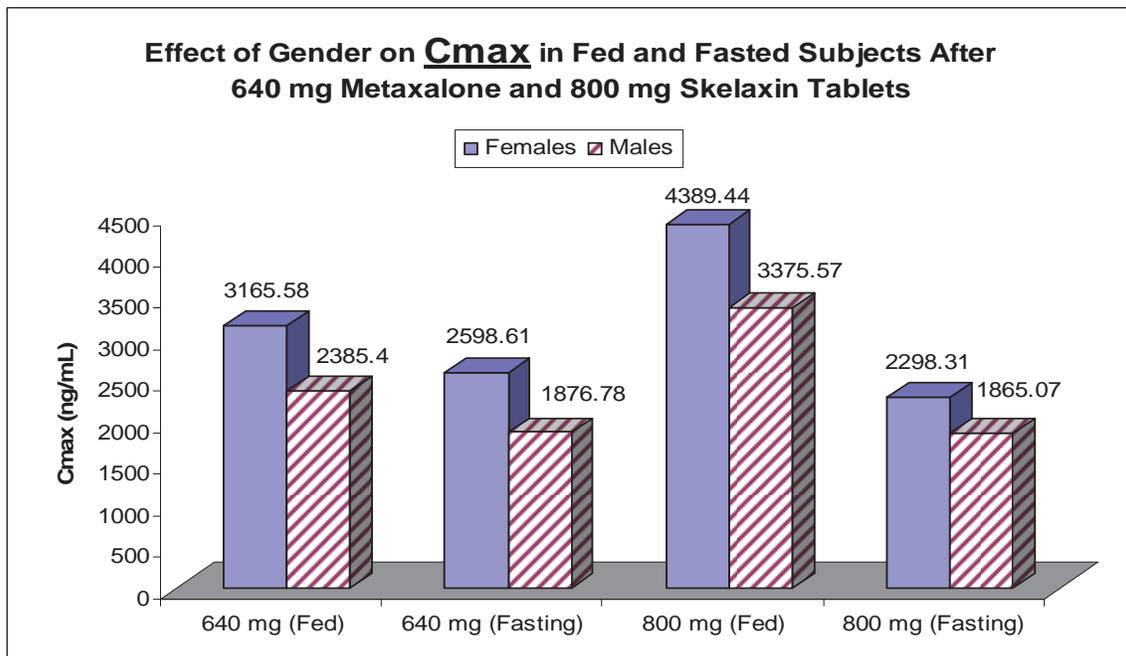


Table 4.2.6. Summary Statistics by Treatment Arm and PK Parameters for Female Subjects

Parameter (units)	Arithmetic Mean (%CV) Median (Range) for T _{max}			
	Metaxalone Tablets (640 mg) Fasting (N=18)	Metaxalone Tablets (640 mg) Fed (N=18)	SKELAXIN [®] Tablets (800 mg) Fasting (N=18)	SKELAXIN [®] Tablets (800 mg) Fed (N=18)
AUC _{0-t} (ng·hr/mL)	19051.31 (40.63)	20036.09 (38.46)	18851.72 (43.65)	26287.75 (44.36)
AUC _{0-inf} (ng·hr/mL)	19490.97 (39.88)	22466.50 (26.87)	21465.29 (44.03)	26594.38 (45.22)
AUC _{0-t} / AUC _{0-inf}	0.98 (2.39)	1.00 (0.44)	0.93 (4.76)	0.99 (0.67)
C _{max} (ng/mL)	2598.61 (56.48)	3165.58 (45.09)	2298.31 (45.13)	4389.44 (56.58)
T _{max} (hr)	4.00 (2.00-8.00)	10.00 (3.50-24.00)	3.50 (2.00-5.00)	4.75 (3.50-24.00)
Kel (1/hr)	0.1388 (32.31)	0.3303 (37.17)	0.0940 (45.82)	0.1600 (34.1)
T _{1/2} (hr)	5.49 (31.58)	2.31 (30.09)	8.46 (32.14)	4.82 (33.26)

Table 4.2.7. Summary Statistics by Treatment Arm and PK Parameters for Male Subjects

Parameter (units)	Arithmetic Mean (%CV) Median (Range) for T _{max}			
	Metaxalone Tablets (640 mg) Fasting (N=29)	Metaxalone Tablets (640 mg) Fed (N=29)	SKELAXIN [®] Tablets (800 mg) Fasting (N=29)	SKELAXIN [®] Tablets (800 mg) Fed (N=29)
AUC _{0-t} (ng·hr/mL)	13658.20 (55.37)	14883.57 (59.62)	14109.48 (54.71)	19957.26 (54.41)
AUC _{0-inf} (ng·hr/mL)	13871.09 (54.54)	18353.04 (54.93)	15808.07 (51.27)	20671.24 (53.47)
AUC _{0-t} / AUC _{0-inf}	0.98 (2.94)	1.00 (0.52)	0.96 (3.81)	0.99 (0.90)
C _{max} (ng/mL)	1876.78 (57.3)	2385.40 (66.82)	1865.07 (70.13)	3375.57 (58.55)
T _{max} (hr)	3.00 (1.50-12.00)	8.00 (3.50-16.00)	3.50 (2.00-6.00)	5.00 (2.50-12.00)
Kel (1/hr)	0.1624 (38.13)	0.3973 (29.84)	0.1321 (45.00)	0.1933 (48.26)
T _{1/2} (hr)	4.97 (47.59)	1.90 (30.84)	6.25 (44.92)	4.44 (50.41)

The statistical summary of the data is shown in **Tables 4.2.8 to 4.2.15**. The 90% CI for AUC after 640 mg and 800 mg products is within 80% to 125% in fasted females and fasted males, but not for the C_{max} (**Tables 4.5.8 and 4.2.12**). In fed conditions, however, none of the PK parameters were within 80% to 125% in males and females following either product (**Tables 4.2.9 and 4.2.13**). The reason (s) for the differences in exposure between males and females is unknown.

Based on this data, the two products are not bioequivalent in either females (**Tables 4.2.8 and 4.2.9**) or males (**Tables 4.2.12 and 4.2.13**) when administered under fasted or fed conditions. As stated above, in fasted conditions, the C_{max} was outside the 80%-125% in both females (**Tables 4.2.8**) and males (**Table 4.2.12**). However, in fed condition both C_{max} and AUC were outside the limits in both females (**Table 4.2.9**) and males (**4.2.13**).

Table 4.2.8. Mean PK Parameters and 90% CI for 640 mg Metaxalone Tablet and 800 mg Skelaxin® in Fasted Female Subjects

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=18				
Parameter (units)	Metaxalone Tablets (640 mg) Fasting	SKELAXIN® Tablets (800 mg) Fasting	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	16785.97	16253.73	103.27	(91.84, 116.14)
AUC _{0-inf} (ng·hr/mL)	17344.43	18094.28	95.86	(85.88, 106.99)
C _{max} (ng/mL)	2080.23	1976.18	105.27	(82.79, 133.85)

Table 4.2.9. Mean PK Parameters and 90% CI for 640 mg Tablet and 800 mg Skelaxin® in Fed Female Subjects

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=18				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	SKELAXIN® Tablets (800 mg) Fed	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	17656.72	22688.95	77.82	(69.20, 87.51)
AUC _{0-inf} (ng·hr/mL)	17460.72	22988.73	75.95	(68.05, 84.78)
C _{max} (ng/mL)	2690.65	3488.53	77.13	(60.66, 98.07)

Table 4.2.10. Mean PK Parameters and 90% CI for 640 mg Tablet in Fed and Fasted Female Subjects

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=18				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	Metaxalone Tablets (640 mg) Fasting	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	17656.72	16785.97	105.19	(93.54, 118.29)
AUC _{0-inf} (ng·hr/mL)	17460.72	17344.43	100.67	(90.19, 112.37)
C _{max} (ng/mL)	2690.65	2080.23	129.34	(101.72, 164.46)

Table 4.2.11. Mean PK Parameters and 90% CI for 800 mg Skelaxin® in Fed and Fasted Female Subjects

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=18				
Parameter (units)	SKELAXIN® Tablets (800 mg) Fed	SKELAXIN® Tablets (800 mg) Fasting	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	22688.95	16253.73	139.59	(124.13, 156.98)
AUC _{0-inf} (ng·hr/mL)	22988.73	18094.28	127.05	(113.83, 141.81)
C _{max} (ng/mL)	3488.53	1976.18	176.53	(138.83, 224.46)

Table 4.2.12. Mean PK Parameters and 90% CI for 640 mg Metaxalone Tablet and 800 mg Skelaxin® in Fasted Male Subjects

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=29				
Parameter (units)	Metaxalone Tablets (640 mg) Fasting	SKELAXIN® Tablets (800 mg) Fasting	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	11744.08	12287.06	95.58	(85.37, 107.01)
AUC _{0-inf} (ng·hr/mL)	11903.45	12864.01	92.53	(83.04, 103.11)
C _{max} (ng/mL)	1582.69	1537.68	102.93	(83.34, 127.12)

Table 4.2.13. Mean PK Parameters and 90% CI for 640 mg Metaxalone Tablet and 800 mg Skelaxin® in Fed Male Subjects

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=29				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	SKELAXIN® Tablets (800 mg) Fed	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	12749.43	17285.40	73.76	(65.88, 82.58)
AUC _{0-inf} (ng·hr/mL)	13371.13	17376.75	76.95	(69.06, 85.74)
C _{max} (ng/mL)	1954.91	2786.62	70.15	(56.80, 86.65)

Table 4.2.14. Mean PK Parameters and 90% CI for 640 mg Metaxalone Tablet in Fasted and Fed Male Subjects

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=29				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	Metaxalone Tablets (640 mg) Fasting	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	12749.43	11744.08	108.56	(96.96, 121.55)
AUC _{0-inf} (ng·hr/mL)	13371.13	11903.45	112.33	(100.81, 125.17)
C _{max} (ng/mL)	1954.91	1582.69	123.52	(100.01, 152.56)

Table 4.2.15. Mean PK Parameters and 90% CI for 800 mg Skelaxin® in Fasted and Fed Male Subjects

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=29				
Parameter (units)	SKELAXIN® Tablets (800 mg) Fed	SKELAXIN® Tablets (800 mg) Fasting	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	17285.40	12287.06	140.68	(125.65, 157.51)
AUC _{0-inf} (ng·hr/mL)	17376.75	12864.01	135.08	(121.23, 150.52)
C _{max} (ng/mL)	2786.62	1537.68	181.22	(146.73, 223.83)

The findings of gender differences in PK from this study are in general agreement to the historical data for Skelaxin®. The gender effect on the PK of metaxalone was addressed in several clinical pharmacology reviews dated October 6, 2004, April 22, 2005, and October 21, 2005 under NDA 13-217. Based on these reviews, the current approved label states that “the bioavailability of metaxalone was significantly higher in females compared to males as evidenced by C_{max} (2115 ng/mL *versus* 1335 ng/mL) and AUC_{∞} (17884 ng·h/mL *versus* 10328 ng·h/mL)”.

Overall Reviewer’s Comments and Summary:

- Based on this study, the 640 mg tablet is equivalent to 800 mg Skelaxin® only under fasted condition.
- Food markedly increased the exposure of Skelaxin® tablet relative to that of 640 mg metxalone tablet. Therefore, the two formulations are not equivalent under fed state.
- The food effect from this study is in general consistent with that stated in the currently approved label with respect to the effect of food on Skelaxin®. Food markedly increases the absorption of metaxalone following Skelaxin® tablet (C_{max} by about 75% and AUC by about 30%) which is in sharp contrast to the effect observed after metaxalone 640 mg tablet. For metaxalone 640 mg tablet, food did not have an effect on the AUC while C_{max} increased by about 23%.
- The exposure to metaxalone in females appears to be consistently higher than in males irrespective of fed/fasted conditions and the products being administered. The general BA/BE guidance for industry recommends that if a product is intended for use in both sexes, sponsor should attempt to include similar proportions of males and females in the study. However, the guidance acknowledges that there may not be sufficient power for BE demonstration for each subgroup and explicitly states that statistical analysis of subgroups is not recommended. As such, the combined data from all fasted subjects (n=47) is considered adequate to conclude that the two products are bioequivalent only in fasted condition.

Conclusions:

Overall, based on data from this study, the 640 mg tablet has equivalent exposure for both C_{max} and AUC under fasted conditions only. The effect of food on the 640 mg tablet is substantially lower when compared to that on Skelaxin® tablet. In spite of a substantial food effect, since data were not available on exposure response for either efficacy or safety (as documented extensively in previous reviews), Skelaxin® tablet does not have any specific dosage and administration instructions related to food effect. Since the effect of food on metaxalone 640 mg tablet is smaller in magnitude when compared to that on Skelaxin® tablet, metaxalone 640 mg can be given irrespective of food as that of Skelaxin® tablet.

4.3 Consult Review (Pharmacometric Review)

No pharmacometric consult was needed for this NDA.

4.4 Filing Memos:

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA/BLA Number	NDA 22-503	Brand Name	(b) (4)	
OCP Division (I, II, III, IV, V)	II	Generic Name	Metazalone	
Medical Division	DAARP	Drug Class	Muscle Relaxant	
OCP Reviewer	Sayed (Sam) Al Habet, RPh., Ph.D.	Indication(s)	Musculoskeletal Pain in >12 years old	
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	640 mg IR Tablet	
Pharmacometrics Reviewer	N/A	Dosing Regimen	640 mg TID-QID	
Date of Submission	August 18, 2009	Route of Administration	Oral	
Estimated Due Date of OCP Review	March 1, 2010	Sponsor	CorePharma, LLC	
Medical Division Due Date	April/May 2010	Priority Classification	Standard	
PDUFA Due Date	June 20, 2010			
<i>Clin. Pharm. and Biopharm. Information</i>				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1	1	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	X	1		
Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:		1	1	Pediatric plan submitted
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -	x	1		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:		1	1	Study #R08-0838 A Relative Bioavailability Study of 640 mg Metaxalone Tablets (Test) Versus 800 mg Skelaxin® Tablets (Reference) Under Fasting and Fed Conditions
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
In Vitro Dissolution	x	ONDQA will review		
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3	3	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the	x			

	evaluation of the validity of the analytical assay?				
5	Has a rationale for dose selection been submitted?		X		
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?			x	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Sponsor is requesting waiver for pediatric study <11 years of age or of weight <50 Kg. According to the current approved label the drug is indicated in patients >12 years of age.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					

18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___yes___ (see also attached filing slides, Attachment 1)

- The sponsor conducted relative bioavailability study using the final-to-be marketed formulation/strength and appropriate approved reference (RLD)
- Relative bioavailability study was conducted in fed/fasted healthy subjects with the final to be marketed formulation of 640 mg IR tablet (b) (4) and Reference Listed Drugs (RLD), Skelaxin 800 mg IR tablet.

Key Issues to be Considered:

- 1) Has the sponsor used appropriate reference?
The sponsor used the approved Skelaxin 800 mg tablet in the comparative bioavailability study. This strength is listed in the Orange Book as RLD.
- 2) Has the food study been conducted with the new formulation?
Yes (see above).

Based on the data, it appears that food may have significant impact on the absorption and bioavailability of the drug. Therefore, an appropriate language will be included in the label to reflect this impact.
- 3) Has the sponsor provided adequate rationale for using 640 mg IR tablet instead of 800 mg IR tablet as the Reference Listed Drugs (Skelaxin)?
The sponsor did not provide rationale for the lower strength of 640 mg tablet than the currently approved tablet of 800 mg.
- 4) Has the sponsor adequately characterized the PK of the drug product?
The sponsor conducted adequate relative bioavailability study for 640 mg IR tablet formulation to the reference listed drug (RLD) 800 mg IR Skelaxin tablet in fed and fasted healthy subjects.
- 5) Is the new formulation bioequivalent to the currently marketed formulations under fasting and fed conditions?
The sponsor conducted study to address this question in fed/fasted subjects. It appears that the two formulations have equivalent Cmax and AUC in fasted subjects, but not in fed subjects (Table 1-3, see also filing slides in Attachment 1).

Table 1. Metaxalone 640 gm Tablets Fasting vs. Skelaxin® Tablets (800 mg) Fasting for All Subjects.

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

Table 2. Metaxalone 640 mg Tablets Fed vs. Skelaxin® Tablets (800 mg) Fed for All Subjects.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	SKELAXIN® Tablets (800 mg) Fed	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	14600.21	19359.95	75.41	(69.53, 81.80)
AUC _{0-inf} (ng·hr/mL)	14840.39	19624.22	75.62	(70.02, 81.67)
C _{max} (ng/mL)	2207.56	3046.51	72.46	(61.96, 84.75)

Table 3. Metaxalone 640 mg Tablets Fed vs. Metaxalone 640 mg Tablets Fasting for All Subjects.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	Metaxalone Tablets (640 mg) Fasting	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	14600.21	13686.84	106.67	(98.35, 115.70)
AUC _{0-inf} (ng·hr/mL)	14840.39	13988.59	106.09	(98.23, 114.57)
C _{max} (ng/mL)	2207.56	1798.83	122.72	(104.93, 143.53)

It should also be noted that the sponsor did not include any language in the proposed labeling in reference to the effect of food. The language under dosage and administration section of the label is similar to that of the currently approved label "The recommended dose for adults and children over 12 years of age is one 640 mg tablet three to four times a day"

- 6) Does the new formulation have similar *in vitro* dissolution profiles to RLD?

The sponsor conducted *in vitro* dissolution study to address this question. It appears that the *in vitro* dissolution profiles of both formulations are similar. Final assessment of this will be deferred to ONDQA.

- 7) Has the sponsor provided any information related to PK/PD relationship and/or exposure-response in terms of safety and efficacy?

The sponsor did not provide any information nor is there any information available in the currently approved label.

- 8) Is there a need for DSI inspection? There is a need for DSI inspection as this is a pivotal bioavailability study:

The relevant study information for DSI inspections are:

Study #: # R08-0838
Analytical Site: (b) (4)
Clinical Site: Cetero Research, 625 Demers Avenue, east Grand Forks, MN 56721
PI: (b) (4)
Sponsor's Rep: Mukti Gande, CorePharma

What are the Regulatory Filing Issues?

As stated above, this is 505(b)(2) application for metaxalone 640 mg tablets. The sponsor referenced NDA 13-217 held by King Pharmaceuticals for Skelaxin® tablets 800 mg (Reference Listed Drug-RLD). The NDA is supported by a relative bioavailability study showing equivalent Cmax and AUC under fasting conditions between the test and reference products. Under fed conditions, the two products were not equivalent. Basically, the new tablet has higher bioavailability (about 20% higher) and if the sponsor had developed an 800 mg tablet, it would have failed bioequivalence test against the RLD 800 mg tablet. Therefore, the sponsor developed 640 mg tablet that would provide equivalent exposure to 800 mg of RLD. The indications and other labeling language are essentially everything similar to the currently approved label.

The draft 505(b)(2) guidance under Bioequivalence bullet (page5) states "Generally, an application for a pharmaceutically equivalent drug product must be submitted under section 505(j) of the Act and the proposed product must be shown to be bioequivalent to the reference listed drug (21 CFR 314.101 (d)(9)). Applications for proposed drug products where the rate (21CFR314.54(b)(2)) and/or extent (21 CFR 314.54 (b)(1)) of absorption exceed, or otherwise different from, the 505 (j) standards for bioequivalence compared to a listed drug may be submitted pursuant to section 505(b)(2) of the Act. Such a proposed product may require additional clinical studies to document safety and efficacy at the different rate and extent of delivery. Generally, the difference in rate and extent of absorption should be reflected in the labeling of the 505(b)(2) product. The proposed product does not need to be shown to be clinically better than the previously approved product; however a 505(b)(2) should not be used as a route of approval for poorly bioavailable generic drug products unable to meet the 505(j) standards for bioequivalence. If the proposed product is a duplicate of an already approved product, it should not be submitted as a 505(b)(2) application (21 CFR 314.101 (d)(9))."

The above issues were shared with Regulatory Project Management Staff in the Office of New Drugs (OND) on October 1, 2009 via e-mail for feedback. On October 14, 2009 Ms. Kim Quaintance responded with the following statement:

“According to the regulations, we can refuse to file an application for a drug product that differs from the referenced product if it is *less* bioavailable. Given that this product is more bioavailable in the fed state, we can review this (it can be filed) as a (b)(2). Of course whether the data support approval is a totally different matter!”

For additional details, see attached filing slides that were presented at the filing meeting held on October 1, 2009.

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

N/A

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

None

- There are no Information requests at time of filing

What are the Mid Cycle Deliverables?

At the mid cycle time it is expected that 80% to 90% of the review will be completed.

Sayed (Sam) Al Habet, RP.h., Ph.D. 2009	November 25,
Reviewing Clinical Pharmacologist	Date
Suresh Doddapaneni, Ph.D. 2009	November 25,
Team Leader/Supervisor	Date

**Attachment 1 (Filing Slides)
Filing Meeting (October 1, 2009)**



**Clinical Pharmacology Review
Filing Meeting
(NDA 22-503 Metaxalone Tablets- (b) (4)
640 mg)
(October 1, 2009)**

**Sayed (Sam) Al Habet, R.Ph., Ph.D.
and
Suresh Doddapaneni, Ph.D.**

1



Submission Summary

NDA #:	22, 503
Date of Submission:	August 18, 2009
Generic Name:	Metaxalon
Trade Name:	(b) (4)
Formulation:	640 mg IR Tablet
Route of Administration:	Oral
Indications:	Adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions
Proposed Dose:	>12 years of age = 640 mg TID-QID
Type of Submission:	New Formulation and strength (505(b)(2) ???
Sponsor:	COREPharma, LLC Middlesex, NJ
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D
Team Leader:	Suresh Doddapaneni, Ph.D.

2

Overview

- 505(b)(2):
 - New formulation
 - New strength (**640 mg**)
 - The same indications
- RLD: Skelaxin® **800 mg** (King Pharma)
- Submission:
 - Fasted and fed single dose study (800 mg RLD vs 640 mg tablet)
 - *In vitro* dissolution (800 mg RLD vs 640 mg tablet)

3

What are the Composition of the Tablet?

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	(b) (4)		
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.
(b) (4)

4

Has the Sponsor Conducted Adequate Relative Bioavailability Study?

- Single dose, four-way, crossover, fed fasted in 48 healthy subjects as follows:

Treatment A (Fasted): 640 mg Metaxalone (b) (4)

Treatment B (Fed): 640 mg Metaxalone (b) (4) (high fat breakfast)

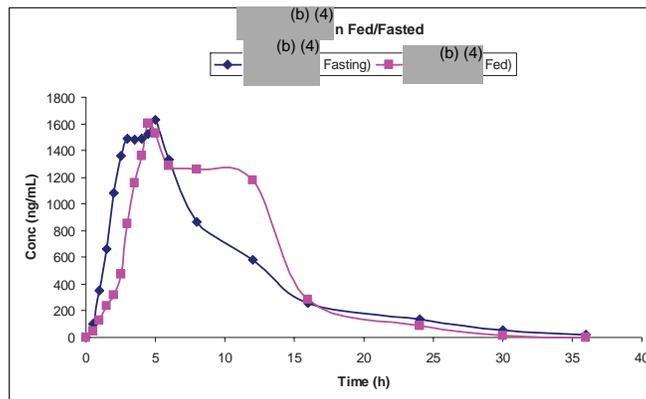
Treatment C (Fasted): 800 mg Skelaxin (King Pharma)

Treatment D (Fed): 800 mg Skelaxin (King Pharma) (high fat breakfast)

Blood for PK analysis was collected over 36 hours.

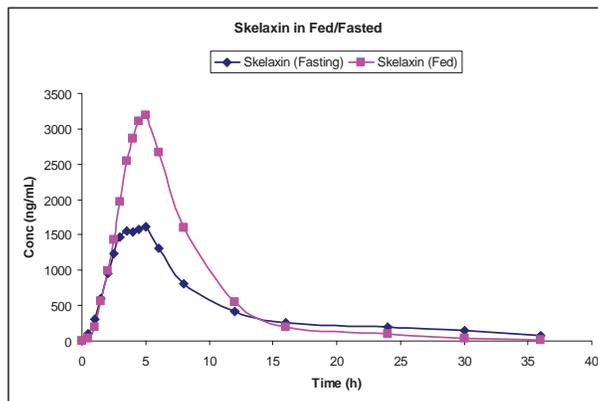
5

(b) (4) (640 mg) in Fasted and Fed



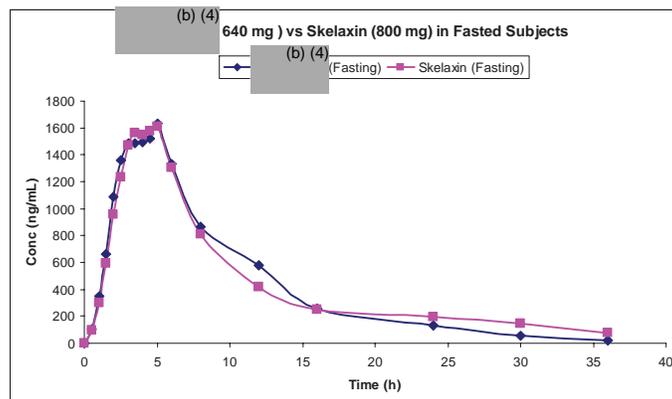
6

Skelaxin 800 mg in Fasted and Fed



7

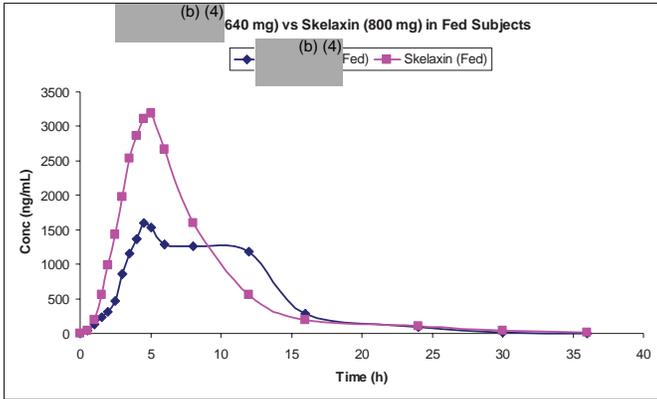
(b) (4) (640 mg) and Skelaxin (800 mg) in Fasted Only



8



(b) (4) (640 mg) and Skelaxin (800 mg) in Fed Only



9



Summary Statistic For All Subjects

Parameter (units)	Arithmetic Mean (%CV) Median (Range) for T _{max}			
	Metaxalone Tablets (640 mg) Fasting (N=47)	Metaxalone Tablets (640 mg) Fed (N=47)	SKELAXIN® Tablets (800 mg) Fasting (N=47)	SKELAXIN® Tablets (800 mg) Fed (N=47)
AUC _{0-t} (ng·hr/mL)	15723.65 (50.87)	16856.88 (51.81)	15925.66 (51.29)	22381.7 (51.27)
AUC _{0-inf} (ng·hr/mL)	16023.38 (50.23)	20035.82 (43.58)	17838.87 (50.01)	22959.73 (50.83)
AUC _{0-t} / AUC _{0-inf}	0.98 (2.73)	1.00 (0.49)	0.95 (4.38)	0.99 (0.81)
C _{max} (ng/mL)	2153.22 (59.22)	2684.20 (58.27)	2030.99 (59.98)	3763.86 (58.84)
T _{max} (hr)	3.50 (1.50-12.00)	8.00 (3.50-24.00)	3.50 (2.00-6.00)	5.00 (2.50-24.00)
Kel (1/hr)	0.1534 (36.96)	0.3699 (33.01)	0.1184 (47.85)	0.1804 (45.15)
T _{1/2} (hr)	5.17 (41.41)	2.07 (31.50)	7.04 (41.77)	4.59 (43.72)

10

90% CI in Fasted and fed (All Subjects)

Fasted

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

Fed

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	SKELEXIN® Tablets (800 mg) Fed	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	14600.21	19359.95	75.41	(69.53, 81.80)
AUC _{0-inf} (ng·hr/mL)	14840.39	19624.22	75.62	(70.02, 81.67)
C _{max} (ng/mL)	2207.56	3046.51	72.46	(61.96, 84.75)

Sample *In Vitro* Dissolution Profiles of 800 mg Skelaxin and 640 mg (b) (4)



In Vitro Dissolution Profiles of 800 mg Skelaxin and 640 mg (b) (4)

Dissolution Comparison	F2 value
Skelaxin [®] Tablets, 800 mg (lot # ES807358A) vs. Corepharma's (b) (4) Tablets, 640 mg (lot # CR0820)	<u>64</u>
Skelaxin [®] Tablets, 800 mg (lot # ES807358A) vs. Corepharma's (b) (4) Tablets, 640 mg # CR0904)	<u>65</u>
Skelaxin [®] Tablets, 800 mg (lot # ES807358A) vs. Corepharma's (b) (4) Tablets, 640 mg (lot # CR0905)	<u>61</u>
Corepharma's (b) (4) Tablets, 640 mg (lot # CR0820) vs. Corepharma's (b) (4) Tablets, 640 mg (lot # CR0904)	<u>91</u>
Corepharma's (b) (4) Tablets, 640 mg (lot # CR0820) vs. Corepharma's (b) (4) Tablets, 640 mg (lot # CR0905).	<u>83</u>

13

Summary

- Adequate Relative Bioavailability study
- Adequate *in vitro* dissolution data
- Bioequivalent to RLD in fasting condition, **but not in fed.**
- DSI inspection is needed

14

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/

SAYED AL HABET
04/21/2010

SURESH DODDAPANENI
04/21/2010

BIOPHARMACEUTICS REVIEW
Office of New Drugs Quality Assessment

Application No.:	NDA 22-503	Reviewer: Sandra Suarez Sharp, Ph.D	
Division:	DAARP		
Sponsor:	Corepharma	Team Leader: Angelica Dorantes, Ph.D	
Trade Name:	(b) (4) IR Tablets	Supervisor: Patrick J. Marroum, Ph.D	
Generic Name:	Metaxalone IR Tablets	Date Assigned:	March 3, 2010
Indication:	Relief discomforts associated with acute, painful musculoskeletal conditions	Date of Review:	April 8, 2010
Formulation	Immediate Release tablets, 640 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
Aug 18, 2009	Aug 21, 2009	March 3, 2010	June 21, 2010
Type of Submission:	Original NDA		
Type of Consult:	Dissolution method and specifications		

REVIEW SUMMARY:

Skelaxin (metaxalone) IR tablets, 800 mg were approved by the Agency in Aug 13, 1962 under NDA 013217. Metaxalone tablets, 800 mg have been also approved by the Agency under the ANDA (40-445) submission path. The sponsor is seeking approval of (b) (4) IR tablets (640 mg) for the relief discomfort associated with acute, painful musculoskeletal conditions under the 505 (b)(2) submission path. The sponsor's proposed dose for adults and children over 12 years of age is one 640 mg tablet three to four times a day.

The development program for this new product consists of one pivotal BE study under fed/fasting conditions comparing (b) (4) tablets, 640 mg to the RLD (Skelaxin tablets, 800 mg). This review focuses on the acceptability of the proposed dissolution method and specifications for this product as follows:

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

The BE study is being reviewed by OCP. According to the sponsor, the formulations were bioequivalent. High bioavailability of the new strength/formulation was possible by optimizing the particle size of API. Different dissolution specifications than those proposed by the sponsor are recommended for (b) (4) Tablets, 640 mg.

RECOMMENDATION:

The ONDQA/biopharmaceutics team has reviewed NDA 22-503(000) submitted on Aug 21, 2010. We found this NDA acceptable from biopharmaceutics perspective. The following comments should be conveyed to the sponsor:

1. It is noted that the percentage metaxalone dissolved at 6 months under accelerated stability (40 °C/75% RH) for the pivotal BE batch was about (b) (4)%. This represents a decrease of about (b) (4)% compared to that at release. Therefore, the Agency cannot accept setting dissolution specifications based on the performance of accelerated stability batches unless you demonstrate that your product with (b) (4)% dissolved at 90 min is equivalent to the same product releasing >(b) (4)% at 90 min.
2. The following dissolution specifications are recommended for (b) (4) tablets, 640 mg:

Acceptance criteria	
30 min:	No more than (b) (4)%
90 min:	Q (b) (4)%

These specifications are based on the mean dissolution values of exhibit batches including a batch used in the pivotal BE study. The earlier point (i.e. 30 min) is recommended given the low solubility nature of the drug substance and taking into consideration that PSD of the API is a critical variable for dissolution and therefore, bioavailability.

3. These specifications will be set as interim. You will have one year upon receiving this letter to submit dissolution information for stability batches under these new specifications.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 22-503, ADorantes, DChristodoulou, EChickhale

INTRODUCTION

Metaxalone, an oxazolidinone derivative, is a central nervous system depressant that has sedative and skeletal muscle relaxant effects. The precise mechanism of action of the drug is not known. When administered orally, its skeletal muscle relaxant effects are minimal and are probably related to its sedative effect. The plasma concentrations required for pharmacologic action of metaxalone are not known. A single, oral 800-mg dose of metaxalone produces a mean peak level of 296 ng/mL in 2 hours. The onset of action is usually within 1 hour and the duration of action is about 4-6 hours. The drug has a plasma half-life of 2-3 hours. Metaxalone is metabolized by the liver and excreted in urine as unidentified metabolites. Metaxalone tablets are available in 400-mg and 800-mg strengths.

Skelaxin (metaxalone) IR tablets, 800 mg were approved by the Agency in Aug 13, 1962 under NDA 013217. Metaxalone tablets, 800 mg have been also approved by the Agency

under the ANDA submission path. The sponsor is seeking approval of (b) (4) tablets (640 mg) for the relief discomfort associated with acute, painful musculoskeletal conditions under the 505 (b)2 submission path. The sponsor's proposed dose for adults and children over 12 years of age is one 640 mg tablet three to four times a day.

This review of this NDA will focus on the acceptability of the proposed dissolution method and specifications.

CHEMISTRY

Drug Substance

The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Metaxalone does not directly relax tense skeletal muscles in man. The physicochemical properties of metaxalone are as follows:

Physical Description : White odorless crystalline powder

pKa : 12.3 ± 0.4 (Calculated)

Polymorphism : No known polymorph (confirmed by Differential Scanning Calorimetry, X-Ray diffraction and Infra Red by Fourier Transform)

Solubility :

Solvent	Solubility
(b) (4)	(b) (4)
Water	Insoluble
(b) (4)	(b) (4)
Ethanol	Soluble

Metaxalone has very low solubility across the pH range evaluated. The aqueous solubility of Metaxalone as a function of pH was also studied in-house and results obtained are as follows:

Table 1. Summary of Solubility of the Drug Substance as a Function of pH

Solvent Media	Solubility (mg/mL)				Dose Solubility Volume*
	Trial # 1	Trial # 2	Trial # 3	Average	
0.1N HCl (pH 1.0)	0	0	0.3	0.3	2667

	3	3			
pH 3.0 Acetate Buffer	0 . 3	0 . 4	0. 5	0.4	2000
pH 4.5 Acetate Buffer	0 . 3	0 . 3	0. 3	0.3	2667
pH 7.5 Phosphate Buffer	0 . 3	0 . 3	0. 3	0.3	2667

*Based upon highest available strength of 800 mg.

The BCS classification for this substance was not provided.

Formulation

Metaxalone Tablets 640 mg is immediate release solid oral dosage form. Metaxalone Tablets 640 mg are peach colored, oval shaped (b) (4) tablets. Debossed (b) (4) on one side and Plain on the other side and free from visible extraneous matter. The components and composition of the product are summarized in Table 2.

Table 2. Components and composition for (b) (4) tablets, 640 mg

Ingredient	Reference to Quality Standard	Function	Quantity/Tablet (mg)	Amount (%) / Tablet
Metaxalone (b) (4)	In-House	Active	(b) (4)	(b) (4)
Metaxalone	In-House	Active		
Lactose Monohydrate (b) (4)	NF	(b) (4)		
FD&C Yellow # 6, (b) (4)	In-House	(b) (4)		
Propylene Glycol Alginate (b) (4)	NF	(b) (4)		
Alginic Acid (b) (4)	NF	(b) (4)		
Povidone (b) (4)	USP	(b) (4)		
(b) (4)		(b) (4)		
Magnesium Stearate	NF		(b) (4)	(b) (4)
Total Weight			752 mg	100%
(b) (4)				

PROPOSED DISSOLUTION METHOD AND SPECIFICATIONS DISSOLUTION METHOD

The proposed dissolution method and specification for the product are as follows:

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

It is noted this the dissolution method proposed for the sponsor for this strength is the same to that approved for metaxalone tablets 400 mg and 800 mg¹. The dissolution profiles of the batches of Skelaxin used in the pivotal BE study are shown in Figure 1. Table 3 summarizes the dissolution of two additional batches (exhibit batches) of (b) (4) tablets.



Figure 1. Dissolution profiles of Skelaxin tablets 800 mg (RLD; batch ES807358A) and metaxalone tablets 640 mg (Test Product) (batch CR0820).

¹ Dissolution methods online at the FDA

Table 3. Dissolution Profiles of Test Product in Comparison with those of Reference Product

	Reference Listed Drug Skelaxin® Tablets 800 mg Lot # ES807358A Exp: 11/2010	Test Product Metaxalone Tablets 640 mg		
		CR0820	CR0904	CR0905
15 Minutes Average (%) Range (%) RSD (%)	(b) (4)			
30 Minutes Average (%) Range (%) RSD (%)				
45 Minutes Average (%) Range (%) RSD (%)				
60 Minutes Average (%) Range (%) RSD (%)				
90 Minutes Average (%) Range (%) RSD (%)				
120 Minutes Average (%) Range (%) RSD (%)				
F2 Value				Lot # CR0820 is evaluated for bio-study F2 = 64 for Lot # CR0820 (up to 90 minutes) compared to Skelaxin 800 mg F2 = 65 for Lot # CR0904 (up to 90 minutes) compared to Skelaxin 800 mg F2 = 61 for Lot # CR0905 (up to 90 minutes) compared to Skelaxin 800 mg F2 = 91 for Lot # CR0904 (up to 120 minutes) compared to Lot # CR0820 F2 = 83 for Lot # CR0905 ((up to 120 minutes) compared to Lot # CR0820

In addition to the dissolution in releasing dissolution conditions, the exhibit batch (Lot # CR0820) was also studied for dissolution in pH 4.5 Acetate Buffer and pH 6.8 Phosphate Buffer in comparison with reference drug product (Table 4).

Table 4. Summary of Dissolution Results for Exhibit Batch (Lot # CR0820)

Dissolution	Lot # CR0820 (Test Product) Vs Skelaxin Tablets 800 mg (RLD)			
	Method: USP Apparatus II, 100 rpm, 37°C ± 0.5°C (n = 3)			
Time Points	900 mL pH 4.5 Acetate Buffer		900 mL pH 6.8 Phosphate Buffer	
	CR0820	ES807358A	CR0820	ES807358A
% of Drug Dissolved in				
15 Minutes	(b) (4)			
Average (%)				
Range (%)				
RSD (%)				
30 Minutes				
Average (%)				
Range (%)				
RSD (%)				
45 Minutes				
Average (%)				
Range (%)				
RSD (%)				
60 Minutes				
Average (%)				
Range (%)				
RSD (%)				
90 Minutes				
Average (%)				
Range (%)				
RSD (%)				
120 Minutes				
Average (%)				
Range (%)				
RSD (%)				
F ₂ Value	57		43	
Reference	RD219-72		RD219-81	

Reviewer's Comments

(b) (4)

² Bioequivalence review for ANDA 40-486 entered in V drive by Dr. Sikta Pradhan

Reviewer’s Comments

The sponsor provided enough information to support the validity of the analytical method for dissolution testing of the metaxalone tablets 640 mg.

REVIEWER’S PROPOSED DISSOLUTION SPECIFICATIONS

The following dissolution specifications are recommended based on the mean dissolution values shown in Tables 3 above for the 3 batches considered:

Acceptance criteria
30 min: No more than (b) (4)%
90 min: Q= (b) (4)%

The earlier point (i.e. 30 min) is recommended given the low solubility nature of the drug substance and taking into consideration that PSD of the API is a critical variable for dissolution and therefore, bioavailability. These specifications will be set as interim. The sponsor will be informed that they will have one year upon receiving this notification to submit dissolution information for stability batches under these new specifications.

Stability testing for dissolution was conducted only at 90 min and up to 6 months. The average dissolution was (b) (4)% at control room temperature (25 oC/60% RH). It is noted that the percentage metaxalone dissolved at 6 months under accelerated stability (40 oC/75% RH) for the pivotal BE batch was about (b) (4)%. This represents a decrease of about (b) (4)% compared to that at release. Therefore, the Agency cannot accept setting dissolution specifications based on the performance of accelerated stability batches unless the

sponsor demonstrates that the product with ^(b)₍₄₎% dissolved at 90 min is equivalent to the same product releasing > ^(b)₍₄₎% at 90 min.

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/

SANDRA SUAREZ
04/16/2010

PATRICK J MARROUM
04/16/2010

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	NDA 22-503	Brand Name	(b) (4)
OCP Division (I, II, III, IV, V)	II	Generic Name	Metazalone
Medical Division	DAARP	Drug Class	Muscle Relaxant
OCP Reviewer	Sayed (Sam) Al Habet, RPh., Ph.D.	Indication(s)	Musculoskeletal Pain in >12 years old
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	640 mg IR Tablet
Pharmacometrics Reviewer	N/A	Dosing Regimen	640 mg TID-QID
Date of Submission	August 18, 2009	Route of Administration	Oral
Estimated Due Date of OCP Review	March 1, 2010	Sponsor	CorePharma, LLC
Medical Division Due Date	April/May 2010	Priority Classification	Standard
PDUFA Due Date	June 20, 2010		

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	X	1		
Healthy Volunteers-				
single dose:	X	1		
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:		1		Pediatric plan submitted
geriatrics:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -	x	1		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:		1		Study #R08-0838 A Relative Bioavailability Study of 640 mg Metaxalone Tablets (Test) Versus 800 mg Skelaxin® Tablets (Reference) Under Fasting and Fed Conditions
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
In Vitro Dissolution	x	ONDQA will review		
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?		X		
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	substantive review to begin?				
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Sponsor requesting waiver for pediatric study <11 years of age or of weight <50 Kg. According to the current approved label the drug is indicated in patients >12 years of age.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	Waiver for ages <11 years.
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

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IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

___yes___ (see also attached filing slides, Attachment 1)

- The sponsor conducted relative bioavailability study using the final-to-be marketed formulation/strength and appropriate approved reference (RLD)
- Relative bioavailability study was conducted in fed/fasted healthy subjects using with the final to be marketed formulation of 640 mg IR tablet (b) (4) and Reference Listed Drugs (RLD), Skelaxin 800 mg IR tablet.

Key Issues to be Considered:

- 1) Has the sponsor used appropriate reference?
The sponsor used the approved Skelaxin 800 mg tablet in the comparative bioavailability study. This strength is listed in the Orange Book as RLD.
- 2) Has the food study been conducted with the new formulation?
Yes (see above).

Based on the data, it appears that food may have significant impact on the absorption and bioavailability of the drug. Therefore, an appropriate language will be included in the label to reflect this impact.
- 3) Has the sponsor provide adequate rationale for using 640 mg IR tablet instead of 800 mg IR tablet as the Reference Listed Drugs (Skelaxin)?
The sponsor did not provide rationale for the lower strength of 640 mg tablet than the currently approved tablet of 800 mg.
- 4) Has the sponsor adequately characterized the PK of the drug product?
The sponsor conducted adequate relative bioavailability study for 640 mg IR tablet formulation to the reference listed drug (RLD) 800 mg IR Skelaxin tablet in fed and fasted healthy subjects.
- 5) Is the new formulation bioequivalent to the currently marketed formulations under fasting and fed conditions?
The sponsor conducted study to address this question in fed/fasted subjects. It appears that the two formulations have equivalent C_{max} and AUC in fasted subjects, but not in fed subjects (Table 1-3, see also filing slides in Attachment 1).

Table 1. Metaxalone (b) (4) Tablets (640 mg) Fasting vs. Skelaxin® Tablets (800 mg) Fasting for All Subjects.

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

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Table 2. Metaxalone (b) (4) Tablets (640 mg) Fed vs. Skelaxin® Tablets (800 mg) Fed for All Subjects.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	SKELAXIN® Tablets (800 mg) Fed	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	14600.21	19359.95	75.41	(69.53, 81.80)
AUC _{0-inf} (ng·hr/mL)	14840.39	19624.22	75.62	(70.02, 81.67)
C _{max} (ng/mL)	2207.56	3046.51	72.46	(61.96, 84.75)

Table 3. Metaxalone (b) (4) Tablets (640 mg) Fed vs. Metaxalone (b) (4) Tablets (640 mg) Fasting for All Subjects.

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	Metaxalone Tablets (640 mg) Fasting	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	14600.21	13686.84	106.67	(98.35, 115.70)
AUC _{0-inf} (ng·hr/mL)	14840.39	13988.59	106.09	(98.23, 114.57)
C _{max} (ng/mL)	2207.56	1798.83	122.72	(104.93, 143.53)

It should also be noted that the sponsor did not include any language in the proposed labeling in reference to the effect of food. The language under dosage and administration section of the label is similar to that of the currently approved label "The recommended dose for adults and children over 12 years of age is one 640 mg tablet three to four times a day"

- 6) Is the new formulation has similar *in vitro* dissolution profiles to RLD?

The sponsor conducted *in vitro* dissolution study to address this question. It appears that the *in vitro* dissolution profiles of both formulations are similar.

- 7) Has the sponsor provided any information related to PK/PD relationship and/or exposure-response in terms of safety and efficacy?

The sponsor did not provide any information nor is there any information available in the currently approved label.

- 8) Is there a need for DSI Inspection? There is a need for DSI inspection as this is a pivotal bioavailability study:

The relevant study information for DSI inspections are:

Study #: # R08-0838
 Analytical Site: (b) (4)
 Clinical Site: Cetero Research, 625 Demers Avenue, east Grand Forks, MN 56721
 PI: (b) (4)
 Sponsor's Rep: Mukti Gande, CorePharma

What are the Regulatory Filing Issues?

As stated above, this is 505(b)(2) application for metaxalone 640 mg tablets. The sponsor referenced NDA 13-217 held by King Pharmaceuticals for Skelaxin® tablets 800 mg (Reference Listed Drug-RLD). The NDA is supported by a relative bioavailability study showing equivalent

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

C_{max} and AUC under fasting conditions between the test and reference products. Under fed conditions, the two products were not equivalent. Basically, the new tablet has higher bioavailability (about 20% higher) and if the sponsor had developed an 800 mg tablet, it would have failed bioequivalence test against the RLD 800 mg tablet. Therefore, the sponsor developed 640 mg tablet that would provide equivalent exposure to 800 mg of RLD. The indications and other labeling language are essentially everything similar to the currently approved label.

The draft 505(b)(2) guidance under Bioequivalence bullet (page5) states "Generally, an application for a pharmaceutically equivalent drug product must be submitted under section 505(j) of the Act and the proposed product must be shown to be bioequivalent to the reference listed drug (21 CFR 314.101 (d)(9)). Applications for proposed drug products where the rate (21CFR314.54(b)(2)) and/or extent (21 CFR 314.54 (b)(1)) of absorption exceed, or otherwise different from, the 505 (j) standards for bioequivalence compared to a listed drug may be submitted pursuant to section 505(b)(2) of the Act. Such a proposed product may require additional clinical studies to document safety and efficacy at the different rate and extent of delivery. Generally, the difference in rate and extent of absorption should be reflected in the labeling of the 505(b)(2) product. The proposed product does not need to be shown to be clinically better than the previously approved product; however a 505(b)(2) should not be used as a route of approval for poorly bioavailable generic drug products unable to meet the 505(j) standards for bioequivalence. If the proposed product is a duplicate of an already approved product, it should not be submitted as a 505(b)(2) application (21 CFR 314.101 (d)(9))."

The above issues were shared with Regulatory Project Management Staff in the Office of New Drugs (OND) on October 1, 2009 via e-mail for feedback. On October 14, 2009 Ms. Kim Quaintance responded with the following statement:

"According to the regulations, we can refuse to file an application for a drug product that differs from the referenced product if it is *less* bioavailable. Given that this product is more bioavailable in the fed state, we can review this (it can be filed) as a (b)(2). Of course whether the data support approval is a totally different matter!"

For additional details, see attached filing slides that were presented at the filing meeting held on October 1, 2009.

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

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None

- There are no Information requests at time of filing

What are the Mid Cycle Deliverables?

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At the mid cycle time it is expected that 80% to 90% of the review will be completed.

Sayed (Sam) Al Habet, RP.h., Ph.D.	November 25, 2009
Reviewing Clinical Pharmacologist	Date
Suresh Doddapaneni, Ph.D.	November 25, 2009
Team Leader/Supervisor	Date

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Attachment 1 (Filing Slides)
Filing Meeting (October 1, 2009)



Clinical Pharmacology Review
Filing Meeting
(NDA 22-503 Metaxalone Tablets- (b) (4)
640 mg)
(October 1, 2009)

Sayed (Sam) Al Habet, R.Ph., Ph.D.
and
Suresh Doddapaneni, Ph.D.

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Submission Summary

NDA #:	22, 503
Date of Submission:	August 18, 2009
Generic Name:	Metaxalon
Trade Name:	(b) (4)
Formulation:	640 mg IR Tablet
Route of Administration:	Oral
Indications:	Adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions
Proposed Dose:	>12 years of age = 640 mg TID-QID
Type of Submission:	New Formulation and strength (505(b)(2) ???
Sponsor:	COREPharma, LLC Middlesex, NJ
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D
Team Leader:	Suresh Doddapaneni, Ph.D.

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Overview

- 505(b)(2):
 - New formulation
 - New strength (**640 mg**)
 - The same indications
- RLD: Skelaxin® **800 mg** (King Pharma)
- Submission:
 - Fasted and fed single dose study (800 mg RLD vs 640 mg tablet)
 - *In vitro* dissolution (800 mg RLD vs 640 mg tablet)

3

What are the Composition of the Tablet?

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

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

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Has the Sponsor Conducted Adequate Relative Bioavailability Study?

- Single dose, four-way, crossover, fed fasted in 48 healthy subjects as follows:

Treatment A (Fasted): 640 mg Metaxalone (b) (4)

Treatment B (Fed): 640 mg Metaxalone (b) (4) (high fat breakfast)

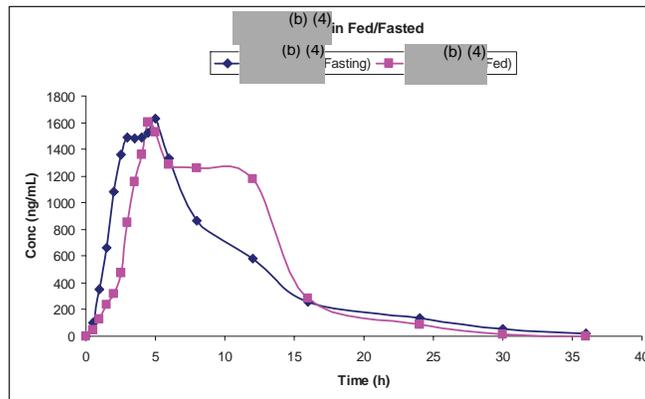
Treatment C (Fasted): 800 mg Skelaxin (King Pharma)

Treatment D (Fed): 800 mg Skelaxin (King Pharma) (high fat breakfast)

Blood for PK analysis was collected over 36 hours.

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(b) (4) (640 mg) in Fasted and Fed

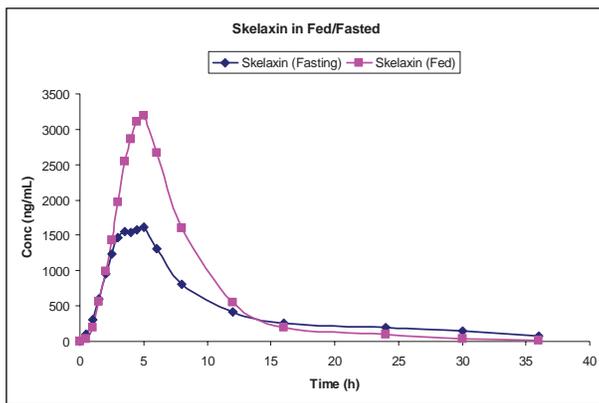


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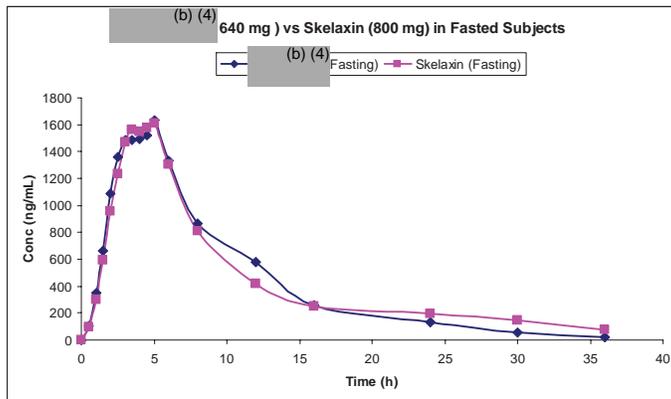
Skelaxin 800 mg in Fasted and Fed



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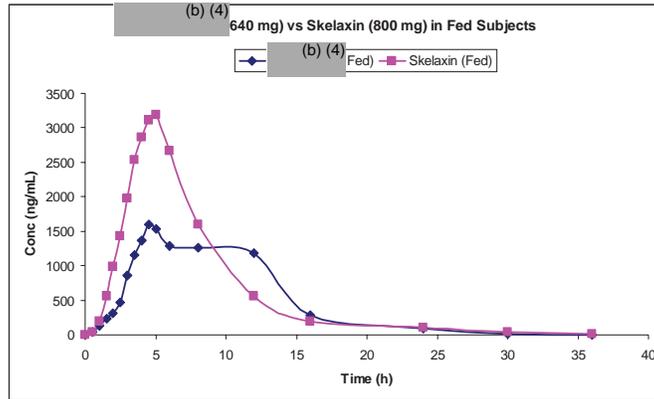
(b) (4)
(640 mg) and Skelaxin
(800 mg) in Fasted Only



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(b) (4) (640 mg) and Skelaxin
(800 mg) in Fed Only



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Summary Statistic For All Subjects

Parameter (units)	Arithmetic Mean (%CV) Median (Range) for T _{max}			
	Metaxalone Tablets (640 mg) Fasting (N=47)	Metaxalone Tablets (640 mg) Fed (N=47)	SKELAXIN® Tablets (800 mg) Fasting (N=47)	SKELAXIN® Tablets (800 mg) Fed (N=47)
AUC _{0-t} (ng·hr/mL)	15723.65 (50.87)	16856.88 (51.81)	15925.66 (51.29)	22381.7 (51.27)
AUC _{0-inf} (ng·hr/mL)	16023.38 (50.23)	20035.82 (43.58)	17838.87 (50.01)	22959.73 (50.83)
AUC _{0-t} / AUC _{0-inf}	0.98 (2.73)	1.00 (0.49)	0.95 (4.38)	0.99 (0.81)
C _{max} (ng/mL)	2153.22 (59.22)	2684.20 (58.27)	2030.99 (59.98)	3763.86 (58.84)
T _{max} (hr)	3.50 (1.50-12.00)	8.00 (3.50-24.00)	3.50 (2.00-6.00)	5.00 (2.50-24.00)
Kel (1/hr)	0.1534 (36.96)	0.3699 (33.01)	0.1184 (47.85)	0.1804 (45.15)
T _{1/2} (hr)	5.17 (41.41)	2.07 (31.50)	7.04 (41.77)	4.59 (43.72)

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90% CI in Fasted and fed (All Subjects)

Fasted

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

Fed

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Metaxalone N=47				
Parameter (units)	Metaxalone Tablets (640 mg) Fed	SKELAXIN® Tablets (800 mg) Fed	% Ratio	90% CI
AUC _{0-t} (ng·hr/mL)	14600.21	19359.95	75.41	(69.53, 81.80)
AUC _{0-inf} (ng·hr/mL)	14840.39	19624.22	75.62	(70.02, 81.67)
C _{max} (ng/mL)	2207.56	3046.51	72.46	(61.96, 84.75)

Sample *In Vitro* Dissolution Profiles of 800 mg Skelaxin and 640 mg (b) (4)



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**In Vitro Dissolution Profiles of 800 mg
Skelaxin and 640 mg (b) (4)**

Dissolution Comparison	F2 value
Skelaxin [®] Tablets, 800 mg (lot # ES807358A) vs. Corepharma's (b) (4) Tablets, 640 mg (lot # CR0820)	<u>64</u>
Skelaxin [®] Tablets, 800 mg (lot # ES807358A) vs. Corepharma's (b) (4) Tablets, 640 mg # CR0904)	<u>65</u>
Skelaxin [®] Tablets, 800 mg (lot # ES807358A) vs. Corepharma's (b) (4) Tablets, 640 mg (lot # CR0905)	<u>61</u>
Corepharma's (b) (4) Tablets, 640 mg (lot # CR0820) vs. Corepharma's (b) (4) Tablets, 640 mg (lot # CR0904)	<u>91</u>
Corepharma's (b) (4) Tablets, 640 mg (lot # CR0820) vs. Corepharma's (b) (4) Tablets, 640 mg (lot # CR0905).	<u>83</u>

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Summary

- Adequate Relative Bioavailability study
- Adequate *in vitro* dissolution data
- Bioequivalent to RLD in fasting condition, **but not in fed.**
- DSI inspection is needed

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Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22503

ORIG-1

COREPHARMA
LLC

(b) (4)
640MG
(METAXALONE)

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

/s/

SAYED AL HABET
11/25/2009

SURESH DODDAPANENI
11/26/2009