CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

017386Orig1s040

Trade Name:	ZAROXOLYN
Generic or Proper Name:	metolazone tablets
Sponsor:	UCB Inc.
Approval Date:	03/30/2015
Indication:	Indicated for the treatment of salt and water retention including: • Edema accompanying congestive heart failure; • Edema accompanying renal diseases including the nephrotic syndrome and states of diminished renal function. ZAROXOLYN is also indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs of a different class.

CENTER FOR DRUG EVALUATION AND RESEARCH

017386Orig1s040

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology / Virology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

017386Orig1s040

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 17386/S-040

APPROVAL LETTER

UCB Inc.
Attention: Ruta Monoenko
Senior Manager, Regulatory Affairs
1950 Lake Park Drive
Building 2100
Smyrna, GA 30080

Dear Ms. Monoenko:

Please refer to your Supplemental New Drug Application (sNDA) dated September 25, 2014, received September 25, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zaroxolyn® (metolazone) Tablets and authorized generic metolazone tablets.

This "Changes Being Effected in 30 days" supplemental new drug application provides for the addition of Dissolution <711> Test 1 of Metolazone Tablets, USP to the drug product specification, (b) (4)

We have completed our review of this supplemental new drug application. This supplement is approved.

However, we strongly suggest that the dissolution acceptance criteria when using the USP Dissolution Test 1 method be revised from Q = 75% at 120 minutes to Q = (b) (4) minutes for the 2.5 mg and 5 mg strength and Q = (b) (4) min for the 10 mg strength. We recommend that dissolution testing using the NDA method be deleted from the drug product specifications if it is replaced by dissolution testing using the USP Dissolution Test 1 method and the suggested revised dissolution acceptance criteria. We also recommend that the acceptance criteria for disintegration test be tightened. These changes should be requested in a CBE-30 Supplement.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Yvonne Knight, Regulatory Project Manager, at (301) 796-2133.

Sincerely,

Hasmukh B. Patel, Ph.D.
Acting Division Director

Division of Post-Marketing Activities 1
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Hasmukh B. Patel -S

Digitally signed by Hasmukh B. Patel -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300068254, cn=Hasmukh B. Patel -S
Date: 2015.03.25 13:28:32 -04'00'

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17386Orig1s040

CHEMISTRY REVIEW(S)

QUALITY (CMC) REVIEW #1	1 ORGANIZATION	2 NDA NUMBER
	ONDQA Division 1 Branch 3	017386

3 NAME AND ADDRESS OF APPLICANT	4 COMMUNICATION, DATE
UCB, Inc. 1950 Lake Park Drive, Building 2100 Smyrna, GA 30080	S040 CBE-30 PDUFA Date: Mar. 25, 2015

5 PROPRIETARY	6 NAME OF THE DRUG	7 AMENDMENTS, REPORT, DATE
Zaroxolyn®	Metolazone, USP Metolazone Tablets, USP	N/A

8 COMMUNICATION PROVIDES FOR:

Addition of Dissolution <711> Test 1 of Metolazone Tablets, USP to the drug product specification, [redacted] (b) (4).

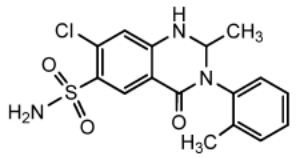
9 PHARMACOLOGICAL CATEGORY	10 HOW DISPENSED	11 RELATED IND, NDA, DMF
Diuretics (1020300)	Rx only	N/A
12 DOSAGE FORM	13 POTENCY	
Tablets, Oral	2.5 mg, 5 mg, 10 mg	

14 CHEMICAL NAME AND STRUCTURE

7-Chloro-1,2,3,4-tetrahydro-2-methyl-3-(2-methylphenyl)-4-oxo-6-quinazoline sulfonamide

CODE NAME:	N/A
EMPIRICAL FORMULA:	$C_{16}H_{16}ClN_3S$
MOLECULAR WEIGHT:	365.83
CASRN:	17560-51-9

CHEMICAL STRUCTURE:



INDICATION:	Treatment of edema and hypertension.

15 COMMENT

The applicant proposed: 1) Addition of Metolazone Tablets, USP's Dissolution Test 1 to the drug product specification; [redacted] (b) (4)
The USP Dissolution is more stringent than the currently approved "NDA Dissolution" method, and harder to meet. [redacted] (b) (4)
There are no changes to the drug product specification other than the added USP Dissolution test 1. The proposed changes are supported adequately by the batch and dissolution data. Biopharmaceutical Quality Review (Salah Hamed, Mar. 23, 2015) has recommended approval for the proposed changes, and advised the tightening of Dissolution specification and deletion of the currently used "NDA Dissolution" method (see the end of review for details). The post-approval stability commitments are acceptable. There are no changes beyond those proposed in this supplement. The proposed change will not impact adversely the identity, strength, purity and quality of the drug product.

16 CONCLUSION AND RECOMMENDATION

From the CMC perspective this supplemental application is recommended for APPROVAL.

17 CMC REVIEWER	18 SIGNATURE	19 DATE COMPLETED
Huai T. (Ted) Chang, PhD	See appended electronic signature sheet	Mar. 25, 2015

REVIEW NOTES—CHEMISTRY, MANUFACTURING AND CONTROLS

BACKGROUND—DRUG SUBSTANCE AND DRUG PRODUCT

ZAROXOLYN® Tablets (metolazone tablets, USP) for oral administration contain 2.5 mg or 5 mg of Metolazone, USP, are a diuretic/saluretic/antihypertensive drug of the quinazoline class. Metolazone is only sparingly soluble in water, but more soluble in plasma, blood, alkali, and organic solvents. Inactive Ingredients are magnesium stearate, microcrystalline cellulose and dye which includes D&C Red No. 33 (for 2.5 mg) and FD&C Blue No. 2 (for 5 mg).

Strength	Description of Zaroxolyn® Tablet
2.5 mg	Pink, (b) (4) ¼ inch round shallow biconvex, one side debossed "2 ½", other side debossed "ZAROXOLYN".
5 mg	Blue, (b) (4) ¼ inch round shallow biconvex, one side debossed "5", other side debossed "ZAROXOLYN"
10 mg	Yellow (b) (4) ¼ inch round shallow biconvex, one side debossed "10", other side debossed "ZAROXOLYN"

Note: Authorized generic metolazone tablets, USP, 2.5 mg, 5 mg and 10 mg are debossed respectively "643", "644" and "645" in place of "ZAROXOLYN".

NDA 017386 for Zaroxolyn Tablets—a 505(b)(1) NME drug application—was initially approved in the U.S. in 1973. Other drug versions include Diulo® Tablets (NDA 018535), Mykrox® Tablets (NDA 019532) and several generic Metolazone tablets. Besides the USP monographs for Metolazone and Metolazone Tablets, there is also one monograph for Metolazone Oral Suspension.

PROPOSED CHANGE

The applicant proposed the following changes:

- Addition of Metolazone Tablets, USP's Dissolution <711> Test 1 (became official in 2012) to the drug product specification to conform to the monograph. (**CMC Review Note**: The original NDA approved on 11/27/1973 did not include a dissolution test. The currently approved "NDA Dissolution Method" was added in 1980 via supplements.)
- And to improve the compliance with the above Dissolution <711> Test 1, (b) (4)

(b) (4)

DETAIL OF PROPOSED CHANGE AND REVIEW

Zaroxolyn and authorized generic tablets are manufactured by (b) (4) (b) (4). A comparison of the approved and proposed Dissolution tests is provided in the table next.

Comparison of Approved and Proposed Dissolution Test

Dissolution Test	Medium and Procedure	Acceptance
Approved Method	• Medium: 0.1 N NaOH at 37±0.5°C, 900 mL. • Apparatus 1 at 50±2 rpm, 60 min. • HPLC-UV	(b) (4)
Proposed Method (i.e. Metolazone Tablets, USP Test 1)	• Medium: 2% w/v SLS in 0.05M monobasic sodium phosphate at 37°C, pH 7.5, 900 mL. • Apparatus 2 at 75 rpm, 120 min. • HPLC-UV	NLT 75% (Q)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Specification and Comparative Batch Data—Drug Product

The revised specification for Zaroxolyn Tablets is provided in the table next. The specifications for the three tablet strengths are the same with the exception of the tablet appearance.

Specification for Zaroxolyn Tablets and Metolazone Tablets, USP—All Strength

Test	Method	Acceptance Criteria	
		Release	Shelf-Life
Description	(b) (4)		
Identity			
(b) (4)			
Dissolution	USP Apparatus 1		
Dissolution	**USP<711> Test 1**	**Q≥75%**	**Q≥75%**
(b) (4)			

CMC Review Assessment: The only change in the DP specification is the addition of Dissolution <711> Test 1, and the rest of the "grandfathered" specification remains unchanged. The applicant is advised to remove the old "NDA Dissolution" method from the DP specification.

Comparative batch studies for the (b) (4) are provided in two 2014 study reports R14060 and R14079. Relevant data (b) (4) Dissolution profile) is provided in the table below. (**CMC Review Note**: The applicant provided batch data for all three strengths. Only the data for 5 mg tablets is presented in this review as a representative example. The data for the other two strengths are similar.)

(b) (4)

(b) (4)

Stability Study

The post approval stability protocol has been revised to include accelerated storage conditions for all three strengths manufactured (b) (4) Thereafter, annually one production batch from each strength will be placed on long-term stability as per the approved stability protocols.

Stability Protocol for 1st Production Batch Manufactured at (b) (4)—All Strength

Storage Condition	Test Interval (months)								
	0	1.5	3	6	9	12	18	24	Expiry[a]
Baseline	B[b]	--	--	--	--	--	--	--	--
25°C/60%RH	--	--	A	A	A	B	A	B	B
30°C/65%RH[c]	--	--	--	A	A	A	--	--	--
40°C/75%RH	--	A	A	A	--	--	--	--	--

a Sample is tested at expiry based on date of manufacture. The current expiry is **36 months**.
b The "A" and "B" designate which testing schedule is performed at each test interval. Testing Schedule A does not include Microbiological Testing, while Testing Schedule B includes Testing Schedule A pluses Microbiological Testing.
c Intermediate Storage Conditions - these samples will be tested only if "significant change" as defined in the ICH Q1A(R2) stability guideline is obtained for the accelerated stability samples (40°C/75%RH).

Stability Protocol for Annual Batch Manufactured at (b) (4) All Strength

Storage Condition	Test Interval (months)							
	0	3	6	9	12	18	24	Expiry[a]
Baseline	B[b]	--	--	--	--	--	--	--
25°C/60%RH	--	A	A	A	B	A	B	B

BIOPHARMACEUTICAL QUALITY REVIEW

"The provided data show the (b) (4) on dissolution, using USP Dissolution Test 1 according the metolazone monograph. From a Biopharmaceutics perspective, (b) (4) NDA 17386 supplement S-040 for Zaroxolyn® Tablets 2.5 mg, 5 mg, and 10 mg is RECOMMENDED FOR APPROVAL."—Biopharmaceutical Quality Review by Salah Hamed, Mar. 23, 2015.

CMC ASSESSMENT, CONCLUSION AND RECOMMENDATION

The applicant proposed the following changes: 1) Addition of Metolazone Tablets, USP's Dissolution Test 1 to the drug product specification; and 2) (b) (4) The USP Dissolution is more stringent than the currently approved "NDA Dissolution" method, and harder to meet. (b) (4) (b) (4) There are no changes to the drug product specification other than the added USP Dissolution test 1.

The proposed changes are supported adequately by the batch and dissolution data. The USP method provides slower dissolution rate, but more discriminatory power for the Zaroxolyn® tablets. Biopharmaceutical Quality Review (Salah Hamed, Mar. 23, 2015) has recommended APPROVAL for the proposed changes and advised the tightening of Dissolution specification and deletion of the currently used "NDA Dissolution" method and acceptance criteria.

The post-approval stability commitments are acceptable. There are no changes beyond those proposed in this supplement. The proposed change will not impact adversely the identity, strength, purity and quality of the drug product.

From the CMC perspective this supplemental application is recommended for APPROVAL.

Comment to be communicated to the Applicant:

We strongly suggest that the dissolution acceptance criteria when using the USP Dissolution Test 1 method be revised from Q = 75% at 120 minutes to Q = (b) (4) minutes for the 2.5 mg and 5 mg strength and Q = (b) (4) min for the 10 mg strength. We recommend that dissolution testing using the "NDA method" be deleted from the drug product specifications if it is replaced by dissolution testing using the USP Dissolution Test 1 method and the suggested revised dissolution acceptance criteria. We also recommend that the acceptance criteria for disintegration test be tightened. These changes should be requested in a CBE-30 Supplement.

Huai T. Chang -A
Digitally signed by Huai T. Chang -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Huai T. Chang -A, 0.9.2342.19200300.100.1.1=1300379936
Date: 2015.03.25 11:53:42 -04'00'

Hasmukh B. Patel -S
Digitally signed by Hasmukh B. Patel -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300068254, cn=Hasmukh B. Patel -S
Date: 2015.03.25 12:28:40 -04'00'

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

017386Orig1s040

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW ONDP/Division of Biopharmaceutics			
Application No.:	NDA 17386/S-040 (SDN 208)	**Biopharmaceutics Reviewer:** Salaheldin S. Hamed, Ph.D.	
Division:	DCRP		
Applicant:	UCB, Inc.	**Acting Biopharmaceutics Lead:** Elsbeth Chikhale, Ph.D.	
Trade Name:	Zaroxolyn® Tablets	**Acting Biopharmaceutics Branch Chief:** Angelica Dorantes, Ph.D.	
Generic Name:	Metolazone Tablets	**Acting Biopharmaceutics Division Director:** Paul Seo, Ph.D.	
Indication:	Treatment of congestive heart failure and high blood pressure		
Dosage form/strength	Tablets, 2.5 mg, 5 mg, and 10 mg	**Date Assigned:**	25-SEP-2014
Route of Administration	Oral	**Date of Review:**	20-MAR-2015

SUBMISSIONS REVIEWED IN THIS DOCUMENT		
Submission date	**CDER Stamp Date**	**PDUFA DATE**
25-SEP-2014	25-SEP-2014	25-MAR-2015
Type of Submission:	NDA Changes Being Effected in 30 Days Supplement (CBE-30)	
Type of Review:	Evaluation of the comparative dissolution data generated for batches executed with the proposed change.	

Submission: This Changes Being Effected in 30 days supplement (CBE-30, S-040) to the original NDA proposes a [redacted (b) (4)] parameters for the approved dosage strengths tablets (2.5 mg, 5 mg, and 10 mg).

Review: To support the proposed change, the Applicant submitted dissolution data using the approved dissolution method in the original NDA and the USP compendial method**.** The Biopharmaceutics review is focused on the evaluation of the dissolution data generated for batches executed with the proposed changes.The other proposed post-approval changes – details of drug product composition, manufacturing process description, and stability – will be reviewed by the OPQ-CMC team.

RECOMMENDATION

The provided data show [redacted (b) (4)] on dissolution, using USP Dissolution Test 1 according the metolazone monograph. From a Biopharmaceutics perspective, [redacted (b) (4)] NDA 17386 supplement S-040 for Zaroxolyn® Tablets 2.5 mg, 5 mg, and 10 mg is **RECOMMENDED FOR APPROVAL**.

Additionally, it is noted that the dissolution is faster for higher dosage strengths. Therefore, it is strongly suggested that the dissolution acceptance criteria when using the USP Dissolution Test 1 method be revised from Q = 75% at 120 minutes to Q = [redacted (b) (4)] minutes for the 2.5 mg and 5 mg strength, and Q = [redacted (b) (4)] min for the 10 mg strength.

COMMENT TO BE CONVEYED TO THE APPLICANT:

We strongly suggest that the dissolution acceptance criteria when using the USP Dissolution Test 1 method be revised from Q = 75% at 120 minutes to Q = [redacted (b) (4)] minutes for the 2.5 mg and 5 mg strength and Q = [redacted (b) (4)] min for the 10 mg strength. We recommend that dissolution testing using the NDA method be deleted from the drug product specifications if it is replaced by dissolution testing using the USP Dissolution Test 1 method and the suggested revised dissolution acceptance criteria. This replacement of the dissolution specifications should be requested in a CBE-30 Supplement.

BIOPHARMACEUTICS ASSESSMENT

Table of Contents

1. INTRODUCTION

The original NDA for Zaroxolyn was approved on 27-NOV-1973 for the treatment Hypertention. In this supplement, (b) (4) The Applicant states that a dissolution test was added to the USP monograph via a USP Revision Bulletin; the revised monograph became official on 01-FEB-2012. The initial lots of Zaroxolyn® tablets tested by USP Dissolution Test 1 met the acceptance criterion; (b) (4)

2. FORMULATION AND MANUFACTURING

Zaroxolyn Tablets (metolazone Tablets, USP) for oral administration contain 2.5 mg, 5 mg or 10 mg of metolazone, USP. The tablets are shallow, biconvex, tablets debossed with the product strength (2.5, 5, or 10) on one side, and either "Zaroxolyn" for the branded product, or a code number (643, 644, or 645) for the Authorized Generic, on the other side.

The commercial, (b) (4)

The formulation components and composition are listed in Table 1. (b) (4)

Table 1. Composition of Zaroxolyn Tablets (metolazone tablets, USP)

Component	Quality Standard	Function	Amount per Tablet (Tablet weight: 100 mg)		
			2 ½ mg	5 mg	10 mg
Metolazone	USP	Active ingredient	2.50 mg	5.00 mg	10.00 mg
Microcrystalline Cellulose (b) (4)	(b) (4)				
Magnesium Stearate					
Dye D&C Red # 33 (b) (4)					
Dye Blue # 2 (b) (4)					
Dye D&C Yellow # 10 (b) (4)					
Dye D&C Yellow # 6 (b) (4)					

(b) (4)

(b) (4)

3. DISSOLUTION

The historical dissolution method, referred to as the "NDA Dissolution" method, was added to the quality control release test via the periodic report submitted on 11-FEB-1979 and to the shelf-life criteria via the periodic report submitted on 17-JAN-1980. The

original NDA did not include a dissolution test. To comply with the USP monograph, USP Dissolution Test 1 was added to the product's release and shelf-life specifications list. The NDA method and the USP method are summarized in Table 4.

Table 4. Zaroxolyn Tablet Dissolution Test Methods

Parameters	NDA Test	USP Test 1
Apparatus	USP Apparatus 1 (baskets)	USP Apparatus 2 (paddles)
Shaft Speed	50±2 RPM	75±2 RPM
Temperature	37±0.5 °C	37±0.5 °C
Medium	0.1N NaOH	2% w/v sodium lauryl sulfate (SDS) in 0.05M monobasic sodium phosphate (NaH_2PO_4), heat the mixture to about 37°C to dissolve SDS, and adjust to pH 7.5 with 10N NaOH
Volume	900 mL	900 mL
Time	60 minutes	120 minutes
Quantitation	UV	HPLC
Specification	(b) (4)	Q=75% at 120 minutes

The Applicant submitted comparative dissolution data (using the NDA method or the USP method) for two batches of each strength manufactured with (b) (4) as summarized in Table 5.

(b) (4)

The provided dissolution data (Tables 6, 7, and 8) (b) (4) In addition, the USP method is more discriminating when compared to the NDA approved method.

Table 6. Results for Metolazone 2.5 mg Tablet (Lot# 2953-082)

USP Method (Avg % Dissolution)		NDA Method (Avg % Dissolution)
Interval (min)		(b) (4)
15	30.5	(b) (4)
30	49.9	
45	62.9	
60	72.0	
120	89.1	

* One individual result for the initial six 2.5 mg tablets (b) (4) was less than 80% (Q+5). The individual result was 78.3%. An additional six tablets were tested; the results of the twelve tablets met the criteria for USP <711> Stage 2. Only (b) (4) were subject to USP <711> Stage 2 testing.

Table 7. Results for Metolazone 5 mg Talets (Lot# 2953-083)

USP Method (Avg % Dissolution)		NDA Method (Avg % Dissolution)
Interval (min)		(b) (4)
15	48.3	(b) (4)
30	67.6	
45	76.5	
60	81.9	
120	86.5	

Table 8. Results for Metolazone 10 mg Talets (Lot# 2953-084)

USP Method (Avg % Dissolution)		NDA Method (Avg % Dissolution)
Interval (min)		(b) (4)
15	70.5	(b) (4)
30	84.9	
45	90.8	
60	93.5	
120	96.6	

Based on the data above all three tablet strengths (b) (4) met the USP and NDA dissolution specifications.

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

The Applicant is proposing to keep the NDA dissolution method and acceptance criterion as part of the drug product specifications, and to add the USP Test 1 dissolution method and acceptance criterion. The proposed drug product dissolution specifications (method and acceptance criteria) are as follows:

Table 9. Dissolution Methods and Acceptance Criteria

Test	Method	Release Criteria	Shelf-Life Criteria
Dissolution	USP Apparatus 1 50±2 RPM 37±0.5°C Media: 0.1 N NaOH 900 mL 60 minutes UV	(b) (4)	
Dissolution – USP Test 1	USP Apparatus 2 75±2 RPM 37±0.5°C Media: 2% w/v sodium lauryl sulfate (SDS) in 0.05M NaH_2PO_4 adjusted to pH 7.5 with 10 N NaOH 900 mL 120 minutes HPLC	Meets USP requirements where Q=75%	Meets USP requirements where Q=75%

Reviewer's Assessment:

The change proposed by the Applicant is considered a level 2 change according to SUPAC IR guidance because it is a process change outside the approved operating range. Therefore, a multi-point dissolution profile comparison in the application/compendial medium (Case B) is required to approve the change. The Applicant provided Case B dissolution testing data in the approved NDA method and the compendial method. The f2 similarity scores were calculated for data generated using each method and are summarized in the following table:

	f2 values (USP Test 1 method)	f2 values (NDA method)
2.5 mg	42.6	70.6
5 mg	30.95	72.69
10 mg	41.39	70.66

(b) (4) *, whereas the USP Test 1 method does as indicated by the Applicant.*

This change is considered low risk for the following reasons:

(1) The faster dissolution (b) (4) *ensures the immediate release nature of the product*

(2) Metolazone is more soluble in alkaline media and complete dissolution in vivo is likely to be occurring in the intestines, so faster dissolution in vitro is not likely to translate to faster dissolution in vivo (because of the acidic environment in the stomach)

(3) The likelihood of safety issue due to altered PK is low because the drug is present in the plasma as early as 2 hours and its presence is sustained due to enterohepatic recirculation (Tmax occurs as late as 8 hours).

This supplement is RECOMMENDED FOR APPROVAL.

It is noted that the dissolution rate increases with dosage strength when using the USP Dissolution Test 1 method, which is likely due to the increased ratio of the API relative to magnesium stearate (see Table 1). Based on the provided dissolution data (see Tables 6, 7 and 8), it is strongly suggested that the dissolution acceptance criteria when using the USP Dissolution Test 1 method be revised from Q = 75% at 120 minutes to Q = (b) (4) minutes for the 2.5 mg and 5 mg strength, and Q = (b) (4) min for the 10 mg strength.

4. OVERALL BIOPHARMACEUTICS RECOMMENDATION

The provided data demonstrate that (b) (4), using USP Dissolution Test 1. In addition, the comparative dissolution profiles for batches manufactured with the proposed changes relative to the reference in-process specifications show that the USP Dissolution Test 1 is more discriminating than the method approved in the NDA. The faster dissolution profiles (b) (4) is not likely to produce significant changes in the PK. Therefore, from a Biopharmaceutics perspective, NDA 17386 supplement S-040 for Zaroxolyn® Tablets 2.5 mg, 5 mg, and 10 mg is **RECOMMENDED FOR APPROVAL.**

Salaheldin S. Hamed

Digitally signed by Salaheldin S. Hamed
DN: cn=Salaheldin S. Hamed, o=US FDA, ou=CDER, email=salaheldin.hamed@fda.hhs.gov, c=US
Date: 2015.03.23 16:49:32 -04'00'

Elsbeth G. Chikhale -S

Digitally signed by Elsbeth G. Chikhale -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300136142, cn=Elsbeth G. Chikhale -S
Date: 2015.03.23 16:53:13 -04'00'

Salaheldin S. Hamed, Ph.D.
Biopharmaceutics Reviewer

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Lead

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

017386Orig1s040

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 17386/S-040

CBE SUPPLEMENT – ACKNOWLEDGEMENT

UCB, Inc.
Attention: Ruta Monoenko, Senior Manager
Regulatory Affairs
1950 Lake Park Drive
Building 2100
Smyrna, GA 30080

Dear Ms. Monoenko:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 17386

SUPPLEMENT NUMBER: 40

PRODUCT NAME: Zaroxolyn® (metolazone) Tablets

DATE OF SUBMISSION: September 25, 2014

DATE OF RECEIPT: September 25, 2014

This supplemental application, submitted as a "Changes Being Effected in 30 days" supplement, proposes the following change:

- [redacted] (b) (4)

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 24, 2014, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 25, 2015.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions please feel free to call me at (301) 796-2133.

Sincerely,

{See appended electronic signature page}

Yvonne Knight, MS
Regulatory Health Project Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research
Food and Drug Administration