CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209089Orig1s000
209090Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 209089
Review # 1

Drug Name/Dosage Form	Xyzal® Allergy 24 HR Levocetirizine Dihydrochloride Tablets
Strength	5 mg
Route of Administration	Oral
Rx / OTC Dispensed	OTC
Applicant	UCB, Inc. 1950 Lake Park Drive Smyrna, Georgia 30080
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	31-Mar-2016	ONDP/OPF
Amendment	06-May-2016	ONDP

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sukhamaya Bain, Ph.D.	ONDP/DNDP-II/ Branch VI
Drug Product	Sukhamaya Bain, Ph.D.	ONDP/DNDP-II/ Branch VI
Process	Tarun Mehta	OPF/DPAII/BranchVI
Microbiology	Denise Miller , Ph.D.	OPF/DPAII/BranchVI
Facility	Tony Wilson	OPF/DIA/B3
Biopharmaceutics	An-Chi Lu, Ph.D.	ONDP/DB/BBII
Regulatory Business Process Manager	Thao, Vu	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Swapan K. De, Ph.D.	ONDP/DNDP-II/ Branch VI
Laboratory (OTR)	NA	NA
ORA Lead	Paul Perdue	ORA/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM	STATUS[1]	DATE	COMMENTS

			REFERENCED		REVIEW COMPLETED	
(b) (4)	Type- III		(b) (4)	Adequate		Sufficient data in the application.
	Type -III			Adequate	13-Feb-2003	The DMF and the components have been reviewed in detail by Dr. Jean Salemme, PhD. (13-Feb-2003), and were found to be adequate.
	Type- III			N/A		Sufficient data in the application.
	Type-III			N/A		Sufficient data in the application.
	Type-III			N/A		Sufficient data in the application.
	Type-III			N/A		Sufficient data in the application.
	Type-III			N/A		Sufficient data in the application.

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22-064	Xyzal tablets
NDA	72-233	Xyzal oral liquid
NDA	22-835	Zyrtec Tablets
NDA	20-346	Zyrtec Oral Syrup.
NDA	21-621	Zyrtec Chewable tablets

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			

Table of Contents

Executive Summary (NDA-209089)

I. Recommendations

Regarding Chemistry Manufacturing and Controls, the application may be approved.

A. Recommendation and Conclusion on Approvability

Regarding quality aspects of the application the drug substance, drug product, quality biopharmaceutics, process and facility sections are reviewed and found adequate to support the approval of the application. The drug product has been granted a shelf life of 36 months under controlled room temperature storage conditions.

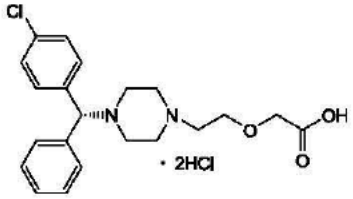
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Quality Assessments;

Drug substance and drug product information is referred to Applicant's previously approved NDA 22-064. The current NDA (NDA-209089) is from the same applicant, and the only difference is that the non-prescription tablet will have a debossed tablet logo instead of a printed tablet logo and will not use any printing ink. Quality information for the drug substance and drug product are included in the quality overall summary section and is acceptable. Some basic information is shown below.

1. **Drug Substance [USAN Name] Quality Summary**

Chemical Name or IUPAC Name/Structure: ®-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetic Acid Dihydrochloride.
Levocetirizine Dihydrochloride
Formula: ($C_{21}H_{25}ClN_2O_3.2HCl$).
CAS Number 130018-87-0
MW= 461.82



The currently approved suppliers of levocetirizine dihydrochloride drug substance are UCB Farchim S.A. Bulle, Switzerland. Currently, other drug substance manufacturing sites (b) (4), (b) (4) are inactive. Specifications for the drug substance includes critical tests for Identification (Levocetirizine dihydrochloride: conforms to (b) (4) (b) (4) Related impurities by (b) (4)

(b) (4)

Levocetirizine dihydrochloride is stored at (b) (4) and a (b) (4) re-test period is assigned based on stability data from long term and accelerated storage conditions.

A. Drug Product [Established Name] Quality Summary

1. Strength: 5 mg

2. Description/Commercial Image:

The proposed OTC drug product, Levocetirizine Dihydrochloride Tablets, 5 mg, are white to off-white, film-coated, oval-shaped scored tablets, debossed "X X" logo on one side of the tablet, with one "X" on each side of the score. The theoretical tablet weight is approximately (b) (4) based on a yield corresponding to (b) (4)%.

3. Summary of Product Design

This application proposes that the only change in the composition of the drug product, going from prescription (approved NDA 022064) to non-prescription (presently submitted NDA 209089), is the (b) (4). Thus, no significant pharmaceutical development work is submitted on the proposed OTC product.

The manufacturing process (b) (4). Content uniformity of the (b) (4) (b) (4) Dissolution comparison between the printed tablets, debossed tablets and split debossed tablets are performed and the values are similar. Dissolution met the criteria of Q = (b) (4)% dissolution in 30 minutes. There is no difference in dissolution performance as a result of the changes from the current printed logo to a debossed logo.

4. List of Excipients:

Microcrystalline cellulose, colloidal anhydrous silica, lactose monohydrate, magnesium stearate, (b) (4) (b) (4) (Hypromellose, Titanium Dioxide (b) (4) 400/ polyethylene glycol). Thus, all excipients listed (Colloidal anhydrous silica, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide) in the proposed labeling are acceptable.

(b) (4)

5. Process Selection (Unit Operations Summary)

The manufacturing process (b) (4) (b) (4).

6. **Container Closure**:

Levocetirizine dihydrochloride Tablets, 5 mg is packaged in a white opaque 30 mL high density polyethylene (HDPE) bottle. The 30 mL bottle is proposed to contain 35, 45, 55 and 80 counts of Levocetirizine dihydrochloride Tablets, 5 mg. The bottles are sealed with an aluminum foil induction inner seal and secured with a (b) (4) closure.

Levocetirizine dihydrochloride Tablets, 5 mg is also packaged in (b) (4) Blister Packs (Counts Not Provided). (b) (4) blister packs will be sealed with (b) (4) (peel push) (b) (4) aluminum foil lidding (b) (4) (b) (4) heat seal coating.

7. **Expiration Date & Storage Conditions**

Proposed expiration date of the drug product of 36 months is acceptable and supported by the real time stability data from the approved prescription product, in conjunction with the six months data from the proposed OTC product obtained at long-term storage conditions (25°C/60% RH) and 6-month study at accelerated conditions (40°C/75% RH). The storage statement will be written as "Store between 20° and 25°C (68°F and 77°F)". This reflects the numerical value of the controlled room temperature [stored at 25°C (77°F) with excursions permitted to 15°C-30°C (59°F-86°F)], and is a modified version of the wording requested by the FDA, but aligns with the currently approved storage statement for the prescription levocetirizine hydrochloride.

8. **List of co-packaged components: None**

B. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Xyzal® Allergy 24 HR
Non Proprietary Name of the Drug Product	levocetirizine dihydrochloride
Non Proprietary Name of the Drug Substance	levocetirizine dihydrochloride
Proposed Indication(s) including Intended Patient Population	For the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever or other upper respiratory allergies. Adults and children 12-64 years of age and Children 6-11years of age.
Duration of Treatment	One tablet (5 mg) a day; ½ tablet (2.5 mg) a day for children 6-11 years of age;
Maximum Daily Dose	5 mg; 2.5 mg for children 6-11 years.
Alternative Methods of Administration	None

C. Biopharmaceutics Considerations

1. BCS Classification: Not applicable (BCS class is determined only when applicant proposed the product as BCS Class I.
   - Drug Substance:

- Drug Product:

2. Biowaivers/Biostudies (For NDA only)
   - Biowaiver Requests: Yes
   - PK studies: N/A
   - IVIVC: No

D. Novel Approaches

E. Any Special Product Quality Labeling Recommendations

Established name of the drug product remains "levocetirizine dihydrochloride tablets" as approved in the prescription NDA 22-064, although based on current FDA guidance ("Naming of drug products containing salt drug substances guidance for Industry"-June 2015) and USP salt policy of the active moiety, the established name should contain the active moiety in neutral form without the name of salt. However, to avoid confusion with the prescription product the established name for the OTC product is accepted as proposed "levocetirizine dihydrochloride tablets".

(b) (4)

Xyzal®Allergy 24HR
(levocetirizine dihydrochloride tablet)
5 mg

F. Life Cycle Knowledge Information (see table below)

Risk Assessment:

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	2	2	2	8	Assay method is deemed acceptable. Impurities are monitored.
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	2	8	Stable based on data provided.

Content uniformity	• Formulation • Raw materials • Process parameters •Scale/equipment • Site	3	2	2	12	(b) (4)
Dissolution	• Formulation • Raw materials • Process parameters •Scale/equipments • Site • Exclude major reformulations • Alcohol dose dumping	2	2	2	8	Similar release profile with the RLD.

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Swapan De

Digitally signed by Swapan De
Date: 12/20/2016 07:50:00AM
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BIOPHARMACEUTICS

Product Background:

NDA: 209089

Drug Product Name / Strength: Levocetirizine dihydrochloride tablet/ 5 mg

Route of Administration:Oral

Applicant Name: UCB Inc.

Review Summary:

The Applicant submitted NDA 209089 for Xyzal® (Levocetirizine dihydrochloride) tablets to propose prescription to over-the-counter (Rx-to-OTC) switch under 505(b)(2). It referenced to the prescription NDA 22-064 which was also submitted under section 505(b)(2) and was approved on 5/25/2007. The Applicant also plans to reference the safety and clinical efficacy of ZYRTEC® (cetirizine dihydrochloride) [5 mg and 10 mg tablets in NDA 19-835, oral syrup (5 mg / ml) in NDA 20-346 and chewable tablets (5 mg and 10 mg) in NDA 21-621].

The proposed nonprescription use for levocetirizine dihydrochloride tablets is for the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever or other upper respiratory allergies.

The proposed tablet formulation is the (b) (4) as shown below:

Table 1: Quantitative Composition of Levocetirizine dihydrochloride Tablets, 5 mg

Component	Amount per tablet (mg)	Function	Reference to Standards
Levocetirizine dihydrochloride	5.00	Active ingredient	In house specification
Microcrystalline cellulose	(b) (4)		NF
Colloidal anhydrous silica			NF
Lactose monohydrate			NF
Magnesium stearate			NF
(b) (4)			In house specification
(b) (4)			USP

(b) (4)

(b) (4)

List Submissions being reviewed (table):

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining: None

BCS Designation

Reviewer's Assessment: Refer to prescription NDA 22-064

Solubility: Refer to prescription NDA 22-064

Permeability: Refer to prescription NDA 22-064

Dissolution: Refer to prescription NDA 22-064

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

(b) (4)

The FDA approved dissolution method and acceptance criterion are shown below:

Apparatus:	Paddle.
Medium:	900ml of water
Speed:	50RPM.
Sampling time:	15, 30, 45min.
Sampling volume:	5ml
Temperature:	37.0 +/-0.5°C

Acceptance Criterion: Q= (b) (4)% in 30 minutes.

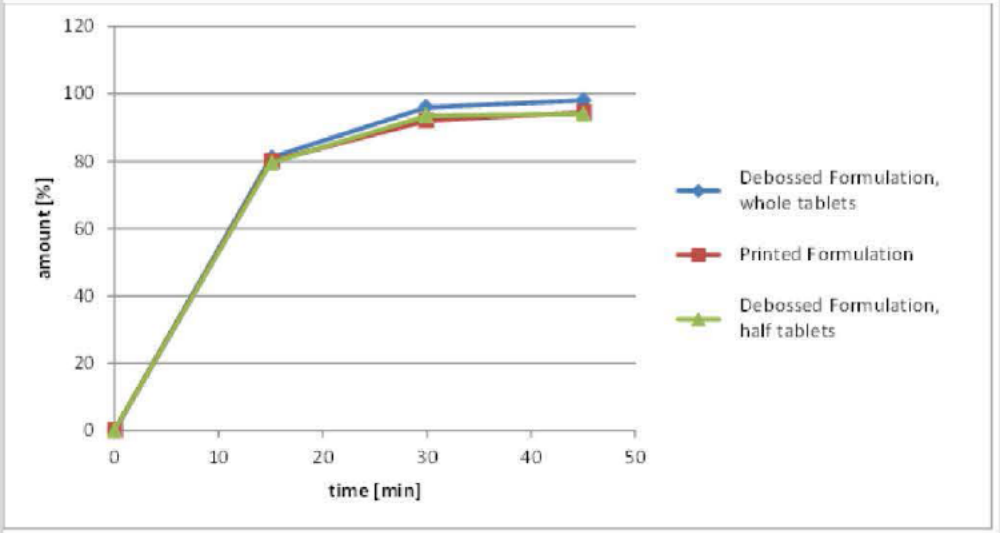
A dissolution comparison between printed tablets, debossed tablets, and split debossed tablets was performed using 12 tablets/batch of each tablet type according to the registered dissolution method UCB method meth-001455. The batch information for the dissolution testing is listed below in Table 2.

Table 2: batch information for the dissolution testing

	Printed Tablet	Debossed Tablet
Product code	(b) (4)	
Batch Number		
Manufacturing Site		
Expiry		

The mean dissolution profile of the printed tablets, debossed tablets, and half debossed tablets are shown in Figure 1. This drug product is immediate release and the drug substance is highly soluble, hence the f2 value is not calculated. The mean dissolution profiles are similar among the whole printed tablets, whole debossed tablets, and half debossed tablets. With the specification of Q = (b) (4)% in 30 minutes, all tablet formulations meet the acceptance criterion. Therefore, there is no difference in dissolution as a result of the changes from the current printed logo to a debossed logo.

Figure 1: Dissolution Profiles of Printed Tablets, Debossed, and Half Debossed Tablets



{Assess method development, method robustness, and criteria; modeling approach}

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: n/a

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: n/a

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: n/a

In-Vitro Release Testing (IVRT) for Semi-Solid Products

Reviewer's Assessment: n/a

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products

Reviewer's Assessment: n/a

In-Vitro Dissolution Testing for Abuse-deterrent Products

Reviewer's Assessment: n/a

In-Vitro BE Evaluation for Pulmonary Products

Reviewer's Assessment: n/a

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: n/a

Bridging of Formulations

Reviewer's Assessment: n/a

Biowaiver Request

Reviewer's Assessment:

The Applicant reported that other than the difference in the physical appearance of the tablet, there are no other changes from the prescription levocetirizine tablet product to the nonprescription levocetirizine tablet product. The applicant submitted a biowaiver request with supporting dissolution data (printed vs. debossed vs. half debossed tablets) based on the fact that the same drug substance, manufacturing process and test methods, and (b) (4) sites are utilized.

R Regional Information

Comparability Protocols

Reviewer's Assessment: n/a

Post-Approval Commitments

Reviewer's Assessment: n/a

Lifecycle Management Considerations

Reviewer's Assessment: n/a

List of Deficiencies: None.

Primary Biopharmaceutics Reviewer Name and Date:

An-chi (Angela) Lu, Pharm D. 8/1/2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I concur. 11/29/16

Tien-Mien Chen, Ph.D.

Acting Biopharm Lead

DB/ONDP/OPQ

Tien Mien Chen

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An-Chi Lu

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

DATE: 23 August 2016

TO: NDA 209-090

FROM: Denise Miller
CDER/OPQ/OPF/DMA/Branch II, Microbiologist

THROUGH: Neal J. Sweeney Ph.D.
CDER/OPQ/OPF/DMA/Branch II, Senior Microbiologist

SUBJECT: Division of Microbiology Review
Product: Xyzal Allergy 24 HR
Sponsor: UCB Inc.

This product is a currently marketed FDA approved product. It is a non-sterile oral solution.

NDA 209-090 is for this same product to be marketed as an over-the-counter (OTC) product. There are no proposed changes to the formulation, manufacturing of the product, or the release specifications, and as such there are no quality microbiology concerns for the subject NDA and further review of the NDA is not required.

The recommendation is for approval from the Product Quality Microbiology review standpoint.

[END]

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW NDA-209090

DIVISION OF NONPRESCRIPTION DRUG PRODUCTS

Application #: 209090	**Submission Type: Standard**	**Established/Proper Name:** Levocetirizine dihydrochloride/ **Xyzal® Allergy 24 HR**
Applicant: UCB Inc.	**Letter Date: March 31, 2016**	**Dosage Form: Oral solution**
Chemical Type: Type 8 – Partial Rx to OTC Switch	**Stamp Date: March 31, 2016**	**Strength: 2.5 mg/5 mL (0.5 mg/mL)**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?			

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW NDA-209090

DIVISION OF NONPRESCRIPTION DRUG PRODUCTS

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☐	☒	
2.	Botanical[1]	☐	☒	
3.	Naturally-derived Product	☐	☒	
4.	Narrow Therapeutic Index Drug	☐	☒	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☐	☒	
8.	Transdermal[1]	☐	☒	
9.	Pediatric form/dose[1]	☐	☒	
10.	Locally acting drug[1]	☐	☒	
11.	Lyophilized product[1]	☐	☒	
12.	First generic[1]	☐	☒	
13.	Solid dispersion product[1]	☐	☒	
14.	Oral disintegrating tablet[1]	☐	☒	
15.	Modified release product[1]	☐	☒	
16.	Liposome product[1]	☐	☒	
17.	Biosimiliar product[1]	☐	☒	
18.	Combination Product	☐	☒	
19.	Other_____	☐	☐	N/A

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW NDA-209090

DIVISION OF NONPRESCRIPTION DRUG PRODUCTS

Regulatory Considerations					
20.	USAN Name Assigned		☒	☐	
21.	End of Phase II/Pre-NDA Agreements		☐	☒	
22.	SPOTS (Special Products On-line Tracking System)		☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☒	
24.	Comparability Protocol(s)[2]		☐	☒	
25.	Other: Pre-NDA meeting		☒	☐	PIND 126506 meeting on 10/01/2015
Quality Considerations					
26.	Drug Substance Overage		☐	☒	
27.	Design Space	Formulation	☐	☒	
28.		Process	☐	☒	
29.		Analytical Methods	☐	☒	
30.		Other	☐	☒	
31.	Real Time Release Testing (RTRT)		☐	☒	
32.	Parametric Release in lieu of Sterility Testing		☐	☒	
33.	Alternative Microbiological Test Methods		☐	☒	
34.	Process Analytical Technology[1]		☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☐	☒	
36.		Excipients	☐	☒	
37.		Microbial	☐	☒	
38.	Unique analytical methodology[1]		☐	☒	
39.	Excipients of Human or Animal Origin		☐	☒	
40.	Novel Excipients		☐	☒	
41.	Nanomaterials[1]		☐	☒	
42.	Hold Times Exceeding 30 Days		☐	☒	
43.	Genotoxic Impurities or Structural Alerts		☐	☒	
44.	Continuous Manufacturing		☐	☒	
45.	Other unique manufacturing process[1]		☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☐	N/A
47.	New delivery system or dosage form[1]		☐	☒	
48.	Novel BE study designs		☐	☒	
49.	New product design[1]		☐	☒	
50.	Other_____		☐	☐	N/A

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	Justification for no extraordinary circumstances has been provided (section 1.12.14) and categorical exclusion for

C. FILING CONSIDERATIONS					
					levocetirizine dihydrochloride oral solution, 2.5 mg/5 mL is claimed according to 21 CFR 25.31(b) and 25.31 (c). requested.
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records o Method Validation Package o Comparability Protocols	☐	☒	☐	No comparability protocol is proposed. Not manufactured with materials of animal or human origin. Quality Overall Summary section is not included and the sponsor will submit this information in June, 2016.
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	☒	☐	☐	Cross –reference to the approved NDA 22-064 (Xyzal tablets, 5 mg (approved May 25, 2007). Approved suppliers of drug substance are UCB Farchim S.A. Bulle, Switzerland; (b) (4) (b) (4) Address and contact information of the drug substance facilities are included (b) (4) following an IR (dated 5/12/16).
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	☒	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW NDA-209090

DIVISION OF NONPRESCRIPTION DRUG PRODUCTS

C. FILING CONSIDERATIONS					
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☐	☐	☒	Refers to NDA 22-064
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture o Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment	☐	☐	☒	Refers to NDA 22-064.
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?	☒	☐	☐	Refers to NDA 22-157. Description and composition of the drug product is included.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW NDA-209090

DIVISION OF NONPRESCRIPTION DRUG PRODUCTS

C. FILING CONSIDERATIONS				
❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes data to demonstrate process consistency (i.e. data on process validation lots) o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System o Include data outlined in container closure guidance document ❑ Stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				Pharmaceutical development includes description of the changes from the approved product (NDA 22-064)
BIOPHARMACEUTICS				

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW NDA-209090

DIVISION OF NONPRESCRIPTION DRUG PRODUCTS

C. FILING CONSIDERATIONS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☒	
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	☐	☐	☒	
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☒	☐	☐	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☐	☒	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	☒	☐	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☐	☐	☒	Refers to NDA 22-064 & 22-157.
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification	☐	☐	☒	

C. FILING CONSIDERATIONS					
	○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production ❑ novel excipients				
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: ○ LAL instead of rabbit pyrogen ○ Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples				

Risk Assessment:

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	2	2	2	8	Refers to approved NDA 22157.
Specific gravity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	2	8	Refers to approved NDA 22157.
Dosing accuracy)	• Formulation Container closure • Raw materials • Process parameters •Scale/equipment • Site	3	2	2	12	Meets USP<698> .

Sterility	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	3	2	18	Meets USP<61>.

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OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW NDA-209089

DIVISION OF NONPRESCRIPTION DRUG PRODUCTS

Application #: 209089	**Submission Type: Standard**	**Established/Proper Name:** Levocetirizine dihydrochloride/ **Xyzal® Allergy 24 HR**
Applicant: UCB Inc.	**Letter Date: March 31, 2016**	**Dosage Form: Tablet**
Chemical Type: Type 8 – Rx to OTC Switch	**Stamp Date: March 31, 2016**	**Strength: 5 mg**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?			

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW NDA-209089

DIVISION OF NONPRESCRIPTION DRUG PRODUCTS

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☐	☒	
2.	Botanical[1]	☐	☒	
3.	Naturally-derived Product	☐	☒	
4.	Narrow Therapeutic Index Drug	☐	☒	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☐	☒	
8.	Transdermal[1]	☐	☒	
9.	Pediatric form/dose[1]	☐	☒	
10.	Locally acting drug[1]	☐	☒	
11.	Lyophilized product[1]	☐	☒	
12.	First generic[1]	☐	☒	
13.	Solid dispersion product[1]	☐	☒	
14.	Oral disintegrating tablet[1]	☐	☒	
15.	Modified release product[1]	☐	☒	
16.	Liposome product[1]	☐	☒	
17.	Biosimiliar product[1]	☐	☒	
18.	Combination Product	☐	☒	
19.	Other_____	☐	☐	N/A

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW NDA-209089

DIVISION OF NONPRESCRIPTION DRUG PRODUCTS

Regulatory Considerations					
20.	USAN Name Assigned		☒	☐	
21.	End of Phase II/Pre-NDA Agreements		☐	☒	
22.	SPOTS (Special Products On-line Tracking System)		☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☒	
24.	Comparability Protocol(s)[2]		☐	☒	
25.	Other: Pre-NDA meeting		☒	☐	PIND 126506 meeting on 10/01/2015
Quality Considerations					
26.	Drug Substance Overage		☐	☒	
27.	Design Space	Formulation	☐	☒	
28.		Process	☐	☒	
29.		Analytical Methods	☐	☒	
30.		Other	☐	☒	
31.	Real Time Release Testing (RTRT)		☐	☒	
32.	Parametric Release in lieu of Sterility Testing		☐	☒	
33.	Alternative Microbiological Test Methods		☐	☒	
34.	Process Analytical Technology[1]		☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☐	☒	
36.		Excipients	☐	☒	
37.		Microbial	☐	☒	
38.	Unique analytical methodology[1]		☐	☒	
39.	Excipients of Human or Animal Origin		☐	☒	
40.	Novel Excipients		☐	☒	
41.	Nanomaterials[1]		☐	☒	
42.	Hold Times Exceeding 30 Days		☐	☒	
43.	Genotoxic Impurities or Structural Alerts		☐	☒	
44.	Continuous Manufacturing		☐	☒	
45.	Other unique manufacturing process[1]		☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☐	N/A
47.	New delivery system or dosage form[1]		☐	☒	
48.	Novel BE study designs		☐	☒	
49.	New product design[1]		☐	☒	
50.	Other_____		☐	☐	N/A

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	Justification for no extraordinary circumstances has been provided (section 1.12.14) and categorical exclusion for

C. FILING CONSIDERATIONS					
					levocetirizine dihydrochloride tablet, 5 mg are claimed according to 21 CFR 25.31(b) and 25.31 (c). requested.
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records o Method Validation Package o Comparability Protocols	☐	☐	☒	No comparability protocol is proposed. Not manufactured with materials of animal or human origin. Quality Overall Summary section is not included and the sponsor will submit this information in June, 2016.
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	☒	☐	☐	Cross –reference to the approved NDA 22-064 (Xyzal tablets, 5 mg). Approved suppliers of drug substance are UCB Farchim S.A. Bulle, Switzerland; (b) (4) (b) (4) Address and contact information of the drug substance facilities are included (b) (4) following an IR (dated 5/12/16).
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	☒	☐	☐	
DRUG SUBSTANCE INFORMATION					

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW NDA-209089

DIVISION OF NONPRESCRIPTION DRUG PRODUCTS

C. FILING CONSIDERATIONS					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☐	☐	☒	Refers to NDA 22-064
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture o Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment	☐	☐	☒	Refers to NDA 22-064.
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product	☒	☐	☐	Refers to NDA 22-064. Description and composition of the drug product is included. Pharmaceutical development includes description of the changes from the

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW NDA-209089

DIVISION OF NONPRESCRIPTION DRUG PRODUCTS

C. FILING CONSIDERATIONS				
❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes data to demonstrate process consistency (i.e. data on process validation lots) o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System o Include data outlined in container closure guidance document ❑ Stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				approved product (NDA 22-157)
BIOPHARMACEUTICS				

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW NDA-209089

DIVISION OF NONPRESCRIPTION DRUG PRODUCTS

C. FILING CONSIDERATIONS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☒	
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	☒	☐	☐	In vitro dissolution test to support (b) (4) (b) (4), a debossed tablet logo which is also employed to support the biowaiver request.
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☒	☐	☐	See Biopharm item# 9 for details
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☐	☒	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	☒	☐	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification	☐	☐	☒	

C. FILING CONSIDERATIONS					
	○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production ❑ novel excipients				
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: ○ LAL instead of rabbit pyrogen ○ Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples				

Risk Assessment:

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	2	2	2	8	Assay method is deemed acceptable. Impurities are monitored.
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	2	8	Stable based on limited data provided.
Content uniformity	• Formulation • Raw materials • Process parameters •Scale/equipment • Site	3	2	2	12	(b) (4)

						(b) (4)
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipments • Site • Exclude major reformulations • Alcohol dose dumping	2	2	2	8	

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1.12.14 ENVIRONMENTAL ASSESSMENT

Claim of Categorical Exclusion from Preparation of an Environment Assessment for levocetirizine dihydrochloride tablet, 5 mg

NDA 209089

Date: 18 February, 2016 Total number of pages: 3

TABLE OF CONTENTS

1 CLAIM OF CATEGORICAL EXCLUSION FROM PREPARATION OF AN ENVIRONMENTAL ASSESSMENT FOR LEVOCETIRIZINE DIHYDROCHLORIDE TABLET

Sanofi-aventis U.S. LLC is claiming Categorical Exclusion from preparation of an Environmental Assessment for the New Drug Application 209089 for nonprescription sale of levocetirizine dihydrochloride tablet, 5 mg.

Compliance with the categorical exclusion criteria is made pursuant to 21 CFR Part 25, Subpart C, Categorical Exclusions, Section 25.31 (b), Human drugs and biologics, since approval of this action would result in a concentration of the active moiety (levocetirizine dihydrochloride) in the aquatic environment of the United States below 1 part per billion. This claim is based upon marketing estimates for maximum sales of all Sanofi levocetirizine dihydrochloride products during the first five years of sales after approval of levocetirizine dihydrochloride tablet in this Application and environmental fate data.

The requested action will not result in extraordinary circumstances per 21 CFR section 25.21 since no adverse effect or other significant effect on the quality of the human environment is predicted from approval of this submission.