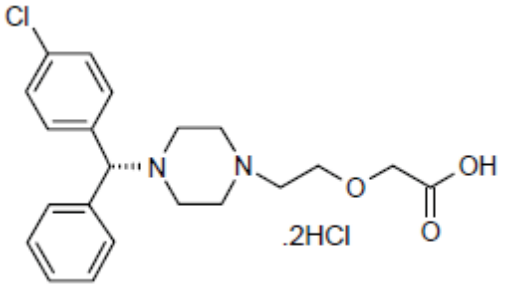
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209089Orig1s000
209090Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW	
NDA Number	209089 and 209090 (related INDs - 126506 & 126507)
Submissions Date	03/31/2016
Submission Type	505(b)(2) – Partial Rx-to-OTC switch
Proposed Brand Name	XYZAL® Allergy 24HR (NDA 209089) Children's XYZAL® Allergy 24HR (NDA 209090)
Generic Name	Levocetirizine Dihydrochloride Tablets (NDA 209089), 5 mg Levocetirizine Dihydrochloride Oral Solution (NDA 209090), 2.5 mg/5 mL
Sponsor	UCB Inc.
Route of Administration	Oral
Dosage Form	Immediate release scored tablet: 5 mg (NDA 209089) Solution: 2.5 mg/5 ml (NDA 209090)
Dosage Strength	Tablet: 5 mg (NDA 209089) Solution: 2.5 mg/5 ml (NDA 209090)
Proposed Dosing Regimen	Adults and children 12 years of age and older: 5 mg qd Children 6 to 11 years of age: 2.5 mg qd Children 2-5 years of age: 1.25 mg qd
Proposed Indication(s)	Temporarily relieves these symptoms due to hay fever or other respiratory allergies: • runny nose • sneezing • itchy, watery eyes • itching of the nose or throat
Proposed Population(s)	Adults and children 12 years of age and older Children 6 to 11 years of age Children 2-5 years of age
OND Divisions	Nonprescription Clinical Evaluation, and Pulmonary, Allergy, and Rheumatology Products
OCP Division	Clinical Pharmacology II
Reviewer	Bhawana (Bavna) Saluja, Ph.D.
Team Leader	Anshu Marathe, Ph.D.
Molecular Structure	

Office of Clinical Pharmacology Recommendation

Office of Clinical Pharmacology/Division of Clinical Pharmacology II, has reviewed NDA 209089 and 209090 submitted by UCB, Inc., requesting partial prescription (Rx) to over-the-counter (OTC) switch of XYZAL® (levocetirizine dihydrochloride) tablet (NDAs 022064) and oral solution (NDA 022157), and found the proposed drug product acceptable from a clinical pharmacology perspective.

FDA Regulatory History of XYZAL® Tablet (NDA 022064) & Oral Solution (NDA 022157)

- On May 25, 2007, XYZAL® (levocetirizine dihydrochloride) 5mg Tablet was first approved under NDA 022064 for the relief of symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR), and for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticarial (CIU) in adults and children *6 years of age or older*.

- On January 25, 2008, XYZAL® (levocetirizine dihydrochloride) 0.5mg/mL oral solution was first approved for the relief of symptoms associated with SAR and PAR, and treatment of uncomplicated skin manifestations of CIU for patients *6 years of age and older*.

- On August 21, 2009, the pediatric supplemental NDA for XYZAL® (levocetirizine dihydrochloride) 0.5mg/mL oral solution was approved for the relief of symptoms associated with SAR in children *2 years of age and older*, and for the relief of symptoms of PAR and treatment of uncomplicated skin manifestations of CIU for children *6 months of age and older*.

Background of This Submission

XYZAL® (levocetirizine dihydrochloride) 5mg tablet and 2.5 mg/5 mL oral solution is currently available in the U.S. as a prescription treatment for SAR, PAR, and CIU. The current submission requests a change of status from prescription to nonprescription use of levocetirizine dihydrochloride tablets (5 mg) and oral solution (2.5 mg/5 mL) for the temporary relief of symptoms due to hay fever or other respiratory allergies (runny nose, sneezing, itchy, watery eyes and itching of the nose or throat).

There is no new human pharmacokinetics and bioavailability or clinical pharmacology studies submitted to support of this Rx-to-OTC switch application. A label comprehension study (CONCENTRICS PROTOCOL #15060) was submitted in support of this switch.

General Pharmacokinetics Information of Levocetirizine Hydrochloride[1]

- **Absorption**:
  Levocetirizine is rapidly and extensively absorbed following oral administration. In adults, peak plasma concentrations are achieved 0.9 hour after administration of the oral tablet. The accumulation ratio following daily oral administration is 1.12 with steady state achieved after 2 days. Peak concentrations are typically 270 ng/mL and 308 ng/mL following a single and a repeated 5 mg once daily dose, respectively. Food had no effect on the extent of exposure (AUC) of the levocetirizine tablet, but Tmax was delayed by about 1.25 hours and Cmax was decreased by about 36% after administration with a high fat meal; therefore, levocetirizine can be administered with or without food. A dose of 5 mg (10 mL) of XYZAL® oral solution is bioequivalent to a 5 mg dose of XYZAL® tablets. Following oral administration of a 5 mg dose of

[1] Prescribing information, NDA 022064 (revised 11/2016)

XYZAL® oral solution to healthy adult subjects, the mean peak plasma concentrations were achieved approximately 0.5 hour post-dose.

- **Distribution**: The mean plasma protein binding of levocetirizine in vitro ranged from 91 to 92%, independent of concentration in the range of 90-5000 ng/mL, which includes the therapeutic plasma levels observed. Following oral dosing, the average apparent volume of distribution is approximately 0.4 L/kg, representative of distribution in total body water.

- **Metabolism**: The extent of metabolism of levocetirizine in humans is less than 14% of the dose and therefore differences resulting from genetic polymorphism or concomitant intake of hepatic drug metabolizing enzyme inhibitors are expected to be negligible. Metabolic pathways include aromatic oxidation, N-and O-dealkylation, and taurine conjugation. Dealkylation pathways are primarily mediated by CYP 3A4 while aromatic oxidation involves multiple and/or unidentified CYP isoforms.

- **Elimination**: The plasma half-life in adult healthy subjects was about 8 to 9 hours after administration of oral tablets and oral solution, and the mean oral total body clearance for levocetirizine was approximately 0.63 mL/kg/min. The major route of excretion of levocetirizine and its metabolites is via urine, accounting for a mean of 85.4% of the dose. Excretion via feces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion. Renal clearance of levocetirizine correlates with that of creatinine clearance. In patients with renal impairment the clearance of levocetirizine is reduced.

- **Drug Interaction**: In vitro data on metabolite interaction indicate that levocetirizine is unlikely to produce, or be subject to metabolic interactions. Levocetirizine at concentrations well above C_{max} level achieved within the therapeutic dose ranges is not an inhibitor of CYP isoenzymes 1A2, 2C9, 2C19, 2A1, 2D6, 2E1, and 3A4, and is not an inducer of UGT1A or CYP isoenzymes 1A2, 2C9 and 3A4. No formal in vivo drug interaction studies have been performed with levocetirizine.

- (b) (4)
    - *Pediatric Patients* –
      Data from a pediatric pharmacokinetic study with oral administration of a single dose of 5 mg levocetirizine in 14 children age 6 to 11 years with body weight ranging between 20 and 40 kg show that C_{max} and AUC values are about 2-fold greater than that reported in healthy adult subjects in a cross-study comparison. The mean C_{max} was 450 ng/mL, occurring at a mean time of 1.2 hours, weight-normalized, total body clearance was 30% greater, and the elimination half-life 24% shorter in this pediatric population than in adults. Dedicated pharmacokinetic studies have not been conducted in pediatric patients younger than 6 years of age. A retrospective population pharmacokinetic analysis was conducted in 323 subjects (181 children 1 to 5 years of age, 18 children 6 to 11 years of age, and 124 adults 18 to 55 years of age) who received single or multiple doses of levocetirizine ranging from 1.25 mg to 30 mg. Data generated from this analysis indicated that administration of 1.25 mg once daily to children 6 months to 5 years of age results in plasma concentrations similar to those of adults receiving 5 mg once daily.

    - *Geriatric Patients* – Limited pharmacokinetic data are available in elderly subjects. Following once daily repeat oral administration of 30 mg levocetirizine for 6 days in 9 elderly subjects (65–74 years of age), the total body clearance was approximately 33% lower compared to that in younger adults. The disposition of racemic cetirizine has been

shown to be dependent on renal function rather than on age. This finding would also be applicable for levocetirizine, as levocetirizine and cetirizine are both predominantly excreted in urine. Therefore, the XYZAL® dose should be adjusted in accordance with renal function in elderly patients.

- *Renal Impairment* - Levocetirizine exposure (AUC) exhibited 1.8-, 3.2-, 4.3-, and 5.7-fold increase in mild, moderate, severe, renal impaired, and end-stage renal disease patients, respectively, compared to healthy subjects. The corresponding increases of half-life estimates were 1.4-, 2.0-, 2.9-, and 4-fold, respectively.
  The total body clearance of levocetirizine after oral dosing was correlated to the creatinine clearance and was progressively reduced based on severity of renal impairment. Therefore, it is recommended to adjust the dose and dosing intervals of levocetirizine based on creatinine clearance in patients with mild, moderate, or severe renal impairment. In end-stage renal disease patients (CLCR < 10 mL/min) levocetirizine is contraindicated. The amount of levocetirizine removed during a standard 4-hour hemodialysis procedure was <10%. The dosage of XYZAL® should be reduced in patients with mild renal impairment. Both the dosage and frequency of administration should be reduced in patients with moderate or severe renal impairment. (b) (4) (b) (4)
  - Mild renal impairment (creatinine clearance [CL_{CR}] = 50-80 mL/min): a dose of 2.5 mg once daily
  - Moderate renal impairment (CL_{CR} = 30-50 mL/min): a dose of 2.5 mg once every other day
  - Severe renal impairment (CL_{CR} = 10-30 mL/min): a dose of 2.5 mg twice weekly (administered once every 3-4 days)
  - End-stage renal disease patients (CL_{CR} < 10 mL/min) or patients undergoing hemodialysis should not receive levocetirizine
  - (b) (4)

- *Hepatic Impairment* – XYZAL® has not been studied in patients with hepatic impairment. The non-renal clearance (indicative of hepatic contribution) was found to constitute about 28% of the total body clearance in healthy adult subjects after oral administration.
  As levocetirizine is mainly excreted unchanged by the kidney, it is unlikely that the clearance of levocetirizine is significantly decreased in patients with solely hepatic impairment.

Detailed Labeling Recommendations

XYZAL® tablet and oral solution are being proposed for a partial OTC switch. The relevant clinical pharmacology discussion is below -

1. In the XYZAL® Allergy 24HR and Children's XYZAL® Allergy 24HR Drug Facts, the recommendation for patients who have kidney disease is "Do not use". This is reasonable as it is known that apparent clearance of levocetirizine correlates with that of creatinine clearance, and is progressively reduced with the severity of renal impairment. Systemic exposure, represented by AUC, exhibited 1.8-, 3.2-, 4.3-, and 5.7-fold increase in mild, moderate, severe renal impaired and end-stage renal disease (ESRD) patients, respectively, compared to healthy subjects. There was a corresponding increase in half-life estimates of 1.4-, 2.0-, 2.9-, and 4-fold, respectively. Accordingly, the current label of prescribing XYZAL® recommends adjustment of the dose and

dosing intervals of levocetirizine based on creatinine clearance in patients aged 12 years and older with mild, moderate, or severe renal impairment (see "Patients with Renal Impairment" under special populations in the section above). In addition, levocetirizine is contraindicated in end-stage renal disease patients (CL_{CR} < 10 mL/min) and in children 6 months to 11 years of age with renal impairment.

2. The Drug Facts under "Directions" section splits the adult patient population into two categories of "adults and children 12- 64 years of age" and "adults 65 years of age and older" with different dosing recommendations for the two groups for both XYZAL® Allergy 24HR and Children's XYZAL® Allergy 24HR (see attached drug facts label in the attachment). This is reasonable as the current label of prescribing XYZAL® states the following in Section 12.3 for "Geriatric Patients" –

   "Limited pharmacokinetic data are available in elderly subjects. Following once daily repeat oral administration of 30 mg levocetirizine for 6 days in 9 elderly subjects (65–74 years of age), the total body clearance was approximately 33% lower compared to that in younger adults. The disposition of racemic cetirizine has been shown to be dependent on renal function rather than on age. This finding would also be applicable for levocetirizine, as levocetirizine and cetirizine are both predominantly excreted in urine. Therefore, the XYZAL dose should be adjusted in accordance with renal function in elderly patients."

   In addition, the current label of prescribing XYZAL® also states that "Some patients may be adequately controlled by 2.5 mg (1/2 tablet or 1 teaspoon [5 mL] oral solution) once daily in the evening" under Section 2 (Dosage and administration). Therefore, this reviewer concurs with the recommendation to have adults 65 years of age and older to "ask a doctor".

3. The current label of prescribing XYZAL® recommends dosing "once daily in the evening", whereas the XYZAL® Allergy 24HR and Children's XYZAL® Allergy 24HR Drug Facts recommends (b) (4). Please note prescription XYZAL® is recommended to be dosed once daily in the evening (QDPM) primarily because all of the confirmatory and supportive clinical trials dosed XYZAL® in the evening, and sedation-related effects of daytime use were not characterized in the application. The clinical reviewer has raised safety concerns (b) (4) dosing recommendation for the proposed OTC tablet and oral solution. Detailed discussion on this issue can be found in Clinical Safety Review by Dr. Brenda S. Gierhart, M.D.

4. Since the extent of metabolism of levocetirizine in humans is less than 14% of the dose, differences resulting from genetic polymorphism or concomitant intake of hepatic drug metabolizing enzyme inhibitors are expected to be negligible. In addition, levocetirizine, at concentrations well above C_{max} level attained after administration of therapeutic doses, is not an inhibitor of CYP enzymes 1A2, 2C9, 2C19, 2A1, 2D6, 2E1, and 3A4, and is also not an inducer of CYP enzymes 1A2, 2C9 and 3A4 and UGT1A1. Therefore, levocetirizine is unlikely to produce, or is subject to metabolic interactions with concomitant medications.[2]

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[2] Prescribing information, NDA 022064 (revised 11/2016)

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

/s/

BHAWANA SALUJA
12/22/2016

ANSHU MARATHE
12/22/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA Number	209089 and 208090 (related IND - 126506 & 126507)	**SDN**	1
Applicant	Sanofi-Aventis	**Submission Date**	03/31/2016
Generic Name	Levocetirizine dihydrochloride	**Brand Name**	XYZAL®
Drug Class	Oral H1-histamine receptor antagonist		
Indication	Temporarily relieves these symptoms due to hay fever or other respiratory allergies: • runny nose • sneezing • itchy, watery eyes • itching of the nose or throat		
Dosage Regimen	Adults and children 12 years of age and older: 5 mg qd Children 6 to 11 years of age: 2.5 mg qd Children 2-5 years of age: 1.25 mg qd		
Dosage Form	Immediate release scored tablet: 5 mg Solution: 2.5 mg/5 ml	**Route of Administration**	Oral
OCP Division	DCP II	**OND Division**	DPARP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Bhawana Saluja, Ph. D.	Anshu Marathe, Ph.D.	
Pharmacometrics			
Genomics			
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	05/30/2016	**74-Day Letter Date**	06/13/2016
Review Due Date	12/27/2016	**PDUFA Goal Date**	01/31/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☐ Yes ☑ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Bioanalytical methods			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			

Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies/Reports	**In Vitro**	0	**In Vivo**	0
Total Number of Studies/Reports to be Reviewed		0		0

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☐Yes ☐No ☑N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☑No ☐N/A	This is a 505(b)(2) submission, where the sponsor is seeking approval for a prescription to over-the-counter (Rx-to-OTC) switch [Listed Drug(s) – Xyzal® Tablets, NDA 022064 & Xyzal® Oral Solution, NDA 022157]
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☐Yes ☐No ☑N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑N/A	This is a 505(b)(2) submission.
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☐Yes ☐No ☑N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☐Yes ☐No ☑N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting	☐Yes ☐No ☑N/A	

studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☐Yes ☐No ☑N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☐Yes ☐No ☑N/A	
4. 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)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. 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?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☐Yes ☐No ☑N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

CLINICAL PHARMACOLOGY
FILING MEMO FOR NDA 209089 & 209090

Regulatory History
Sanofi-aventis submitted NDA 209089 and NDA 209090 under 505(b)(2) seeking approval for a partial Rx-to-OTC switch. The listed drug(s) (original approved Rx) NDA 022064 levocetirizine dihydrochloride tablet and NDA 022157 levocetirizine dihydrochloride oral solution are indicated for the relief of symptoms associated with seasonal and perennial allergic rhinitis, and for the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and pediatric patients 6 months of age and older.

The major change proposed in this OTC NDA is that the proposed OTC label will omit hives indication (i.e., chronic idiopathic urticaria), which will remain on Rx status.

The sponsor proposes debossed tablets in NDA 209089, while the listed drug is a printed tablet (See Figure 1 below).

Printed Tablet Logo	Debossed Tablet Logo
	

Figure 1. Comparison of the listed drug and proposed tablets

The sponsor states that this change needed minor modifications (b) (4), and indicated that this modification had no impact on quality of the product. The sponsor also submitted comparative multiple-time point dissolution profiles for whole printed tablets (listed drug) and whole debossed tablets.

No new clinical pharmacology studies were conducted in the two NDA submissions; however, the submission is cross-referenced to NDA 022064 (levocetirizine dihydrochloride tablet) and NDA 022157 (levocetirizine dihydrochloride oral solution). The clinical pharmacology review for the NDA submissions will focus on the adequacy of the drug facts label from a clinical pharmacology perspective.

These two NDAs are considered fileable from the clinical pharmacology perspective.

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

/s/

BHAWANA SALUJA
05/20/2016

ANSHU MARATHE
05/20/2016