CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209089Orig1s000
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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 9, 2017
From	Steven Osborne, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #, Supplement#	NDAs 209089 (tablet), 209090 (oral solution)
Applicant	UCB, Inc. (Union Chimique Belge, Agent: Sanofi US Services Inc.)
Date of Submission	March 31, 2016
PDUFA Goal Date	January 31, 2017
Proprietary Name (Proposed)/ Non-Proprietary Name	a) Xyzal® Allergy 24HR (levocetirizine dihydrochloride) b) Children's Xyzal Allergy 24HR
Dosage form(s) / Strength(s)	a) Tablet, 5 mg b) Oral solution, 2.5 mg/5 mL
Applicant Proposed Indication(s)/Population(s)	Allergic rhinitis (seasonal and perennial): • Tablet, 5 mg (Patients ages 6-64) • Oral solution 2.5 mg/5 mL (Patients ages 2-64)
Recommendation on Regulatory Action	**Approval**
Recommended Indication(s)/Population(s) (if applicable)	Allergic rhinitis (seasonal and perennial): • Patients ages 6-64: tablet, 5 mg • Patients ages 2-64: oral solution 2.5 mg/5 mL

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

ecommend **approval** of:

- levocetirizine tablets 5 mg (Xyzal Allergy 24HR) for over-the-counter (OTC) use for the treatment of seasonal and perennial allergic rhinitis in consumers ages 6-64 years
- levocetirizine oral solution 2.5 mg/5 ml (Children's Xyzal Allergy 24HR) for the treatment of seasonal and perennial allergic rhinitis in consumers ages 2-64 years

note:

- Both approval recommendations are for the indications and intended populations the sponsor has requested
- The proposed Drug Facts Label (DFL) directs children below age 2 to "not use" and adults ages 65 and older to ask a doctor.
- Overall, the benefit-risk is favorable for OTC use for these indications.
- There are 6 potential safety issues all of which are adequately addressed either by the sponsor, through the discipline reviews, or by a warning in the Drug Facts Label. See Section 8 of this review (Safety).
- These products will offer another option to consumers as an oral antihistamine.
- (b) (4) **the drug should be dosed "in the evening" to match the current Rx labeling.**

vocetirizine dihydrochloride (also referred to as levocetirizine, LCTZ, Xyzal, or ucb 28556 in this document) is an oral histamine H_1-receptor tagonist (antihistamine), the active R-enantiomer of the approved racemate, cetirizine, which itself is the main metabolite of hydroxyzine, a st generation antihistamine.

lergic rhinitis (AR) affects up to 30% of the adult population and has a significant negative impact on quality of life, adversely affecting notional well-being and social behavior, and often resulting in sleep disturbance, impaired performance, and loss of productivity. A key bect of the management of AR is avoidance; however, total avoidance is not practical, and pharmacotherapy has been the mainstay of atment. OTC pharmacological treatments include oral antihistamines (first and second generation), antihistamine/decongestant mbination products, oral and nasal decongestants, cromolyn nasal spray, antihistamine eye drops and intranasal corticosteroids. It is clear whether levocetirizine tablets and oral solution provide any benefit over the racemate, cetirizine, although they provide an ditional choice for consumers.

e effectiveness of levocetirizine for treatment of AR, including seasonal allergic rhinitis and perennial allergic rhinitis (SAR and PAR), was ll established in the development program for US approval of the prescription (Rx) products, Xyzal tablets 5 mg NDA 022064 on 5/25/07 and zal (levocetirizine) oral solution NDA 022157 on 1/28/08. In addition to submitting final study reports for 33 clinical pharmacology and nical studies prior to the US approvals of these two NDAs, the sponsor performed 2 more studies for US post approval commitments or quirements (PREA). While no new clinical pharmacology or clinical studies were conducted to support the current two NDAs under review

9089 and 209090, the sponsor submitted final study reports for an additional 21 clinical pharmacology and clinical studies for NDA 209089. e sponsor also submitted a draft DFL, a summary of clinical trial experience, and a postmarket safety update. The widespread use of other tihistamines in the OTC setting provides assurance that consumers can appropriately self-diagnose the conditions or symptoms for which this oduct will be indicated and use the product safely and effectively.

vocetirizine has a favorable safety profile based on many years of clinical use and postmarketing experience. There is over 8 years of perience with use of this drug product in the United States with an estimated 10.7 million patient-years exposure. LCTZ was first proved overseas in 2001 in Germany and Spain. As of 2016, levocetirizine tablets and oral solution have been registered in 60 countries tially as an Rx drug product, with levocetirizine tablets now available nonprescription in 12 countries, pharmacist only in 3 countries, d oral solution in Australia and the Ukraine (oral drops are available as Rx in 30 countries). To date, LCTZ tablets, drops, and oral lution have not been withdrawn in any country for safety reasons.

llectively, data from nonclinical, clinical pharmacology, and clinical safety studies, as well as postmarketing safety surveillance data monstrate that levocetirizine has low toxicity, is well-tolerated, and results in minimal medically significant systemic effects when ministered at recommended doses. Levocetirizine has few significant drug-drug interactions. The most common side effects are nerally mild and reversible. Common adverse events in clinical trials and reports to postmarket databases include drug ineffective, igue, headache, nasopharyngitis, and somnolence. Serious events, including wheezing, bronchopneumonia, and febrile seizure were orted in clinical trials. In the sponsor's postmarket database, SAEs reported include suicide attempt, seizures, dyspnea, and somnolence, s of consciousness, angioedema, overdose, and anaphylaxis, all of which have been reported infrequently in adults.

e proposed OTC labeling is similar to approved labeling for Xyzal and includes information regarding potential drug interactions, itations of duration of use, and appropriate instructions regarding when to ask a doctor, and when to stop use. (b) (4)

In clinical trials, somnolence was n less commonly with nocturnal dosing. The Rx drug is currently labeled to take: "once daily in the evening". This reviewer ommends the proposed OTC Xyzal (tablet and oral solution) be dosed in the evening to match the current Rx label.

stmarket pharmacovigilance for any liver disorders may be warranted with OTC Xyzal given the occasional postmarket reports of liver-ated adverse events, including the 3 deaths (no causal link, see p. 16 of this review) and the disproportionate AEs (weak association) for er disorders from the sponsor's FAERS analysis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Allergic Rhinitis (AR) affects up to 30% of the adult population in the United States (Wallace DV et al, J Allergy Clin Immunol 2008; 112:S1-84) • AR is associated with sleep disturbance, impaired performance and productivity loss (Blaiss MS et al, Allergy Asthma Proc. 2007a; 28 (Supp 1): S4-10, and Meltzer EO, Clinical Therapeutics. 2007; 29 (7): 1428-1440) • Approximately 30% of patients with AR report that AR symptoms have caused them to miss work. Half (51%) reported that AR adversely affects their daily lives to a moderate extent (Blaiss MS, Allergy Asthma Proc. 2007b; 28 (2):145-52). • Two studies suggested that allergies are among the major contributors to the total cost of health-related absenteeism and contribute to decreased productivity (Lamb CE et al, Curr Med Res Opin, 2006; 22:1203-1210, and Burton WM et al, Occu Environ Med, 2001; 43:64-71).	There is a significant negative impact of Allergic Rhinitis (AR) on quality of life. Significant economic loss is associated with AR due to missed work, decreased productivity, and frequent doctor visits.
Current Treatment Options	• A key aspect of the management of AR is avoidance; however, total avoidance is not practical. • OTC pharmacological treatments for AR include oral antihistamines, antihistamine/decongestant combination products, oral and nasal decongestants, cromolyn nasal spray, antihistamine eye drops, and intranasal corticosteroids.	Pharmacotherapy has been the mainstay of treatment for SAR and PAR. The high prevalence and chronic nature of this condition, and the fact that most sufferers self-treat (Malone 1997, Conner 2002) highlight the importance of OTC allergy treatments with established efficacy and safety.
Benefit	• The efficacy and safety of levocetirizine for the treatment of nasal and ocular symptoms associated with AR has been established in the original NDA. The clinical studies supporting the efficacy and safety were reviewed for approval of prescription Xyzal. No new clinical data were submitted with this application. • There is over 8 years of experience with use of levocetirizine in the United States with an estimated 10.6 million patient-years exposure. For a benefit assessment in this application, the sponsor submitted a draft DFL a Label Comprehension Study, and an Integrated Summary of Effectiveness.	Overall, the effectiveness of levocetirizine for treatment of AR was well established for the approval of the Rx product, Xyzal. The consumer is well-versed in the use of oral antihistamines in the OTC setting. Consumers can appropriately self-diagnose AR and use the product safely and effectively. In addition, levocetirizine provides an additional choice for consumers.

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