

**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#	NDA#s 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): <ul style="list-style-type: none"> • 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): <ul style="list-style-type: none"> • 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

I recommend **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

Of 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.**

Levocetirizine dihydrochloride (also referred to as levocetirizine, LCTZ, Xyzal, or ucb 28556 in this document) is an oral histamine H₁-receptor antagonist (antihistamine), the active R-enantiomer of the approved racemate, cetirizine, which itself is the main metabolite of hydroxyzine, a first generation antihistamine.

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

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

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

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

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

The proposed OTC labeling is similar to approved labeling for Xyzal and includes information regarding potential drug interactions, limitations 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 seen less commonly with nocturnal dosing. The Rx drug is currently labeled to take: "once daily in the evening". This reviewer recommends the proposed OTC Xyzal (tablet and oral solution) be dosed in the evening to match the current Rx label.

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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><u>Analysis of Condition</u></p>	<ul style="list-style-type: none"> 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). 	<p>There is a significant negative impact of Allergic Rhinitis (AR) on quality of life.</p> <p>Significant economic loss is associated with AR due to missed work, decreased productivity, and frequent doctor visits.</p>
<p><u>Current Treatment Options</u></p>	<ul style="list-style-type: none"> 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. 	<p>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.</p>
<p><u>Benefit</u></p>	<ul style="list-style-type: none"> 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. 	<p>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.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><u>Risk</u></p>	<ul style="list-style-type: none"> For a risk assessment in this application, the sponsor submitted an Integrated Summary of Safety (ISS), and Postmarket safety data. Collectively, data from nonclinical, clinical pharmacology, and clinical safety studies, as well as postmarketing safety surveillance data demonstrate that levocetirizine has low toxicity, is well-tolerated, and results in minimal medically significant systemic effects when administered at recommended doses. Levocetirizine has few significant drug-drug interactions. The most common side effects are generally mild and reversible, including somnolence, fatigue, and asthenia. Serious adverse events, including wheezing, pneumonia, seizures, suicide attempt, and anaphylactic shock have been reported infrequently in adults, with no deaths in clinical trials. In the postmarket setting, 32 deaths have been reported, including cardiac arrest and liver failure, although there is no certain link between levocetirizine use and the events. Postmarket AEs of drug ineffective, asthenia, fatigue and somnolence, are the most common AEs, likely-related to levocetirizine use (see Clinical, Section 7 of this review and Dr. Gierhart’s review). 	<p>Levocetirizine has a favorable safety profile based on 8 years of clinical use and postmarketing experience in the United States and 15 years worldwide.</p> <p>The potential for somnolence, fatigue, and asthenia were seen more often with morning administration in clinical trials.</p> <p>Serious adverse events are uncommon with labeled use. Deaths with cardiac arrest or liver toxicity were confounded by preexisting disease and multiple drugs, making a causal link with levocetirizine use impossible.</p>
<p><u>Risk Management</u></p>	<ul style="list-style-type: none"> The proposed OTC labeling has the essential warnings translated from the prescription label from Xyzal . Proposed OTC labeling includes information regarding potential drug interactions and instructions regarding when to ask a doctor, and when to stop use. Of note, the sponsor has proposed OTC labeling stratifying adults into two categories: “up to age 64” and “65 years and older” with different dosing recommendations for the two groups. However, there is no such differentiation in the Rx Xyzal labeling (i.e., the Rx Xyzal labeling recommending 5 mg once daily in the evening for “adults and children 12 years of age and older”). Proposed OTC labeling for the oral solution directs to ask a doctor for (b) (4); whereas Rx labeling provides dosing instructions for children down to 6 months of age. 	<p>The information provided in proposed OTC labeling will mitigate the risks of serious adverse events. <i>Specifically, the proposed recommendations to ask a doctor for adults ages 65 and older for the tablets and oral solution and to ask a doctor</i> (b) (4) (u) (4) (b) (4) will help to minimize risks in these age groups.</p>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none">• See Section 2.1, pages 12-13 of Dr. Gierhart’s clinical review.	

2. Background

UCB, Inc. (Agent: Sanofi US Services Inc.) submitted a supplemental 505 b(1) NDA seeking over-the-counter (OTC) marketing approval for its levocetirizine dihydrochloride 5 mg tablet and 2.5 mg/5 ml oral solution, currently marketed as the prescription (Rx) products, named Xyzal. This product would be the fourth-in-class OTC second generation antihistamine, following loratadine (2002), cetirizine (2007), and fexofenadine (2011).

Prior use of levocetirizine as an Rx drug

The sponsor submitted sales data available from IMS Health for levocetirizine from January 1, 2006 through June 30, 2015 for 5 mg tablets and oral solution, and estimated that (b) (4) tablets and (b) (4) of oral solution and oral drops were distributed globally. These distributed amounts equate to approximately 10,726,521 patient-years of worldwide exposure to levocetirizine 5 mg tablets, and 491,351 patient-years of worldwide exposure to levocetirizine oral solution and oral drops.

Proposed OTC Indications and Dose

The proposed indications for levocetirizine are similar or identical to the claims of other OTC antihistamines, are consistent with the Prescribing Information of Rx Xyzal, and are expressed in the proposed OTC product labeling as follows:

- Temporarily relieves (b) (4) symptoms (b) (4) hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watery eyes, itching of the nose or throat

In the proposed Drug Facts Label (DFL) for the 5 mg tablet, adults and children age 12-64 years of age (b) (4)

For the oral solution, adults and children 12-64 years of age (b) (4)

Proposed OTC Name

On March 16, 2016, the FDA notified Sanofi US that the two proposed proprietary names Xyzal Allergy 24HR (5 mg tablet) and Children's Xyzal Allergy 24HR (oral solution 2.5 mg/5 ml) were both conditionally acceptable.

Presubmission Regulatory Activity

As noted in Dr. Gierhart's review, presubmission regulatory activity was conducted under the two pre-investigational new drug development programs (preINDs). On May 29, 2015, Sanofi US Services Inc. (Agent for UCB Inc., holder of the two Xyzal Rx NDAs 022064 and 022157) submitted a Type B preIND meeting request to both preINDs (126506 (Xyzal tablets and

126507 Xyzal solution) for a single preIND meeting to discuss a Rx to OTC switch for both Xyzal Rx NDAs. The meeting package was submitted on August 20, 2015 to both preINDs, the meeting was held on October 1, 2015 and the FDA meeting minutes were finalized on November 9, 2015. Some issues resolved during this meeting and listed in the FDA meeting minutes included:

- Sanofi US Services Inc. (Sanofi US) could provide one comprehensive Summary of Clinical Efficacy (SCE) in the tablet NDA to support the switch of both the levocetirizine tablet and the oral solution formulation.
- Sanofi US could provide one comprehensive Summary of Clinical Safety (SCS) and one Integrated Summary of Safety (ISS) located in the tablet NDA to support the switch of both levocetirizine tablets and oral solution to OTC status.
- Sanofi US would analyze postmarketing safety data and note adverse events most likely to occur with accidental or intentional overdose in the OTC population and adverse events most likely to occur with the labeled dose and duration in the OTC population.
- The cut-off date for data included in the sponsor's clinical study summary would be October 31, 2015.

In writing this review, I have used the following primary FDA reviews in Table 1 below:

Table 1: Primary Reviews

<i>Materials Reviewed</i>	<i>Name of Discipline Primary Reviewer</i>
DMEPA Human Factors Study Review	Grace P. Jones, PharmD, BCPS
DNDP Labeling Review	Karen Livornese, MSN
DNDP Medical Officer Review	Brenda Gierhart, M.D.
DNDP Pharmacology/Toxicology Review	Donald C. Thompson, Ph.D.
DNDP Social Science Review	Amanda Pike-McCruden, MAA
DPARP Medical Officer Review	Xu Wang, M.D.
Office of Biostatistics Review	Rongmei Zhang, Ph.D.
Office of Clinical Pharmacology Review	Bhawana Saluja, Ph.D.
OPQ CMC Review	Swapan De, Ph.D.
OPQ Division of Microbiology Review	Not needed for this application

CMC = Chemistry, Manufacturing and Controls

DMEPA = Division of Medication Error Prevention and Analysis

DNDP = Division of Nonprescription Drug Product

DPARP = Division of Pulmonary, Allergy, and Rheumatology Products

OPQ = Office of Pharmaceutical Quality

3. Product Quality

The Product Quality (Chemistry, Manufacturing, and Controls; CMC) Review was conducted by Dr. Swapan De, who recommended **approval**.

Dr. De notes that per the Original NDA 209089 (tablet 5 mg) cover letter, there were no changes, except as noted below, to the previously approved Chemistry, Manufacturing, and Controls (CMC)/Quality information, including tablet size and shape, drug substance and drug

product specifications, drug substance and drug product manufacturers, container closure systems, and expiration dates associated with this Rx-to-OTC switch. NDA 209089 does include the following CMC changes:

- inclusion of a debossed tablet (with updated appearance specification)
- new packaging configurations for HDPE bottles
- addition of a peel-push aluminum lidding (b) (4) (b) (4) to the blister packages
- addition of new packaging sites

Per the Original NDA 209090 (oral solution 2.5 mg/5ml) cover letter, there were no changes to previously approved CMC/Quality information, including drug substance and drug product specifications, drug substance and drug product manufacturers and packagers, container closure systems, and expiration dates associated with this Rx-to-OTC switch. However, NDA 209090 includes a dosing cup administration device.

See the Chemistry review for additional details.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology / Toxicology review was conducted by Dr. Donald C. Thompson who recommended **approval**.

Dr. Thompson determined that no new nonclinical pharmacology or toxicology data were submitted for this application. Rather, the Sponsor cross referenced nonclinical data submitted under its own NDA 022064 for the prescription oral tablet levocetirizine dihydrochloride 5 mg drug product. These same data had previously been referenced by the Sponsor in support of NDA 022157 (levocetirizine oral solution).

Dr. Thompson noted that Dr. Lawrence Sancilio from DPARP-PharmTox conducted the original PharmTox review for NDA 022064 and determined that:

- “Levocetirizine is the R-enantiomer of cetirizine, a marketed H1 receptor antagonist. In view of this, the long term toxicity, fertility and early developmental and prenatal postnatal developmental toxicity studies with cetirizine represent the toxicity profile of levocetirizine with supplemental bridging toxicity, and embryofetal developmental studies of levocetirizine.
- In chronic oral toxicity studies in mice and rats with cetirizine, the liver was the target organ. The liver changes were enzyme induction and fat deposition. In Beagle dogs, the targeted organ was the gastrointestinal system. The major clinical sign was emesis. In a dietary carcinogenicity study in rats, cetirizine was not tumorigenic, but the livers showed hypertrophy, vacuolation and fat deposition. In a dietary carcinogenicity study, male mice showed hepatic hypertrophy and benign liver tumors, the latter was due to enzyme induction. In embryofetal development studies in mice, rats and rabbits, cetirizine was not teratogenic although increased skeletal anomalies/variants were observed in rabbits.

- Levocetirizine was not mutagenic in the Reverse Bacterial Mutation Assay and not genotoxic in the Mouse Lymphoma, Human Lymphocyte Chromosomal Aberration and Micronucleus Assays. In a bridging Embryofetal Developmental study in rats and rabbits with levocetirizine and cetirizine, both compounds were not teratogenic although cetirizine did increase skeletal anomalies/variants in rabbits.

Dr. Thompson concluded that Dr. Sancilio's review "...confirms that all required toxicological endpoints have been sufficiently and adequately addressed for levocetirizine and that the data do not identify adverse effects that would raise safety concerns in the OTC environment. Thus, it is concluded that the current applications proposing a switch from prescription to nonprescription status for levocetirizine dihydrochloride oral tablets and solution may be considered approvable from a nonclinical perspective"

5. Clinical Pharmacology

The Clinical Pharmacology review was conducted by Dr. Bhawana Saluja, who recommended **approval**.

No new clinical pharmacology data or information was submitted in NDAs 209089 and 209090. No new biopharmaceutical or clinical pharmacology studies were conducted in support of the switch from Rx to OTC status. The sponsor provided a clinical pharmacology summary, including cross-references to information previously submitted in the two Rx NDAs 022064 and 022157, in Modules 2.7.1 "Summary of Biopharmaceutic Studies and Associated Analytical Methods (Allergic Rhinitis)" and 2.7.2 "Summary of Clinical Pharmacology Studies (Allergic Rhinitis)" of NDAs 209089 and 209090.

Dr. Saluja noted no significant clinical pharmacology issues except for the potential for reduced renal excretion in patients with renal impairment, ranging from a doubling in plasma levels for mild renal impairment to a 6-fold increase in end stage renal disease. However, Dr. Saluja stated that the proposed DFL warning: **do not use** in consumers with kidney disease covered the potential for reduced excretion with renal impairment and no further warning is needed.

For the purpose of analyzing somnolence TEAEs from Phase 1 and 2 studies, Dr. Gierhart also provided a list of the 31 Clinical Pharmacology studies summarized in Modules 2.7.1 and 2.7.2 and/or listed in the "Tabular listing of all clinical studies" located in Module 2.7.6

6. Clinical Microbiology

A Microbiology Review was not needed for this application.

7. Clinical Efficacy

Xu Wang, MD from the Division of Pulmonary Allergy, and Rheumatology Products (DPARP) reviewed the efficacy of the two Rx-to-OTC switch NDAs and recommended **approval**.

In his review, Dr. Wang noted that no new clinical trial data were submitted with this application and the efficacy of LCTZ was previously established in the original NDAs and is described in Xyzal prescription labeling as follows:

- Seasonal Allergic Rhinitis (SAR): Xyzal is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 2 years of age and older
- Perennial Allergic Rhinitis (PAR): Xyzal is indicated for the relief of symptoms associated with perennial allergic rhinitis in adults and children 6 months of age and older
- Chronic Idiopathic Urticaria (CIU): Xyzal is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) in adults and children 6 months of age and older (the CIU indication will remain Rx)

CDTL Comment

For OTC, the sponsor proposes use in children down to age 2 rather than down to age 6 months. Below age 2, it is appropriate to have a physician diagnose PAR and oversee use of LCTZ. For a comparator, loratadine is also indicated down to age 2.

Dr. Wang noted that 12 clinical studies supported the original NDA, of which 6 are efficacy and safety studies in adult and adolescent patients with SAR and PAR, 2 are efficacy and safety studies in pediatric patients 6 to 12 years of age with SAR and PAR, 2 are environmental exposure unit studies, and 2 are long term safety studies (shown in the Table 2 below from Dr. Xu's review).

Dr. Wang noted the sponsor's studies supported efficacy in adults and adolescents 12 years of age and older and, separately through 2 pediatric studies, efficacy in children 6 to less than 12 years of age. Efficacy for pediatric patients under 6 years of age was extrapolated from the adult and adolescent data.

Table 2. Efficacy studies of levocetirizine that supported original Rx approval

Study /Population	Design/objective LCTZ dose	Age range (years)	Treatment Duration	Number Exposed to study treatment	Number of Males/Females
Allergic Rhinitis Studies – Adults and Adolescents 12 years of age and older					
A217/SAR	Dose ranging 2.5, 5, 10 mg	17-72	2 weeks	470	235/235
A219/PAR	Dose-ranging 2.5, 5, 10 mg	12-66	4 weeks	421	205/216
*A222/SAR	Efficacy 5 mg	12-66	1 week	797	398/399
A265/PAR	Dose ranging 2.5, 5, 10 mg	12-74	2 weeks	519	206/313
A266/PAR	Efficacy 5 mg	12-71	6 weeks	294	126/168
A268/SAR	Efficacy 5 mg	12-71	2 weeks	236	89/147
Allergic Rhinitis Studies – Pediatric Patients 6 to 12 years of age					
A303/SAR	Efficacy 5 mg	6 -12	6 weeks	177	117/60
A304/PAR	Efficacy 5 mg	6-12	4 weeks	306	186/120
Long term Safety studies Adults and adolescents 12 years of age and older					
A264/PAR		18-70	6 months	551	241/310
**A306/SAR		12-68	16 weeks	459	203/256
Environmental Exposure Unit studies					
A379/SAR		16-69	Single dose	570	233/337
A412/SAR		16 -71	Single dose	551	239/312
*Study A222 is only used for the safety database because the study duration is too short for confirmatory efficacy. This study included a cetirizine arm (n = 318), placebo (n =160) and LCTZ 5 mg (n = 319). Of 319 patients on LCTZ there were 168 males and 151 females.					
** In Study A306 one study arm had 153 patients treated for the first 8 weeks with placebo followed by treatment with LCTZ 5mg for the last 8 weeks. Therefore, these 153 patients are excluded from the safety analysis.					

Table 2 above is taken from Dr. Xu's review.

For adults and adolescents 12 years of age and older:

Study A217 was conducted in patients with SAR and the other two studies (A265 and A219) were conducted in patients with PAR. The primary efficacy variables were the change from baseline in the average of the reflective total symptom score (rT4SS) over the first week and over the entire treatment period. All three studies A217, A219, and A265, evaluated three doses of LCTZ 2.5, 5, and 10 mg compared to placebo for the treatment of the symptoms of SAR (study A217) and PAR (studies A219 and A265).

Two confirmatory efficacy studies were conducted. The primary efficacy variables were the change from baseline in the average of the reflective total symptom (4) score (rT4SS) and reflective total symptom (3) score (rT3SS). In study A268, patients who had a history of SAR for at least 2 years and a positive allergen skin test to grass or weed pollen were randomized to LCTZ 5 mg or placebo for 2 weeks. Patients in study A266 had a history of PAR to house dust

mites for at least 2 years, and were randomized to LCTZ 5 mg or placebo for 6 weeks. Study A268 also showed that LCTZ 5 mg was efficacious at the end of 24-hour dosing interval in the treatment of SAR.

CDTL Comment

1. *Study A268 validates one of the sponsor's claims of 24-hour relief of symptoms of SAR.*

For children 6 to less than 12 years of age

The clinical program of LCTZ included 2 pediatric studies in children 6 to <12 years of age.

Study A303 was “A double-blind, placebo-controlled, randomized, multicenter Phase 4 trial: evaluation of the efficacy and safety, for children from 6 years to 12 years old, suffering from SAR, of LCTZ 5 mg tablets, administered orally once daily in the evening for 6 weeks.” The data summarized in Table 4 below showed that LCTZ 5 mg was statistically superior to placebo in relieving the symptoms of SAR in children 6 to 12 years of age.

Study A304 was “A double-blind, placebo-controlled randomized multicenter Phase 3 trial: Evaluation of the efficacy and safety, on 6 to 12 year old children suffering from PAR due to house dust mites, of LCTZ 5 mg tablets, administered orally once daily in the evening for four weeks.” The study was conducted in South Africa. A total of 306 subjects, male or female, were randomized to receive LCTZ 5 mg or placebo daily for 4 weeks. This study showed that LCTZ 5 mg was statistically superior to placebo in relieving the symptoms of PAR caused by house dust mites in children 6 to 12 years of age.

Clinical pharmacology studies showed that a single dose of 5 mg LCTZ in children age 6 to <12 years of age resulted in C_{max} and AUC values about 2-fold greater than that reported in healthy adult subjects. Based on pharmacokinetic measures it is expected that 2.5 mg in patients 6 to <12 years would provide exposure comparable to 5 mg in patients less than 12 years of age and older. Therefore, the dosing approved for ages 6 to <12 years was 2.5 mg rather than the 5 mg dose that was studied.

For children less than 6 years of age

There were no efficacy studies in children less than 6 years of age. Efficacy for pediatric patients under 6 years of age was extrapolated from the adult and adolescent data as the indicated conditions (SAR, PAR) share the same pathophysiology and behave similarly from a clinical perspective in both children and adults.

LCTZ dosing of 1.25 mg was approved for allergic rhinitis in children 2 to < 6 years of age because pharmacology studies showed that administration of 1.25 mg once daily to children 6 months to 5 years of age resulted in plasma concentrations similar to those of adults receiving 5 mg once daily

CDTL Comments

1. *Dr. Wang's review focused on the 12 studies in Table 2 above and how these studies supported efficacy in SAR and PAR, which are the proposed OTC indications. Dr. Wang*

commented on the specific efficacy endpoints in these studies and these details can be found in his review.

2. Dr. Gierhart discusses 31 clinical pharmacology studies and another 31 studies that the sponsor completed involving levocetirizine for other purposes or in in foreign countries . This explains the difference between the 12 studies discussed by Dr. Wang for efficacy and the remaining 49 studies Dr. Gierhart mentions in her safety review.

8. Safety

This safety information is taken from Dr. Gierhart’s NDA Rx-to-OTC switch review, which includes safety data from all 62 of the studies in the sponsor’s Summary of Clinical Safety (SCS), which are noted in Table 3 below, as well as data from the postmarket setting and the literature.

This section summarizes:

- Listing and categorization of sponsor’s 62 studies
- deaths in clinical trials or postmarket
- common adverse events
- potential safety issues for drugs in the same class
- focus on somnolence
- postmarket experience

62 studies

The 62 studies, collated in Table 3 below, were conducted by UCB with levocetirizine formulations in the range from 1.25 mg/day to 30 mg/day. *Of note, the sponsor’s SCS is essentially identical for both NDAs, the tablet (NDA 209089) and oral solution (NDA209090).*

Table 3: Categorization of study groups for 62 studies

Study group	Study numbers
Clinical pharmacology studies (n=31)	
Clinical pharmacology (n=29)	A184, A190, A221, A232, A233, A238, A245, A246, A252, A254, A256, A00260, A00263, A00280, A00297, A00305, A00318, A00324, A00331, A00340a b, A00351, A00373, A00379, A00380, A00412b, A00414b, A00415b, A00419b, A00428b
Studies in special populations (n=2)	A230, A234
Phase 2-3-4 studies in adults 12 years old and older (n=22)	
Short-term studies (≤ 12 weeks; n=19)	A217, A219, A222, A00265, A00266, A00268, A00269, A00270, A00299, A00333, A00334, A00348, A00349, A00391b, A00394b, A00401b A00410a b, A00430b, A00431b,

Study group	Study numbers
Long-term studies (4-18 months; n=3)	A00264, A00306, A00392b
Phase 2-3-4 studies in children 6 months to 12 years old (n=8)	
Short-term studies (≤ 12 weeks; n=6)	A00303, A00304, A00315, A00385, A00423b, A00426b
Long-term studies (4-18 months; n=2)	A00309b, A00384b
Other studies (n=1)	
Non-interventional, retrospective data collection study in children 2 to 12 years of age	A00420 bc
Special groups (subset of studies listed above) (n=12)	
Dose ranging studies (n=4)	A217, A219, A00265, A00270
Special <u>Cetirizine</u> Comparison studies (n=8)	A184, A190, A221, A222, A00379, A00380, A00410a b, A00412b

Table 3 Source: Dr. Gierhart’s review, as are a,b, and c modifiers .

a Clinical databases unavailable, individual study summaries will be presented.

b Not in pooled safety database for original NDA 022064.

c Available data will be integrated; data summaries from CSR will be presented.

Deaths

Clinical Trials

In the 62 UCB-sponsored clinical studies, no deaths were reported in any levocetirizine-treated subjects.

Postmarket 32 reports

There were no deaths associated with levocetirizine reported in the National Poison Control Centers database from 2007-2015 or in the DAWN database during the study period of 2007-2011.

Separately, thirty two (32) fatal postmarketing cases¹ have been reported directly to the sponsor or discovered through Dr. Gierhart’s review in patients treated with LCTZ. Dr. Gierhart summarized the 32 deaths and then concluded: “two of the above 32 deaths are potentially concerning”.

Possible QT prolongation-related deaths

- A 39 year old healthy female from Oman taking levocetirizine 5 mg and Atarax (hydroxyzine) for urticaria (unknown length of time) who died from cardiac arrest after an unknown time of taking both drugs.

¹ The ISS submitted in Original NDA 209089 stated that 22 postmarketing death reports listed LCTZ. The 120 Day Safety Update Report submitted to NDA 209089 on 7/29/16 included two additional death reports that listed LCTZ [i.e., Case #2016006121 diabetic ketoacidotic hyperglycemic coma SAE was listed as cause of death of 86 year old male in France; Case # 2016005847 somnolence/sedation SAE in 79 year old man in Japan with existing renal impairment who received a higher than appropriate dose of LCTZ for someone with renal impairment (i.e., 5 mg once daily) and experienced renal failure that progressed to death]. FAERS and PharmaPendium searches conducted by Dr. Gierhart revealed eight additional postmarketing death reports that listed LCTZ. None of these eight additional reports were submitted by UCB.

- An 11 month old female taking levocetirizine 2.5 mg/5ml, amoxicillin, and procaterol (beta agonist, associated with QT prolongation) for an apparent upper respiratory infection who died 4 days later
- Regarding these 2 deaths, Dr. Gierhart noted:
 - both of these patients could have experienced QT prolongation and torsades de pointes
 - it is difficult to determine a cause of death for these two patients because of the limited amount of information that was provided in the submitted reports
 - in addition, the 39 year old female was concomitantly taking both Atarax (hydroxyzine hydrochloride) and LCTZ, with Atarax generally considered to be a more frequent cause of QT prolongation than LCTZ.

Possible liver-failure-related deaths

Three additional reports involving patients who experienced liver failure are confounded:

- 68 year old male in the US with a history of a liver transplant and cardiovascular disease experienced jaundice, liver toxicity and renal failure 2 days after starting levocetirizine 5 mg for a “bad cold”.
- 81 year old female in the US taking oral LCTZ 5 mg for 3 days erythema, xeroderma and pruritus developed a liver disorder after 2 days later. She was hospitalized for jaundice and malaise and developed ascites, hepatic atrophy and oliguria. A physician assessed that the patient developed a drug-induced hepatitis.
- 69 year old male in Austria took levocetirizine 5 mg for up to two weeks for eczema, then developed jaundice and died. He was also taking diclofenac. This was a 1-page report with minimal information.

CDTL Reviewer Comments

1. It is unclear what to make of postmarket reports of deaths wherein limited information is provided and a clear pattern has not emerged. Dr. Gierhart noted 2 deaths that could be related to a prolonged QT effect, but information was limited. I agree with Dr. Gierhart’s assessment that a causal relationship between these 2 deaths and LCTZ use is uncertain.

2. Separately, this CDTL reviewer is alerted by 3 reports of liver-related deaths. However, with no reports of serious liver injury in clinical trials, no conclusions can be made from the postmarket deaths of the 68, 69, and 81 year-old patients.

Common Adverse Events from Clinical Trials

From Dr. Gierhart’s review:

- The most common TEAEs in the combined LCTZ group dosed with 2.5 mg, 5 mg or 10 mg, with an incidence of $\geq 2\%$, in the adult (subjects 12 years and older) double-blind, placebo-controlled, confirmatory and dose-ranging short-term Phase 2 to 4 studies were: headache (9.4%), somnolence (5.3%), fatigue (3.1%), and nasopharyngitis (2.5%). When the combined LCTZ group in the adult (subjects 12

years and older) double-blind, placebo-controlled, confirmatory and dose-ranging Phase 2 to 4 studies was compared with the placebo group, i.e., incidence $\geq 2\%$ and difference $\geq 1\%$ versus placebo, the most common TEAEs were somnolence (5.3% versus 1.6%) and fatigue (3.1% versus 1.4%).

- Using the same criteria in the long-term Phase 2 to 4 studies in adult (subjects 12 years and older), the most common TEAEs reported in $\geq 2\%$ of subjects in the LCTZ group were: headache (16.9%), nasopharyngitis (8.5%), oropharyngeal pain (7.7%), fatigue (5.8%), somnolence (4.7%), pharyngitis (4.5%), back pain (3.2%), sinusitis (2.9%), bronchitis and cough (2.7% each), dry mouth (2.6%), gastroenteritis and pyrexia (2.4% each), and influenza, rhinitis, and abdominal pain (2.3% each). The proportion of subjects who reported the following TEAEs was higher in the levocetirizine group compared with the placebo group (i.e., incidence $\geq 2\%$ in the levocetirizine group and difference $\geq 1\%$ versus placebo): somnolence (4.7% versus 1.7%), fatigue (5.8% versus 4.8%), and dry mouth (2.6% versus 1.4%).
- In Phase 2 to 4 short-term studies in children, the most common TEAEs that were reported in $\geq 2\%$ of subjects in the combined LCTZ group were: headache (5.8%), upper respiratory tract infection (5.6%), pyrexia (5.4%), cough (3.4%), diarrhea (3.4%), bronchitis (2.7%), epistaxis (2.5%), somnolence (2.2%), vomiting (2.2%), and influenza (2.0%). The proportion of subjects who reported the following TEAEs was higher in the combined levocetirizine group compared with the placebo group (i.e., incidence $\geq 2\%$ in the combined levocetirizine group and difference $\geq 1\%$ versus placebo): pyrexia (5.4% versus 3.1%), diarrhea (3.4% versus 2.2%), bronchitis (2.7% versus 1.5%), epistaxis (2.5% versus 0.6%), and somnolence (2.2% versus 1.2%).
- Using the same criteria in the long-term Phase 2 to 4 studies in children, a total of 48 different TEAEs were reported in $\geq 2\%$ of subjects in the LCTZ group and the following were TEAEs that occurred with at least a 2% incidence rate in the LCTZ group and at least 1% higher incidence than the placebo group included the following: upper respiratory tract infection (51.2% versus 45.7%), pyrexia (34.8% versus 28.1%), nasopharyngitis (32.8% versus 30.1%), rhinitis (30.9% versus 25.2%), gastroenteritis (24.6% versus 20.9%), conjunctivitis (20.3% versus 16.6%), diarrhea (19.9% versus 15.9%), ear infection (16.4% versus 14.2%), rhinitis allergic (10.5% versus 7.9%), influenza (9.8% versus 7.3%), teething (8.6% versus 7.0%), laryngitis (8.2% versus 4.6%), constipation (5.9% versus 3.0%), enteritis (4.3% versus 2.0%), viral upper respiratory infection (3.9% versus 2.6%), rash (3.9% versus 2.3%), bronchopneumonia (3.1% versus 1.3%), sinusitis (2.7% versus 1.3%), head injury (2.7% versus 1.3%), arthropod sting (2.7% versus 1.0%), scarlet fever (2.3% versus 1.0%), tracheitis (2.3% versus 1.0%), and dyspepsia (2.3% versus 1.0%). This list contains many TEAEs that are difficult to link with LCTZ exposure, e.g., upper respiratory infection, pyrexia, diarrhea.

Potential Safety Issues for Drugs in the Class

Dr. Gierhart also reviewed six potential safety issues for related second generation antihistamines that could be applicable to levocetirizine. These safety issues include:

- QT prolongation
- somnolence/sedation
- urinary retention
- hypersensitivity reactions (ex. urticaria, fixed drug eruptions and rash)
- drug-induced acute generalized exanthematous pustulosis (AGEP)
- hepatotoxicity

QT Prolongation

There are three cases of asymptomatic QT prolongation associated with levocetirizine in FAERS², three cases of “torsadogenic signal” associated with levocetirizine in the German spontaneous reporting system³ and no reports of TdP or symptomatic QT prolongation with levocetirizine as the single suspect drug⁴.

There are three cases of asymptomatic QT prolongation associated with levocetirizine in FAERS, three cases of “torsadogenic signal” associated with levocetirizine in the German spontaneous reporting system and no reports of TdP or symptomatic QT prolongation with levocetirizine as the single suspect drug. In addition, to support approval of Rx NDA 022064 (Xyzal 5 mg oral tablet),

UCB conducted a single-dose QT study in healthy subjects using 5 mg and 30 mg levocetirizine with moxifloxacin as a positive control. The study showed QT prolongation of 3 msec with 5 mg dose, (-)1 msec with 30 mg dose, and 14 msec with moxifloxacin. This study was considered to be negative for levocetirizine, but the study is of limited value because a single dose of levocetirizine was used. The effects of levocetirizine may not be at steady state for single dose. However, levocetirizine steady state was achieved in UCB’s Study A238 only 2 days after the start of the once a day repeated administration, with only a slight increase in concentration from Day 1 to Day 2.

A QT/QTc study using a single dose of 30 mg of levocetirizine did not demonstrate an effect on the QTc interval. While a single dose of levocetirizine had no effect, the effects of levocetirizine may not be at steady state following single dose. The effect of levocetirizine on the QTc interval following multiple dose administration is unknown. Levocetirizine is not expected to have QT/QTc effects because of the results of QTc studies with the racemate, cetirizine, and the marketing history of cetirizine without significant reports of QT prolongation. Specifically, no QT prolongation was noted in four clinical studies of healthy males taking up to 6 times the recommended dose of cetirizine^{5,6}, and cetirizine had lower

² Poluzzi E et al. Pro-arrhythmic potential of oral antihistamines (H1): combining adverse event reports with drug utilization data across Europe. *PLoS ONE*. 2015 Mar 18; 10(3): e0119551. doi: 10.1371/journal.pone.0119551.

³ Raschi E et al. The contribution of national spontaneous reporting systems to detect signals of torsadogenicity: issues emerging from the ARITMO Project. *Drug Saf*. 2016 Jan; 39 (1): 59-68.

⁴ Per [No authors listed] Cetirizine and loratadine: minimal risk of QT prolongation. *Prescribe Int*. 2010 Feb; 19 (105): 26-8, “Two cases of QT prolongation with cetirizine have been published, one of which involved overdose and renal failure. The reports are too vague to conclude that cetirizine was implicated. We found no reports of QT prolongation attributed to levocetirizine.”

⁵ Per the latest approved Zyrtec (cetirizine hydrochloride) tablets and syrup Rx labeling (2003):

“In four clinical studies in healthy adult males, no clinically significant mean increases in QTc were observed in ZYRTEC treated subjects. In the first study, a placebo-controlled crossover trial, ZYRTEC was given at doses up to 60 mg per day, 6 times the maximum clinical dose, for 1 week, and no significant mean QTc

reporting rates for cardiac adverse drug reactions reports from 1986 to 1996 in the WHO ADR database than four other second-generation antihistamines⁷. When seven antihistamines were compared in 2004, cetirizine, desloratadine and levocetirizine had the lowest risk of triggering severe ventricular arrhythmias.⁸ However, when a search of the FDA Adverse Event Reporting System (FAERS) and drug utilization data from 13 European countries was conducted, cetirizine was one of five antihistamines with an alert signal for arrhythmogenic potential.^{9,10}

Dr. Gierhart noted that : “Analyses of ECG data revealed no clinically significant mean increases in QTc in *single-dose clinical studies at doses 6 times higher than the recommended upper dose and including elderly subjects at increased risk*. There was no effect on the QT interval and no individual subject had clinically significant changes, regardless of correction factor applied in analyzing the data. These conclusions are supported by analyses of the ECGs measured at controlled time points in a large double-blind, placebo-controlled efficacy study”.

Dr. Gierhart concluded that “The currently available postmarketing safety data for levocetirizine supports the findings of the dedicated QT study conducted by UCB for levocetirizine, i.e., it does not appear that levocetirizine significantly induces the cardiac arrhythmia Torsades de Pointes (TdP) secondary to QT prolongation”.

CDTL Comment

I have reviewed the data Dr. Gierhart presented and agree with her conclusion that levocetirizine does not pose a risk of QT-related SAEs at labeled doses.

prolongation occurred. In the second study, a crossover trial, ZYRTEC 20 mg and erythromycin (500 mg every 8 hours) were given alone and in combination. There was no significant effect on QTc with the combination or with ZYRTEC alone. In the third trial, also a crossover study, ZYRTEC 20 mg and ketoconazole (400 mg per day) were given alone and in combination. ZYRTEC caused a mean increase in QTc of 9.1 msec from baseline after 10 days of therapy. Ketoconazole also increased QTc by 8.3 msec. The combination caused an increase of 17.4 msec, equal to the sum of the individual effects. Thus, there was no significant drug interaction on QTc with the combination of ZYRTEC and ketoconazole. In the fourth study, a placebo-controlled parallel trial, ZYRTEC 20 mg was given alone or in combination with azithromycin (500 mg as a single dose on the first day followed by 250 mg once daily). There was no significant increase in QTc with ZYRTEC 20 mg alone or in combination with azithromycin.”

⁶ Sale ME et al. The electrocardiographic effects of cetirizine in normal subjects. *Clin Pharmacol Ther.* 1994 Sept; 56 (3): 295-301.

⁷ Per Lindquist M, Edwards IR. Risks of non-sedating antihistamines. *Lancet.* 1997 May 3; 349 (9061): 1322, cetirizine had 59 ADR reports for cardiac rate and rhythm disorders in the WHO ADR database, of which 19 were selected disorders (i.e., arrhythmia, ventricular arrhythmia, cardiac arrest, ventricular fibrillation, QT prolongation, supraventricular tachycardia, and torsade de pointes) and two were cardiac or sudden deaths. In contrast, terfenadine had 864 ADR reports for cardiac rate and rhythm disorders in the WHO ADR database, of which 429 were selected disorders and 29 were cardiac or sudden deaths.

⁸ Lange B, Bachet C. Adverse reaction profiles of antihistamines and their clinical relevance. *Allergologie.* 2004; 27 (2): 49-71. [NOTE: In this review, the adverse reaction profiles of cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine and mizolastine were compared.]

⁹ Godman B et al. Pro-arrhythmic risk of oral antihistamines (H1): Combining adverse event reports data with drug utilization data across Europe. *Basic Clin Pharmacol Toxicol.* 2014 July; 115 Suppl 1: 83.

¹⁰ Poluzzi E et al. Pro-arrhythmic potential of oral antihistamines (H1): combining adverse event reports with drug utilization data across Europe. *PLoS ONE.* 2015 Mar 18; 10(3): e0119551.

Somnolence/Sedation

Cetirizine and Somnolence

Dr. Gierhart's review discusses somnolence/sedation with the racemate, cetirizine. This discussion is applicable to levocetirizine, since it is the active enantiomer of cetirizine. When compared to the second-generation H₁-antihistamines fexofenadine, loratadine and desloratadine, cetirizine is more sedating.¹¹ In adult, adolescent and pediatric patients aged 2-11 years, the incidence of somnolence with cetirizine was dose related and the sedative effect of cetirizine was greater than that of fexofenadine in some clinical trials and that of loratadine or fexofenadine in a postmarketing surveillance study.¹² In placebo-controlled studies in adults, the most common adverse experiences associated with cetirizine ≤10 mg/day were somnolence 14% (compared to 6% with placebo) and fatigue 6% (compared to 2% placebo).¹³ In clinical trials in adults, the most common adverse effects of levocetirizine were similar to those reported for cetirizine and included mild-to moderate somnolence (which was dose-related).¹⁴

Levocetirizine and Somnolence

In a small, three-way crossover study evaluating the cognitive and psychomotor functions of levocetirizine 5 mg, diphenhydramine 50 mg and placebo in 19 healthy male volunteers aged 20-39 years dosed once daily for 5 days in each period, no significant differences were noted between levocetirizine and placebo.¹⁵ In a small, five-way crossover study evaluating the cognitive and psychomotor functions of levocetirizine 5 mg, cetirizine 10 mg, loratadine 10 mg, promethazine 30 mg and placebo in 20 healthy male volunteers aged 18-50 years dosed once daily for 4 days in each period, no significant differences were noted between levocetirizine, cetirizine, loratadine and placebo.¹⁶

A randomized, double-blind trial (Study A246) in 48 healthy volunteers given a standardized on-the-road driving test 1.5 hours after taking levocetirizine 5 mg, diphenhydramine 50 mg or placebo found that diphenhydramine reduced driving ability while levocetirizine did not.¹⁷

Dr. Gierhart noted the following points re "sedation" TEAEs in clinical trials

- The sponsor considered **sedation** [preferred terms (PT) lethargy, neonatal oversedation, sedation, somnolence, somnolence neonatal, sopor, stupor and lower level term (LLT) narcosis to be Adverse Events of Special Interest (AESI).

¹¹ [No authors listed] Levocetirizine (Xyzal) for allergic rhinitis and urticaria. *Med Lett Drug Ther.* 2007 Dec; 3; 49 (1275): 97-9.

¹² Curran MP et al. Cetirizine: a review of its use in allergic disorders. *Drugs.* 2004; 64 (5): 523-61.

¹³ Ibid.

¹⁴ [No authors listed] Levocetirizine (Xyzal) for allergic rhinitis and urticaria. *Med Lett Drug Ther.* 2007 Dec; 3; 49 (1275): 97-9.

¹⁵ Gandon JM, Allain H. Lack of effect of single and repeated doses of levocetirizine, a new antihistamine drug, on cognitive and psychomotor functions in healthy volunteers. *Br. J Clin Pharmacol.* 2002 Jul; 54 (1); 51-8.

¹⁶ Hindmarch I et al. The acute and sub-chronic effects of levocetirizine, cetirizine, loratadine, promethazine and placebo on cognitive function, psychomotor performance, and weal and flare. *Curr Med Res Opin.* 2001; 17 (4): 241-55.

¹⁷ Verster JC et al. Driving ability after acute and sub-chronic administration of levocetirizine and diphenhydramine: a randomized, double-blind, placebo-controlled trial. *Psychopharmacology (Berl).* 2003 Aug; 169 (1); 84-90.

- 362 (5.4%) of the 6685 subjects exposed to levocetirizine reported at least one sedation-related TEAE, compared to 90 (2.3%) of the 3963 subjects exposed to placebo and 111 (4.0%) of the 2808 subjects exposed to an active comparator. The incidence of sedation-related TEAEs tended to increase with increasing dose of levocetirizine and sedation-related TEAEs was more frequently reported when levocetirizine was dosed in the morning, compared to evening/nighttime dosing.
- Of the 77 subjects in the levocetirizine group across all clinical studies who discontinued prematurely due to an adverse event, 21 of these subjects prematurely discontinued due to somnolence.

CDTL Comments

1. Dr. Gierhart wrote that the sponsor's cognitive function study A00260 and the driving information study A246 (cited above) do not fully address the concern of potential somnolence if levocetirizine is taken in the daytime. The driving information study A246 enrolled only 51 subjects; however, a total of 809 TEAEs were reported in this study, of which 326 were somnolence TEAEs (i.e., 69 somnolence TEAEs in 32 PBO subjects, **93 somnolence TEAEs in 36 LCTZ subjects** and 164 somnolence TEAEs in 46 DIP subjects).

2. This information about the sedating potential of levocetirizine seems confusing between results from clinical trials, literature assessments and postmarket adverse event reports.

Fatigue

Dr. Gierhart noted that, in all clinical studies, fatigue was reported by 3.4% (n=229) of the 6685 subjects in the combined levocetirizine group, compared to 1.9% (n=76) of the 3963 placebo subjects. Of the 77 subjects in the levocetirizine group across all clinical studies who discontinued prematurely due to an adverse event, 4 of these subjects prematurely discontinued due to fatigue.

Asthenia

Dr. Gierhart noted that, in the short-term clinical studies conducted in subjects ≥ 12 years of age, there were 45 asthenia AEs reported by the 3042 subjects in the levocetirizine treatment group compared to 12 asthenia AEs reported by the 1813 subjects in the placebo group. While the cumulative rate of asthenia in the levocetirizine group was greater than the placebo group in these short-term clinical studies at each time interval analyzed, the relative difference in the cumulate rates between the two treatments was small. The cumulative estimate of the probability of asthenia during the first 14 days of treatment reached 1.3% with levocetirizine as compared with 0.5% with placebo treatment. This cumulative risk increased to 2.1% and 1.1%, respectively, over 30 days of treatment. Of the 77 subjects in the levocetirizine group across all clinical studies who discontinued prematurely due to an adverse event, 4 of these subjects prematurely discontinued due to asthenia.

Sponsor's (b) (4) dosing for OTC Xyzal

The sponsor stated: “

(b) (4)

In support of this statement,

the sponsor compared the 935 subjects in their three studies A00401, A00391 and A00394 dosed with LCTZ 5 mg in the morning to the 1896 subjects in their eight studies A217, A219, A222, A00265, A00266, A00268, A00269 and A00270 dosed with LCTZ the evening (421 subjects dosed with LCTZ 2.5 mg; 1070 subjects dosed with LCTZ 5 mg; 414 subjects dosed with LCTZ 10 mg), with the conclusion that there was no significant difference in the incidence of the TEAE somnolence in these two groups.¹⁹ It should be noted that all of the subjects in placebo-controlled, double-blind clinical trials included in the pooled analysis of safety in the Rx oral tablet NDA 022064 were dosed with levocetirizine once daily in the evening or at bedtime²⁰; thus, the Rx labeling for once daily LCTZ tablet and solution instructs the patient to dose once daily in the evening.

CDTL Comment

Dr. Gierhart made the following points in her review, with which I agree. See Dr. Gierhart's Tables 10 and 11 from her review pp. 99-102 in Appendix 3 of this CDTL review

- Levocetirizine was associated with significant somnolence in the 62 clinical trials conducted by UCB; however, driving ability was not significantly affected in an on-the-road driving test conducted in 48 healthy volunteers approximately 1.5 hours after taking a single dose of LCTZ 5 mg. Due to the known occurrence of somnolence, this reviewer recommends that LCTZ continue to be dosed once daily in the evening (see Section 2.7.4 of her review.*
- The labeling for both Rx Xyzal drug products recommend that the dose be taken once daily in the evening because all of the placebo-controlled, double-blind clinical trials included in the pooled analysis of safety for the Rx oral tablet NDA 022064 dosed levocetirizine once daily in the evening. The extent to which sedation-related effects would be different if levocetirizine was used during the daytime was not characterized in the original NDAs; thus, the levocetirizine Dosing and Administration section of the current prescription label reflects dosing as it occurred in the pivotal clinical studies (i.e., once daily in the evening). Due to levocetirizine's rapid and extensive absorption, it is anticipated that dosing in the evening would result in the patient sleeping through this drug product's maximal plasma concentration (i.e., $t_{max} = 0.9$ hour).²¹ If a patient took levocetirizine upon arising in the morning, this drug product's maximal plasma concentration would likely be occurring when they were driving to work. ... This reviewer evaluated all 62 UCB clinical studies to determine which studies dosed only in the evening bedtime and only in the AM and concluded that significantly fewer somnolence/sedation, fatigue and asthenia TEAEs were reported when levocetirizine was dosed only in the evening/bedtime (i.e., when 3821 subjects*

¹⁸ Original NDA 209089 Section 2.7.4 on pg. 32 of 65.

¹⁹ Per the sponsor, 61 (5.7%) of 1070 subjects dosed with LCTZ 5 mg in the evening reported the TEAE somnolence, compared to 44 (4.7%) of the 935 subjects dosed with LCTZ 5 mg in the morning. See Original NDA 209089 Section 2.7.4 Summary of Clinical Safety on pg. 34 of 65.

²⁰ Per the sponsor; see Original NDA 209089 Section 2.7.4 Summary of Clinical Safety on pg. 32 of 65.

²¹ Ferrer M. Pharmacokinetics evaluation of levocetirizine. *Expert Opin Drug Metab Toxicol*. 2011 Aug; 7 (8): 1035-47.

were dosed with only-evening/bedtime LCTZ in 17 studies) compared to when it was dosed only in the morning (i.e., when 2496 subjects were dosed with only-morning LCTZ in 32 studies; see Table 10 in Section 7.5.2 of her review).

- *This reviewer was concerned that the above 11 studies selected by the sponsor (i.e., three studies with dosing in only in the morning and eight studies with dosing only in the evening) may not be representative of the sponsor's 52 studies that dosed LCTZ only in the morning (n=32 studies) or LCTZ only in the evening (n=17 studies). In addition, this reviewer was also concerned that approximately half of the subjects in the eight studies selected by the sponsor with dosing only in the evening were dosed with LCTZ 2.5 mg once daily or LCTZ 10 mg once daily, while all of the subjects in the three studies selected by the sponsor with dosing only in the morning were dosed with LCTZ 5 mg. It is well known that the frequency of the adverse event "somnolence" markedly increases when the once daily dosing of LCTZ is increased from 5 mg to 10 mg. To address these two concerns, this reviewer compared the frequency of somnolence (as well as the frequency of fatigue and asthenia) in the sponsor's 32 studies (in 2496 subjects) that only dosed levocetirizine in the morning compared to their 17 studies (in 3821 subjects) that only dosing levocetirizine in the evening (see Section 7.5.2 of this review). In this section is a comparison of the results for all morning-only dosed subjects versus all evening-only dosed subjects, as well as a comparison of subjects dosed with LCTZ 5 mg only in the morning versus subjects dosed with LCTZ 5 mg only in the evening.*

Urinary Retention

The Xyzal (levocetirizine) Rx label has a subsection entitled "Urinary Retention", which states:

"Urinary retention has been reported post-marketing with XYZAL. XYZAL should be used with caution in patients with predisposing factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as XYZAL may increase the risk of urinary retention. Discontinue XYZAL if urinary retention occurs."

Reviewer's comment: Per the Sponsor's "Section 2.7.4 Summary of Clinical Safety" (on pg. 43 of 65) submitted to NDA 209089 in SDN 2, only 2 of the 6685 subjects exposed to LCTZ at any dose in all studies pooled reported at least one TEAE "urinary retention" and both were for the adverse event "pollakiuria" (i.e., frequent small voids; daytime urinary frequency). Per the sponsor, the UCB LCTZ postmarketing safety based revealed eight serious cases of urinary retention with none of these cases having either a positive rechallenge or plausible time to onset. Three of these eight cases were confounded by predisposing medical conditions, i.e., prostatic hyperplasia and Parkinson's Disease in two elderly patients and by a concomitant medication (mequitazine, an antihistamine) in a 6-year old child.

CDTL Comment

Dr. Gierhart did not find a safety signal for urinary retention in the submission or the scientific literature. I agree.

Hypersensitivity reactions (ex. urticaria, fixed drug eruptions and rash)

Dr. Gierhart noted that reported reactions to antihistamines include urticaria/angioedema, fixed drug eruption (FDE), contact dermatitis and anaphylaxis.²² And, “almost all antihistamines have been reported as causing reactions, with cetirizine being the most common oral drug product followed by its parent drug, hydroxyzine.²³ Although hypersensitivity to antihistamines appears to be very rare, a causal relationship is often difficult to recognize because the reaction may be similar to the disease being treated.²⁴

Urticaria: at least 35 reports (with 18 associated with use of cetirizine, hydroxyzine or levocetirizine) occurring in 19 patients treated with antihistamines are in the medical literature”.

Drug-induced acute generalized exanthematous pustulosis (AGEP)

On May 18, 2016, the FDA Division of Pharmacovigilance (DVP) finalized a review evaluating the FDA Adverse Events Reporting System (FAERS) reports and the medical literature for an association between hydroxyzine, cetirizine, levocetirizine and AGEP. Based on the data analyzed in this review, DPV identified an association between hydroxyzine and cetirizine with AGEP, including a temporal relationship, positive dechallenges and positive rechallenges. DPV was not able to find sufficient evidence of an association between levocetirizine and AGEP at this time. (b) (4)

On June 13, 2016, a tracked safety issue (TSI 1703) was opened in DARRTS. (b) (4)

It was noted that the current cetirizine OTC Drug Facts label states:

- *Do not use if you have ever had an allergic reaction to this product or any of its ingredients or to any antihistamine containing hydroxyzine.*
- *Stop use and ask a doctor if an allergic reaction to this product occurs. Seek medical help right away.*

DNDP determined that the cetirizine DFL contains sufficient allergy warnings and that additional label revisions for OTC cetirizine are not warranted at this time.²⁵

CDTL comment:

Dr. Gierhart noted that the DNDP decision, at this time, has been to not add AGEP to the OTC labeling for either cetirizine or the pending switch, levocetirizine. I agree.

Hepatotoxicity

²² Shakouri AA, Bahna SL. Hypersensitivity to antihistamines. *Allergy Asthma Proc.* 2013 Nov-Dec; 34 (6): 488-96.

²³ Ibid.

²⁴ Ibid.

²⁵ TSI Integrated Review Memorandum, DNDP re: TSI 1703 by Valerie Pratt, MD finalized on 8/4/16

Dr. Gierhart noted that there is one report in the medical literature of levocetirizine-induced hepatotoxicity caused by an idiosyncratic reaction in a patient with chronic urticaria dosed with levocetirizine 5 mg twice daily, first appearing after dosing for 2 weeks and on rechallenge, appearing after dosing for 3 days.²⁶ In this case, liver enzymes gradually normalized 20 days after first stopping the levocetirizine and 4 weeks after stopping the levocetirizine during the rechallenge.

The Rx label states under “8.7 Hepatic impairment : “As levocetirizine is mainly excreted unchanged by the kidneys, it is unlikely that the clearance of levocetirizine is significantly decreased in patients with solely hepatic impairment”

CDTL Comment:

The mode of elimination (largely renal and not hepatic for levocetirizine) is different from the potential of a drug to cause idiosyncratic hepatic toxicity. Despite the three confounded reports of fatal AEs noted above, it does not appear that there is a concern that levocetirizine has hepatic risks for the consumer population.

Kidney Disease

The Rx label recommends the following dose adjustments of Xyzal based on renal function:

- Mild renal impairment (creatinine clearance [CLCR] = 50-80 mL/min): a dose of 2.5 mg once daily is recommended;
- Moderate renal impairment (CLCR = 30-50 mL/min): a dose of 2.5 mg once every other day is recommended;
- Severe renal impairment (CLCR = 10-30 mL/min): a dose of 2.5 mg twice weekly (administered once every 3-4 days) is recommended;
- End-stage renal disease patients (CLCR < 10 mL/min) and patients undergoing hemodialysis should not receive XYZAL

CDTL Comment

The proposed DFL warns to “do not use” if you have kidney disease (b) (4) (b) (4). It may be appropriate to replace the “do not use” with ask a doctor before use (see labeling recommendations, Section 12 of this review.

Drug-Drug Interactions (DDIs)

Dr. Gierhart noted that no studies of drug-drug interactions were conducted in the UCB clinical development program for levocetirizine because metabolism in humans is less than 14% of the dose, so no significant interactions are expected with concomitant CYP450 inhibitors or inducers by levocetirizine. Dr. Gierhart stated “In vitro studies have shown that levocetirizine does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 or induce CYP1A2, CYP2C9 and CYP3A4. In the original prescription tablet NDA 22-064, the MedDRA AE terms were reviewed for possible indication of drug interaction terms. There were no TEAEs that suggested drug-drug interactions”.

²⁶ Ekiz F et al. Levocetirizine induced hepatotoxicity in a patient with chronic urticaria. *Ann Hepatol.* 2011 Apr-Jun; 10 (2): 237-8.

CDTL Comment

The draft DFL for Xyzal does not warn of any DDIs, and I agree there is no need.

Safety in Geriatric Population

Regarding the sponsor's proposed direction for consumers age 65 and older to ask a doctor, Dr. Gierhart noted in her review that only limited clinical study data is available regarding the safety of levocetirizine in geriatric patients, stating: "Per the ISS submitted in NDA 209089, only 221 (1.8%) of the 11,991 subjects in the safety population were ≥ 65 years of age.²⁷ Per the ISS Tables and Listing submission, 38 of the 171 subjects aged ≥ 65 years of age in the Phase 2-3-4 short-term studies reported at least one TEAE, including 8 subjects with headache, 7 subjects with somnolence, 3 subjects with fatigue and 2 subjects with asthenia.²⁸ Thus, only limited clinical study data is available pertaining to the safety of levocetirizine HCl in geriatric patients".

CDTL Comment

The sponsor's proposal for consumers age 65 and older to ask a doctor before use is reasonable given the possibility of sedation, potentially higher drug exposure due to reduced renal function with age, and the limited clinical trial experience in this population.

Postmarket Safety

- General safety of antihistamines
- Drug Abuse Warning Network (DAWN) database
- National Poison data System (NPDS) database
- Overdosage
- UCB internal database

General Safety of Antihistamines

The safety of oral antihistamines as a class for OTC use has been established with first and second generation antihistamines as noted earlier. Adverse drug reactions could be potentially differ between enantiomers and their racemate (stereoselective metabolism). The sponsor's review of the French Pharmacovigilance Database from January 1, 2005 to June 15, 2010 revealed no significant differences in the number of case reports or types of adverse drug reactions for the racemate cetirizine compared to the R-enantiomer levocetirizine.²⁹

²⁷ Per the ISS on pg. 38-49: in Table 16 "Phase 2-3-4 short term studies in adults/adolescents 12 years and older", 171 of 6869 subjects were aged ≥ 65 years, in Table 17 "Phase 2-3-4 long term studies in adults /adolescents 12 years and older", 7 of 1068 subjects were aged ≥ 65 years, in Table 18 "Phase 2-3-4 short term studies in children 6 months to 12 years old", 0 of 770 subjects were aged ≥ 65 years, in Table 19 "Phase 2-3-4 long term studies in children 6 months to 12 years old", 0 of 510 subjects were aged ≥ 65 years, in Table 20 "Clinical pharmacology studies", 39 of 2835 subjects were aged ≥ 65 years and in Table 21 "Pharmacokinetic studies in special population", 4 of 17 subjects were aged ≥ 65 years.

²⁸ Per the ISS Tables and listing, Table 1.4.3.1.4 on pg. 1810-1817 of 5088 (also marked as pg. 1765-1772 of 4793).

²⁹ Per "Caillet C et al. Safety profile of enantiomers vs. racemic mixtures: it's the same? *Br J Clin Pharmacol.* 2012 Nov; 74 (5): 886-9", for cetirizine/levocetirizine, the number of case reports was 25/20 and the number of adverse drug reactions were 41/40, which was determined by the authors as no significant difference. Cetirizine

CDTL Comments

1. Postmarketing data have limitations, including overlap or duplication of reports within databases, incomplete reports, underreporting, unknown number of people exposed, lack of a control group to provide baseline rate of occurrence of event, and stimulated reporting from lawsuits or media reports.

2. The sponsor analyzed postmarket safety data with dose-response analyses, age analyses, gender analyses, time-to-onset analyses, adverse events most likely to occur with accidental or intentional overdose in the OTC population and adverse events most likely to occur with the labeled dose and duration in the OTC population. These analyses did not reveal any preponderance of adverse events that would affect the labeling for the OTC Xyzal products. Therefore, the analyses below are differentiated by the source and not subdivided further.

Per the sponsor's analysis of AEs reported in the **FAERS database** (up to December 2014) and the WHO VigiBase (2001 to June 2015), spontaneous reporting systems both showed similar patterns of disproportionate AE reporting for events associated with levocetirizine including: pregnancy-related and abortion outcomes, liver disorders, anaphylactic reactions, psychiatric-related disorders, skin conditions, and somnolence. Some of these AEs (notably, somnolence) are listed on the Rx label for levocetirizine or are one of the indicated conditions (skin conditions like rash, urticaria). Others such as liver toxicity, spontaneous abortions, and psychiatric disorders (such as suicide attempt) which may be potential signals have been reviewed and discussed in detail in the sponsor's safety database report located in the sponsor-submitted ISS. Per the sponsor, the closely-related OTC product, cetirizine, had very similar safety signals for these AEs in the same databases, suggesting the disproportionality ratios are not remarkable.

CDTL Comment

If these NDAs are approved for OTC marketing, the reviewer assigned to postmarket pharmacovigilance could be alerted to recognize any liver disorders, given the occasional reports of liver-related adverse events, including the 3 deaths and the disproportionate AEs from the sponsor's FAERS analysis.

The Drug Abuse Warning Network (DAWN)

This database was a public health surveillance system that monitored drug-related hospital emergency department (ED) visits in a representative sample of US hospitals and select US metropolitan areas, in order to report on the impact of drug use, misuse and abuse.³⁰ While DAWN was initiated in the early 1970s and continued until the end of calendar year 2011, comparisons across data collection years can only be made for 2004-2011 because of significant changes made to DAWN in 2004, e.g., changes in the eligibility criteria for being a DAWN case.³¹ Levocetirizine was first approved in the USD in 2007. Per the sponsor, 66

was first marketed in France in 1987 and levocetirizine in 2002; thus the time period of 2005-2010 was selected to minimize a 'notoriety bias' and to be three years after the initial marketing of levocetirizine.

³⁰ Substance Abuse and Mental Health Services Administration (SAMHSA) website accessed on August 30, 2016 at: <http://www.samhsa.gov/data/emergency-department-data-dawn>

cases of ED visits associated with levocetirizine were reported during the period of 2007 to 2011 in the DAWN database, which included approximately 32 million ED visits in the US during this time period. About two-thirds of the cases were reported among females and about 22.7% were reported in the age group of ≥ 65 years followed by 16.7% in the age group of 45 to 54 years. Over 80% of the cases were adverse reactions, followed by 8% which were reported as suicide attempts. Accidental ingestion, primarily reported in children ≤ 5 years, and over-medication were the other types of reported cases.

National Poison Data System (NPDS)

This database is a large poisoning surveillance database in the US, which collects and relays real-time poisoning events for specific drugs across its 57 Poison Control Centers and contains over 60 million exposure case records. Per the sponsor, of the 498 reports to the National Poison Control Centers from 2007 to 2015, approximately 92% of the cases associated with levocetirizine use in the NPDS database were due to an unintentional exposure of which 65% were under the age of 10 years and which resulted in an outcome with either no signs/symptoms or minimal toxicity. Overall, the NPDS data showed that there is little intentional misuse or abuse of levocetirizine in the US, the majority of unintentional exposures were in very young children, and there were no outcomes from any of the levocetirizine exposures reported which resulted in a major life-threatening effect or death.

Overdosage

The Rx label notes that Overdosage has been reported with XYZAL, and states: “Symptoms of overdose may include drowsiness in adults and initially agitation and restlessness, followed by drowsiness in children. The acute maximal non-lethal oral dose of levocetirizine was 240 mg/kg in mice (approximately 190 times the maximum recommended daily oral dose in adults, approximately 230 times the maximum recommended daily oral dose in children 6 to 11 years of age, and approximately 180 times the maximum recommended daily oral dose in children 6 months to 5 years of age on a mg/m basis). ...”

CDTL Comment

Although drowsiness can occur with the labeled dose of levocetirizine, it appears that there is little potential for abuse in the OTC population and there is a large margin of safety in an intentional or unintentional overdose.

The sponsor concluded that no new safety signals warranting further investigation for levocetirizine from the AE reporting databases were detected, nor is there evidence of drug abuse from analysis of the DAWN database or that the misuse of levocetirizine causes life-threatening effects or deaths in the NPDS database which would prohibit it from switching to an OTC product.

UCB internal database

³¹ Center for Behavioral Health Statistics and Quality. *Drug Abuse Warning Network Methodology Report, 2011 Update*. Rockville, MD: Substance Abuse and Mental Health Services Administration. 2013; accessed on August 17, 2016 at: <http://www.samhsa.gov/data/sites/default/files/DAWN2k11ED/DAWN2k11ED/rpts/DAWN2k11-Methods-Report.htm>

The sponsor prepared a summary of spontaneously reported safety data in UCB's internal postmarketing safety, pharmacovigilance database that was received by UCB up to the cut-off date of October 31, 2015. Dr. Gierhart noted that up to the cut-off date, a total of 5783 levocetirizine AE reports were processed in the UCB Global Safety Database (Argus) from all marketing territories. Of these, 843 (14.6%) were considered serious using standard regulatory criteria. If these totals were restricted to only the 2 formulations for which the Sponsor is seeking a switch to OTC status (5 mg tablets and oral solution), there were 3757 total AE reports, 484 of which (12.9%) were serious. The AE report distribution by country showed that most levocetirizine reporting was derived from major markets, in particular Japan, which accounted for about one-half of all AE reporting attributable to levocetirizine for both the 5 mg tablet and the oral solution formulations. The other countries that contributed significantly to levocetirizine AE reporting were France, Germany, and the US. The most commonly reported AEs that are attributable to levocetirizine were neuropsychiatric events, in particular somnolence, fatigue, and dizziness. A total of 39 cases of somnolence progressed to become serious, and none led to fatality.

CDTL Comment

The sponsor reported 3757 total AEs, of which 484 (12.9%) were serious and 39 of the 484 (8%) were somnolence, with no fatalities from somnolence (not sure how a fatality related to somnolence would be detected unless it involved a motor vehicle accident). These data do not seem worrisome for somnolence but we cannot assume that wider use in the consumer population would not present a greater risk of somnolence-related SAEs unless the risk is minimized by dosing in the evening, similar to the Rx product label.

Literature Review

The sponsor listed 283 references in Section 5.3.5.3 of NDA 209089, and 77 references in Section 5.4 in the submission for NDA 209089 (tablet), with no additional references for NDA 209090 (oral solution). The sponsor provided bullet points regarding the "Principal results" of each of the 283 references. Dr. Gierhart looked at the sponsor's summaries or individual references, plus performed her own PubMed and EMBASE search and determined that 190 literature references provided pertinent information for levocetirizine, which she listed in Section 9.1 of her review, and captured throughout her review as citations or footnotes about adverse events and the six potential safety topics noted above.

Statistical Review:

The statistical review was done by Rongmei Zhang, Ph.D. who did not make an approval or complete response recommendation, although did state: "Overall, we do not have any major statistical concern with this pivotal LCS study". Dr. Zhang noted that the sponsor submitted one Label Comprehension Study for the tablet NDA 209089. There was no self-selection or actual use study in the submissions. Dr. Zhang noted that she was able to reproduce the results in the primary and secondary analyses for the LCS study using the submitted data, and no major data quality issue was found.

The LC study was a multi-site, single-visit LCS. The purpose of the LCS was to evaluate the consumer's ability to comprehend specific warnings and directions on the proposed DFL related to kidney disease and urinary retention.

Dr. Zhang noted:

The results from this LCS showed that the participants generally understood three specific warnings and directions related to kidney and urinary retention on the proposed Xyzal OTC label. Specifically, subjects had high comprehension rates on what to do if you have kidney disease and what to do if you have trouble urinating or emptying your bladder. Subjects had some difficulty in correctly understanding what to do if you have ever had trouble urinating or emptying your bladder. However, most of the subjects who had incorrect responses chose the more conservative action "Do Not Use" or "Stop Use and Ask a Doctor" than the correct answer "Ask a Doctor before Use".

9. Advisory Committee Meeting

There was no Advisory Committee meeting for this fourth-in-class Rx-to-OTC switch of a second generation oral antihistamine. Earlier switches included loratadine, fexofenadine, and cetirizine.

10. Pediatrics

The application does not trigger the Pediatric Research Equity Act (PREA) because the active ingredients indication, dosage form, route of administration, and dosing regimen (except the nocturnal dosing vs. anytime dosing) is unchanged from the Rx products for this submission. In addition, the levocetirizine oral solution is indicated for children down to age 2, so PREA is not a factor.

11. Other Relevant Regulatory Issues

Overall, the integrity of the sponsor's submission was good. Financial disclosures were not applicable because no new clinical studies were conducted in support of this application.

12. Labeling

In general, the sponsor's proposed labeling is acceptable (b) (4), discussed in Sections 2, 7, and below. Specific recommendations as well as the Social Science, Labeling Team, and DMEPA reviews, will be discussed below.

Proposed directions for dosing for Xyzal Allergy 24HR (tablet) and Children's Xyzal Allergy 24HR (oral solution) are shown below in Table 4.

Table 4. Proposed OTC dosing directions for Xyzal tablets and oral solution

(b) (4)

Proprietary Name Review by the Division of Medication Error Prevention and Analysis (DMEPA)

A proprietary name review was conducted by Grace P. Jones, PharmD, BCPS, (DMEPA).

On March 16, 2016, the FDA notified Sanofi US that the two proposed proprietary names Xyzal Allergy 24HR (5 mg tablet) and Children’s Xyzal Allergy 24HR (oral solution 2.5 mg/5 ml) were both (conditionally) acceptable.

On December 20, 2016, DMEPA concluded that the proposed proprietary names, Xyzal Allergy 24HR and Children’s Xyzal Allergy 24HR, are **acceptable** and do not misbrand the proposed product.

Social Science Review:

The social science review was conducted by Ms. Amanda Pike-McCruden MAA, who evaluated the Label Comprehension Study of the draft DFL. For detailed protocol description, please see her review. Ms. Pike-McCruden noted that this study was not discussed with the FDA in advance. Ms. Pike-McCruden noted that consumers had difficulty distinguishing the bladder warning from the kidney warning and stated that *if the kidney warning, which is already underlined in the draft DFL were to be in bold, then possibly it would be clearer that consumers with kidney disease are not to use the product.*

Labeling Review

The labeling review was conducted by Ms. Karen Livornese. The sponsor submitted a proposed Principal Display Panel (PDP) and Drug Facts Label (DFL), and the submission included 11 labels under NDA 209089 (tablet) and 2 labels under NDA 209090 (oral solution, includes a dosing cup). See Figures 1 and 2 and Ms. Livornese’s labeling review for details.

Ms. Livornese noted that the key messages are similar or the same as the approved Xyzal product except for differences in proprietary name, inactive ingredients, and directions or information relating to the patient population. The proposed population for the tablet, down to age 6 (choking hazard for lower ages) is the same for the OTC and Rx; however, the oral

solution allows use down to 2 years of age OTC whereas the approved Xyzal Rx allows use down to 6 months of age. Ms. Livornese identified the important labeling issues, of which I note a few as follows:

Original Prescription Strength

1. "Original Prescription Strength" is acceptable on the PDP of the tablet 5mg. The sponsor did not request similar language on the PDP for the oral solution (reason: age range different, down to 2 years OTC vs. 6 months Rx for oral solution).

CDTL Comments re: Original Prescription Strength

- *On January 4, 2017, DNDP and ODE IV discussed allowing "Original Prescription Strength" on the PDP for the Xyzal 5 mg tablet formulation and agreed to allow it. An idea considered was to allow "Full Prescription Strength"; however, Zyrtec (cetirizine racemate) tablet 10 mg had "Original Prescription Strength" on the PDP approved in 2007 at the time of its OTC switch, with a difference being that Zyrtec tablet was a full switch (no CIU indication) and Xyzal tablet is a partial switch, with chronic idiopathic urticaria (CIU) remaining Rx for Xyzal. Allowing "Original Prescription Strength" on the Xyzal 5 mg tablet PDP matches terminology that still appears on the Zyrtec 10 mg tablet PDP on a label found on Drugs@FDA on January 4, 2017.*
- *For clarity, the "Original Prescription Strength" tag is permitted in the sponsor's case since no other strength of tablet or dosing regimen is available (for the current Xyzal levocetirizine Rx product) for the proposed OTC indications of SAR or PAR. If the sponsor submits a sNDA for Rx Xyzal that adds a population, an indication, a new tablet strength or new dosing regimen, the "Original Prescription Strength" statement would need to be reconsidered.*
- *Nothing on the approved labeling for OTC Xyzal will have a reference for any use except for symptoms of SAR or PAR. Even if current patients being treated for CIU by physicians determine they can buy the OTC product, there is no safety concern since they will not be self-diagnosing or using a different strength OTC Xyzal tablet (5 mg) vs the current Xyzal Rx tablet (5 mg).*
- *For the Xyzal oral solution, the indications for AR and PAR will remain Rx for ages 6 months to <2 years of age, so "Original Prescription Strength" could be misleading on the OTC oral solution, which is indicated only down to 2 years of age.*

Principal Display Panel (PDP):

In general, the sponsor's proposed Principal Display Panel, shown below, is acceptable.

- *PDP claims such as "Clinically Proven Relief from Indoor and Outdoor Allergies; (b) (4) Clinically Proven Relief in 60 Minutes"*

(for the tablet), and “24 Hour Relief of sneezing, runny nose, itchy nose or throat, itchy, watery eyes” were confirmed by the CMC and DPARP clinical team to be accurate (DNDP prefers Clinically proven 24 hour relief to Clinically proven all night, all day relief).

Per Ms. Livornese’s review: Potential Comments to the sponsor re: PDP:

2. The statement "**Clinically proven relief from indoor and outdoor allergies**" is acceptable per correspondence from DPARP
3. The statement "**Clinically proven relief in 60 minutes**" is acceptable per correspondence from DPARP
4. **Revise the statement, [REDACTED] (b) (4) to "Clinically proven 24 hour relief" or “24 hour relief”** on 10-count carton to comply with drug class labeling.
5. The [REDACTED] (b) (4) flag is acceptable but will need removal from the PDP after 6 months of marketing.

Drug Facts Label (DFL)

CDTL Comments

1. *In general, the sponsor’s proposed Principal Display Panel, shown below, is acceptable.*
2. *The Rx labeling for the tablet and oral solution instructs the patient to take the drug once daily in the evening; [REDACTED] (b) (4)*
3. *Of note, the parent drug cetirizine (e.g. Zyrtec) directs patients to take the drug “once daily”, without regard to timing. The cetirizine DFL carries a drowsiness warning, as does the proposed levocetirizine switch. Together, the parent drug allowing “anytime” dosing and the presence of a drowsiness warning, might suggest a direction to dose levocetirizine in the evening is not necessary. However, that approach would leave the Rx levocetirizine dosing in the evening, [REDACTED] (b) (4)*
4. *See comments under Ms. Livornese’s review, namely: In Directions, change [REDACTED] (b) (4) to “once daily in the evening” to be consistent with prescription labeling.*
5. *Consider replacing the “do not use” with ask a doctor before use in consumers with kidney disease to “ask a doctor before use.*

Per Ms. Livornese’s review: Potential Comments to the sponsor re: DFL

- 1. In Directions, change [REDACTED] (b) (4) to "once daily in the evening" to be consistent with prescription labeling.**

2. *In Inactive ingredients*, change "polyethylene glycol" to "polyethylene glycol 400" which states the correct excipient used.

3. *In Questions or Comments?*:

- Replace the placeholder Xs with actual telephone number on cartons and immediate container bottles.
- We also recommend that the label include the days of the week and times that the toll-free number is in operation.

CDTL Comment:

I agree with Ms. Livornese's labeling comments and advice for revising the sponsor's proposed labeling.

Figure1: Sponsor's Proposed PDP and DFL for Xyzal Allergy 24HR Tablet 5 mg

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

13. Postmarketing Recommendations

No special postmarket requirements or commitments are recommended for this application.

14. Recommended Comments to the Applicant

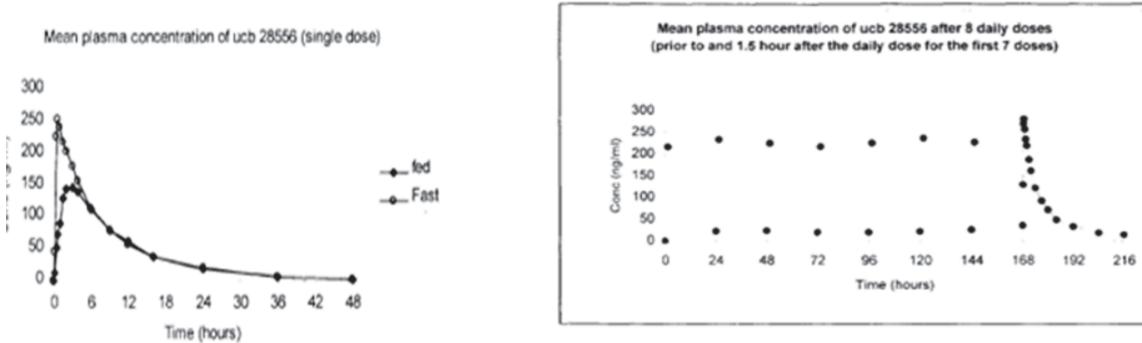
I recommend approval of this application involving levocetirizine dihydrochloride 5 mg tablets and 2.5 mg/5 ml oral solution, with the recommendation that the DFL directs consumer to take the product in the evening. Comments to the applicant regarding labeling, are described in Section 12 above and are under negotiation with the sponsor at the time of this writing. I have no additional recommendations.

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

Appendix 3 Somnolence and Sedation Tables from Dr. Gierhart’s Review

Somnolence/Sedation

The graphs below show that the C_{max} is achieved within approximately 1 hour after ingestion of a 5 mg single dose and the peak drug level remains fairly steady at 200-250 ug/ml 1.5 hours after the daily dose for the first 7 days. These data provide some reassurance that levocetirizine will not accumulate when taken daily by consumers with normal renal function



Per Table 10 Levocetirizine Only-Morning Dosing Studies (n=32), the 2496 subjects dosed with LCTZ only in the morning reported a total of 411 LCTZ somnolence/sedation, fatigue and asthenia TEAEs, which accounted for 31.2% of the total number of LCTZ TEAEs (i.e., 1319) reported in these 32 studies. When the 24 subjects only administered LCTZ 10 mg in the morning and the 42 TEAEs (including 11 somnolence, 12 fatigue and 0 asthenia TEAEs) reported by a subject after administered LCTZ 10 mg or 30 mg only in the morning were removed from this table, the remaining 2472 subjects dosed with LCTZ ≤ 5 mg only in the morning reported a total of 388 LCTZ somnolence/sedation, fatigue and asthenia TEAEs, which accounted for 30.4% of the total number of LCTZ ≤ 5 mg TEAEs (i.e., 1277) reported in these 32 studies.

Table 10 Levocetirizine Only-Morning Dosing Studies (n=32)

Study	# LCTZ Treated Subjects	# LCTZ TEAEs	# LCTZ Somnolence/Sedation TEAEs	# LCTZ Fatigue TEAEs	# LCTZ Asthenia TEAEs
A184	18 (all 2.5 mg)	1	0	0	0
A190	28	1	0	0	0
A221	24 (all 10 mg)	14	0	6	0
A230	18	8	0	0	0
A232	24	22	4	3	0
A233	4	3	0	0	0
A238	21	28	5	6	0
A245	38	2	0	0	0
A246	49	236	93	30	9
A252	19	3	0	1	0

Study	# LCTZ Treated Subjects	# LCTZ TEAEs	# LCTZ Somnolence/Sedation TEAEs	# LCTZ Fatigue TEAEs	# LCTZ Asthenia TEAEs
A254	15	1	0	0	0
A256	70	1	0	0	0
A00260	18	15	4	0	4
A00263	36	75	20	11	0
A00280	18	17	13	2	0
A00297	24	13	0	2	0
A00318	24	51	17	0	0
A00331	141	87	6	4	0
A00340	12	0	0	0	0
A00351	30	3	0	1	0
A00373	18	1	0	0	0
A00379	240	44	0	5	0
A00391	100	108	0	26	0
A00392	62	24	4	0	0
A00394	438	284	40 (including one premature discontinuation)	19	2
A00401	342	93	15 (including one premature discontinuation)	7	8
A00412	235 (116 on 2.5 mg; 119 on 5 mg)	31 (18 on 2.5 mg; 13 on 5 mg)	2 (1 on 2.5 mg; 1 on 5 mg)	2 (both on 5 mg)	0
A00414	157	16	2	3	0
A00415	152	35	5	3	0
A00419	52 (each dosed 5 mg & 30 mg)	46 (18 on 5 mg, 28 on 30 mg)	18 (7 on 5 mg; 11 on 30 mg)	7 (1 on 5 mg, 6 on 30 mg)	0
A00423	45 (all 1.25 mg)	54	2	0	0
A00428	24	2	0	0	0
Totals	2496	1319	250	138	23

Sources: from Dr. Gierhart's review p.99

NDA 209089 "Tabular Listing of Clinical Studies" and manually abstracted (by the primary reviewer of this document) from the clinical study reports, clinical study synopses, clinical study summaries and clinical study protocols submitted for the 32 studies. The information in the column labeled "# LCTZ Somnolence/Sedation TEAEs" listed was then confirmed with Table 1.4.9.4 entitled "Listing of adverse events of interest for sedation – Safety population" located on pg. 2451 to 2546 of 5088 (also marked as pg. 2406 to 2501 of 4793) of NDA 209089, ISS Tables and Listings.

NOTE: 3 studies dosing LCTZ in the morning [i.e., A00334 (67 LCTZ treated subjects with 21 LCTZ TEAEs, including at least 3 LCTZ somnolence TEAEs), A00348 (34 LCTZ treated subjects with 10 LCTZ TEAEs, including at least 1 LCTZ somnolence TEAE) and A00349 (35 LCTZ treated subjects with unknown number of LCTZ TEAEs, including at least 3 somnolence TEAEs) were excluded from this table because CSRs were not available and no data regarding the number of LCTZ somnolence, fatigue or asthenia TEAEs were available in the limited clinical summaries provided by the sponsor.

NOTE: all subjects were dosed with LCTZ 5 mg, unless noted differently in the column labeled “# LCTZ Treated Subjects”.

Per Table 1111 (from Dr. Gierhart’s review), the 3821 subjects dosed with LCTZ only in the evening/bedtime reported a total of 389 LCTZ somnolence, fatigue and asthenia TEAEs, which accounted for 9.4% of the total number of LCTZ TEAEs (i.e., 4139) reported in these 17 studies. When the 416 subjects only administered LCTZ 10 mg in the evening/bedtime and the 424 TEAEs (including 38 somnolence, 11 fatigue and 16 asthenia TEAEs) reported by a subject after administered LCTZ 10 mg only in the evening/bedtime were removed from this table, the remaining 3405 subjects dosed with LCTZ ≤ 5 mg only in the evening/bedtime reported a total of 321 LCTZ somnolence, fatigue and asthenia TEAEs, which accounted for 8.6% of the total number of LCTZ ≤ 5 mg TEAEs (i.e., 3715) reported in these 17 studies.

Table 11: Levocetirizine Only Evening/Bedtime Dosing Studies (n=17)

Study	# LCTZ Subjects	# LCTZ TEAEs	# LCTZ Somnolence/Sedati on TEAEs	# LCTZ Fatigue TEAEs	# LCTZ Asthenia TEAEs
A217	351 (117 on 2.5 mg, 116 on 5 mg, 118 on 10 mg) [NOTE: no TEAE safety information located in study report; so all AE information was presumed to be for TEAEs.]	201 (56 on 2.5 mg, 51 on 5 mg, 94 on 10 mg)	17 (3 on 2.5 mg, 1 on 5 mg, 13 on 10 mg, including 3 premature discontinuations due to somnolence, all on 10 mg)	14 (1 on 2.5 mg, 6 on 5 mg, 7 on 10 mg)	4 (1 on 2.5 mg, 1 on 5 mg, 2 on 10 mg)
A219	317 (105 on 2.5 mg, 103 on 5 mg, 109 on 10 mg)	208 (71 on 2.5 mg, 66 on 5 mg, 71 on 10 mg)	16 (7 on 2.5 mg, 5 on 5 mg, 4 on 10 mg, including 1 premature discontinuation due to somnolence on 2.5 mg)	1 (5 mg)	5 (1 on 2.5 mg, 4 on 10 mg)
A222	319	319	28	8	7
A00264	278	995	21 including 6 premature discontinuation of treatment due to	32 (including 4 premature discontinuati on of	5

Study	# LCTZ Subjects	# LCTZ TEAEs	# LCTZ Somnolence/Sedation TEAEs	# LCTZ Fatigue TEAEs	# LCTZ Asthenia TEAEs
			somnolence, of which 1 premature discontinuation due to somnolence)	treatment due to tiredness)	
A00265	391 (133 on 2.5 mg, 128 on 5 mg, 130 on 10 mg)	507 (183 LCTZ 2.5 mg, 165 LCTZ 5 mg, 159 LCTZ 10 mg)	26 (7 on 2.5 mg, 7 on 5 mg, 12 on 10 mg) including 5 premature discontinuations due to somnolence (2 on 2.5 mg, 1 on 5 mg, 2 on 10 mg)	17 (3 on 2.5 mg, 11 on 5 mg, 3 on 10 mg) including 1 premature discontinuation due to fatigue on 5 mg	10 (4 on 2.5 mg, 1 on 5 mg, 5 on 10 mg)
A00266 bedtime	150	384	8	7	1
A00268	119	163	7	4	0
A00269	81	89	0	10	1
A00270	194 (70 on 2.5 mg, 65 on 5 mg, 59 on 10 mg)	263 (71 LCTZ 2.5 mg, 92 LCTZ 5 mg, 100 LCTZ 10 mg)	25 (5 on 2.5 mg, 8 on 5 mg, 12 on 10 mg, including 2 premature discontinuation due to somnolence, both on 10 mg)	5 (4 on 5 mg, 1 on 10 mg)	5 (all on 10 mg)
A00299 bedtime	30	12	0	0	0
A00303	89	45	1	1	2
A00304	154	150	6	3	0
A00306	303 (150 LCTZ/LCTZ; 153 PBO/LCTZ)	424 (217 LCTZ/LCTZ; 207 PBO/LCTZ); including 1 sedation	7 (5 LCTZ/LCTZ; 2 PBO/LCTZ; including 1 premature discontinuations in LCTZ/LCTZ due to	15 (12 LCTZ/LCTZ; 3 PBO/LCTZ)	6 (3 LCTZ/LCTZ; 3 PBO/LCTZ including 1 premature discontinuation)

Study	# LCTZ Subjects	# LCTZ TEAEs	# LCTZ Somnolence/Sedation TEAEs	# LCTZ Fatigue TEAEs	# LCTZ Asthenia TEAEs
		TEAE in LCTZ/LCTZ resulting in premature discontinuation)	somnolence)		on in LCTZ/LCTZ due to asthenia)
A00333	226	165	18 (including 4 premature discontinuations due to somnolence)	6	6 (including one premature discontinuation due to asthenia)
A00410 bedtime	231	12	2	0	0
A00430	301	120	16	9	0
A00431	287	82	2	5	0
Totals	3821	4139	200	137	52

Sources: from Dr. Gierhart's review p.100

NDA 209089 "Tabular Listing of Clinical Studies" and manually abstracted (by the primary reviewer of this document) from the clinical study reports, clinical study synopses, clinical study summaries and clinical study protocols submitted for the 17 studies. The information in the column labeled "# LCTZ Somnolence/Sedation TEAEs" listed was then confirmed with Table 1.4.9.4 entitled "Listing of adverse events of interest for sedation – Safety population" located on pg. 2451 to 2546 of 5088 (also marked as pg. 2406 to 2501 of 4793) of NDA 209089, ISS Tables and Listings.

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/s/

STEVEN F OSBORNE

01/10/2017

Rx-to-OTC switch CDTL Review Xyzal Tablets 5 mg and Oral Solution 2.5 mg /5mL