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APPLICATION NUMBER:

209089Orig1s000

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CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA (Rx to OTC switch)
Application Number(s)	209-089 Xyzal Allergy 24 HR tablets 209-090 Xyzal Allergy 24 HR solution
Priority or Standard	Standard
Submit Date(s)	March 18, 2016
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Division / Office	DPARP/ODE 2/OND
Reviewer Name(s)	Xu Wang, M.D., Ph.D.
Review Completion Date	December 9, 2016
Established Name	Levocetirizine dihydrochloride
Rx Trade Name	Xyzal tablets/solution
OTC Trade Name	Xyzal Allergy 24HR tablets/solution
Therapeutic Class	Antihistamine
Applicant	UCB Inc.
Formulation(s)	tablets/solution
Dosing Regimen	≥12 years: One tablet (5 mg) daily/10 mL solution (5 mg) daily; 6 – 11 years: 1/2 tablet (2.5 mg) daily/5 mL solution (2.5 mg) daily; 2 – 5 years: 2.5 mL solution (1.25 mg) daily
Indication(s)	Temporarily relieve these symptoms due to hay fever or other upper respiratory allergies: <ul style="list-style-type: none">• running nose,• sneezing,• itchy, watering eyes,• itching of nose or throat
Intended Population(s)	Tablets: ≥6 years of age Solution: ≥2 years of age

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Applicant proposes a partial Rx to OTC switch of Xyzal (levocetirizine dihydrochloride). Xyzal tablets (NDA 22-064) and Xyzal solution (NDA 22-157) were approved on 05/25/2007 and 01/28/2008, respectively, for the treatment of seasonal and perennial allergic rhinitis, and chronic idiopathic urticaria (CIU) in patients 6 years of age and older (Xyzal tablets/solution prescription labeling). On 02/24/2009, the Applicant submitted pediatric study reports, as requested in a pediatric Written Request, and on 08/24/2009 Xyzal was approved in pediatric patients 6 months to <6 years of age.

The Applicant proposes an OTC switch for allergic rhinitis in patients 2 years of age and older. The proposed OTC labeling states that levocetirizine dihydrochloride (LCTZ) is “for temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: ●running nose, ●sneezing, ●itchy, watering eyes, ●itching of nose or throat.” The proposed OTC dosing regimen is the same as that of the prescription drug Xyzal. For patients ≥ 12 years: One tablet (5 mg) daily/10 mL solution (5 mg) daily; For patients 6 – 11 years: $\frac{1}{2}$ tablet (2.5 mg) daily or 5 mL solution (2.5 mg) daily; For patients 2 – 5 years: 2.5 mL solution (1.25 mg) daily.

The recommended action for this prescription (Rx) to over-the-counter (OTC) switch for Xyzal Allergy 24HR (levocetirizine dihydrochloride) tablets and solution is Approval.

1.2 Risk Benefit Assessment

Allergic rhinitis is a well-established OTC indication in the U.S., and both oral medications and nasal sprays are available OTC to treat this condition. Dose selection and efficacy of the product for adults and children ≥ 2 years of age were established during the prescription approval process, and efficacy is not expected to be different in the OTC setting. Thus, the benefit provided by LCTZ is well established and prior precedents exist for consumer self-selection for treatment of allergic rhinitis using oral drugs (Zyrtec, Claritin, and Allegra) in the OTC setting. It would benefit the public to have an additional oral antihistamine readily available as a nonprescription drug product. The safety of LCTZ is supported by the clinical development program for the prescription Xyzal, as well as by the post-marketing experience. Thus, the risk benefit assessment supports approval of LCTZ tablets and solution for the proposed partial OTC switch.

2 Introduction and Regulatory Background

2.1 Product Information

Levocetirizine dihydrochloride (LCTZ) is an oral histamine H_1 -receptor antagonist (antihistamine) and the active R-enantiomer of the approved racemate, cetirizine (Zyrtec). In the United States, prescription drug Xyzal tablets, NDA 22-064, was approved 05/25/2007 with pediatric studies deferred. On 01/28/2008 prescription drug Xyzal solution, NDA 22-157, was approved. On 01/24/2009 FDA issued a pediatric Written Request to NDAs 22-064 and 22-157. On 02/24/2009, study reports for the requested

Clinical Review studies were submitted and pediatric exclusivity was granted for both NDAs on August 25, 2009. M.D., Ph.D.
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LCTZ tablets and solution have been registered in many countries worldwide, including as prescription drugs in 60 countries and OTC drugs in 12 countries. To date, there have been no market withdrawals for LCTZ in any country due to safety reasons.

2.2 Currently Available Treatments for Proposed Indications

In addition to avoidance of allergens, antihistamines are the first-line treatment for symptoms of allergic rhinitis. Several antihistamines are currently marketed as OTC monograph drugs in the US, including first-generation agents such as brompheniramine, chlorpheniramine, diphenhydramine, and doxylamine. These products are indicated for the treatment of symptoms of “hay fever or other upper respiratory allergies” [21 CFR 341.72]. The first-generation antihistamines are characterized by sedation as an adverse effect. There are also antihistamines marketed OTC in the US that were initially approved as NDA products, such as clemastine, and the second-generation antihistamine, loratadine and loratadine/PSE. Loratadine and other second-generation antihistamines typically have limited penetration of the CNS and are associated with less or minimal sedation. There are numerous antihistamines which are available only by prescription in the US, including hydroxyzine, cyproheptadine, fexofenadine, and Xyzal tablets and solution.

2.3 Availability of Proposed Active Ingredient in the United States

Xyzal tablets (NDA 22-064) and Xyzal oral solution (NDA 22-157) are the only two drug products containing LCTZ that are currently available in the US. Both are currently available in the US as Rx drug products for the following approved Rx indications:

- 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 in adults and children 6 months of age and older.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On 05/29/2015, the sponsor submitted a Type B pre-IND meeting request for both Xyzal tablets (pre-IND 126,506) and Xyzal solution (pre-IND 126,507) to discuss the Rx to OTC switch for both Xyzal Rx NDAs. The meeting package was submitted on 08/20/2015 to both pre-INDs, and the meeting was held on 10/01/2015. Significant issues discussed during this meeting listed in the meeting minutes included:

- One comprehensive Summary of Clinical Efficacy (SCE) located in the tablet NDA to support the switch of both LCTZ tablets and the solution formulation; An Integrated Summary of Efficacy (ISE) would not be required.

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- One comprehensive Summary of Clinical Safety (SCS) and one Integrated Summary of Safety (ISS) located in the tablets NDA to support the switch of both LCTZ tablets and solution to OTC status.
- Resubmit of the clinical study databases (i.e., SAS datasets of the clinical data of either individual studies or pooled studies) are not required if a listing indicating the location of the SAS datasets of the clinical data for each individual clinical study was provided. Sponsor was informed that if any SAS dataset could not be easily located, their submission may be requested.

On 09/21/2015, two separate proprietary name requests for review (i.e., Xyzal® Allergy 24HR and (b) (4)) were submitted to both pre-INDs. On 03/16/2016, the FDA notified the sponsor that the two proposed proprietary names were acceptable.

On 12/11/2015, the sponsor submitted “General Correspondence”, amended the sponsor’s switch proposal for Xyzal tablets and solution to partially switch only two of the three approved Rx indications, i.e., SAR and PAR. On 12/22/2015, a tele-conference was held with sponsor and DNDP to clarify that the CIU (hives) indication would remain Rx for both Xyzal tablets and solution.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA submission is adequately indexed, organized and complete to allow for review. There are no new clinical studies contained in this submission, instead the submission relies on previously reviewed clinical trial data for safety and efficacy. Therefore, data integrity is not an issue for this Rx to OTC switch.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Per the Original NDA 209-089 LCTZ tablet 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.

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

Per the Original NDA 209-090 LCTZ solution 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 209-090 includes an administration device (dosing cup).

These minor CMC changes in the proposed OTC LCTZ tablets and solution are unlikely to affect the safety and effectiveness of the drugs.

4.3 Preclinical Pharmacology/Toxicology

No new preclinical and toxicological data were submitted in the Rx to OTC switch NDAs. The summary of nonclinical pharmacology and toxicology, including a cross-reference to previously submitted information, is provided in Module 2.4 of both NDAs. Summary review of the preclinical and toxicological data can be found in the DNDP Pharmacology/Toxicology NDA Review by D. Charles Thompson, R.Ph., Ph.D., D.A.B.T.

4.4 Clinical Pharmacology

No new clinical pharmacology studies were conducted in support of this submission. A clinical pharmacology summary, including cross-references to information previously submitted in the two Rx Xyzal tablets and solution (NDAs 22-064 and 22-157), is provided in Modules 2.7.1 “Summary of Biopharmaceutical Studies and Associated Analytical Methods (Allergic Rhinitis)” and 2.7.2 “Summary of Clinical Pharmacology Studies (Allergic Rhinitis)”.

The prescription Xyzal labeling recommends a dose of LCTZ for children 6 to 11 years of age is 2.5 mg and for children less than 6 years of age is 1.25 mg. The clinical pharmacology studies showed that a single dose of 5 mg LCTZ in children age 6 to 11 years of age resulted in C_{max} and AUC values about 2-fold greater than that reported in healthy adult subjects, and 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.

5 Sources of Clinical Data

The clinical program of Xyzal prescription NDA included 14 clinical studies to support the proposed indication. Of these studies, 6 are efficacy and safety studies in adult and adolescent patients with seasonal and perennial allergic rhinitis, 2 are efficacy and safety studies in pediatric patients 6 to 12 years of age with seasonal and perennial allergic rhinitis, 2 are environmental exposure unit studies, and 2 are long term safety studies (Table 1).

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5.1 Tables of Studies/Clinical Trials

Table 1 Overview of 14 randomized, placebo-controlled studies for allergic rhinitis

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.					

5.2 Review Strategy

The OTC switch application does not seek any new indications, and no new clinical trial data were included in the NDA. As efficacy was already established during the prescription approval process, this review only summarizes the efficacy data that have been reviewed previously. Additional sections and subsections of the standard NDA template that are redundant or not relevant to this Rx to OTC switch have been deleted from this review; per standard review practice the sections have not been renumbered¹.

This review is focused on the efficacy of LCTZ, because the safety of LCTZ, both from the clinical development program and from post-marketing experience, were reviewed by the Division of Non-prescription Drug Products (DNPD) Medical Officer [NDA 22-089/NDA 22-090, Medical Officer Review, Brenda S. Gierhart, M.D., 11/14/2016].

¹ MAPP 6010.3, effective date 12/10/2010

6 Review of Efficacy

Efficacy Summary

The proposed OTC dosing and indication for LCTZ are consistent with the dosing and indications approved for the prescription drug product. The proposed OTC indication is as follows: “temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: runny nose, sneezing, itchy, watering eyes, and itching of nose or throat.” As no new claims or changes in dosing are proposed, the efficacy data previously submitted in support of the prescription drug are adequate to support the proposed OTC LCTZ drug. No additional trials are required.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy variables were the mean 24 hours reflective composite scoring of rhinitis symptoms (T4SS) over the treatment period by the subjects with SAR and PAR. T4SS is the sum of the scores for sneezing, rhinorrhea, nasal pruritus and ocular pruritus. In 2 environment exposure unit studies (A379 and A412) the major symptoms complex (MSC) score (running nose, itchy nose, sniffles, nose blows, sneezes, and watery eyes) was used as the primary efficacy variable. Each symptom was rated on a 0 - 3 scale.

0 = no symptoms

1 = mild symptoms - present but not troublesome

2 = moderate symptoms - frequently troublesome, but not sufficient to interfere with normal daily activity or night-time sleep

3 = severe symptoms - sufficiently troublesome to interfere with normal daily activity or night-time sleep

A Clinical Summary of Efficacy was submitted to support the OTC indication of this Rx to OTC switch NDA. The original efficacy data were reviewed at the prescription drug clinical development program and not resubmitted to this NDA. Following are summaries of the clinical data used to support efficacy labeling in the OTC Drug Facts Label.

Efficacy – adults and adolescents 12 years of age and older

Efficacy in this patient population was assessed from 5 placebo-controlled clinical studies. Of these, 3 were dose-ranging studies and 2 were confirmatory efficacy studies.

Dose-ranging studies

The 3 dose-ranging studies were identical in design except that study A217 was conducted in patients with SAR and the other two studies (A265 and A219) were conducted in patients with PAR. 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).

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A total of 470 patients 18 - 72 years of age with SAR were enrolled in study A217 whereas, 5211 PAR subjects were randomized in A265, and 421 PAR patients were randomized in study A219. SAR patients had a positive skin test or radioallergosorbent test (RAST) to grass and/or weed pollen and had a history of SAR for at least 2 years. Patients with PAR had at least a 2-year history of PAR due to house dust mites and a positive skin test or RAST to house dust mites.

Following a screening period of approximately 7 days, patients were randomized to treatment with LTCZ 2.5, 5, 10 mg or placebo once daily in the evening for 14 days (study A217) or 4 weeks (study A265, A219). Patients recorded the severity of four symptoms (runny nose, itchy nose, sneezing, and ocular pruritus) once daily in a diary based on a severity scale of 0 to 3 to reflect how they felt over the entire 24 hour treatment period and recorded that score in their diary just before taking the next dose of study medication (reflective score). 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). The baseline score was the mean of the daily reflective T4SS (assessed in the evening) over the 7-day screening period (period from the day of the initial visit to the day preceding the randomization visit). The results were analyzed using an analysis of covariance (ANCOVA).

The efficacy results for the dose-ranging studies are shown in Table 2. There was evidence of a dose-ordering effect in studies A217 and A265 but not in study A219 where the 5 mg dose did not reach statistical significance level. However, the change from baseline in symptom scores was numerically better than placebo. A dose effect was seen in study A217 across all three doses. In study A265 all three doses had a statistically significantly greater improvement compared to placebo, but the effect size was similar in all 2 doses.

Table 2 Dose-ranging studies mean rT4SS change over treatment period

Treatment	N	Baseline mean (SD)	Adjusted mean change from baseline (SE)	Difference vs. placebo (98% CI)	p-value
Study a 217 (SAR – 2 week treatment period)					
Placebo	118	7.94 (2.06)	5.18 (0.19)		
LTCZ 2.5mg	116	7.83 (2.14)	4.27 (0.19)	0.91 [0.27, 1.55]	0.001
LTCZ 5mg	115	7.45(2.07)	4.06 (0.20)	1.11[0.47, 1.75]	<0.001
LTCZ 10mg	118	7.15(2.08)	3.57(0.19)	1.61[0.96, 2.25]	<0.001
Study a 265 (PAR – 4-week treatment period)					
Placebo	128	7.22 (1.75)	5.29 (0.17)		
LTCZ 2.5mg	133	7.14(1.64)	4.12 (0.17)	1.17 (0.71; 1.63)	< 0.001
LTCZ 5mg	127	7.18 (1.68)	4.07 (0.17)	1.22(0.76; 1.69)	<0.001
LTCZ 10mg	129	7.58 (1.79)	4.19 (0.17)	1.10 (0.64; 1.57)	<0.001
Study A219 (PAR – 4 week treatment period)					
Placebo	104	6.77 (1.62)	4.84		
LTCZ 2.5mg	105	6.64 (1.59)	4.03	0.81 (0.18; 1.45)	0.003
LTCZ 5mg	103	7.00 (1.75)	4.28	0.56 (-0.07;1.20)	0.041
LTCZ 10mg	109	6.82 (1.56)	3.64	1.21 (0.58; 1.84)	<0.001

Source: From 2.7.3 Clinical Summary of Efficacy (Allergic Rhinitis) and the Biostatistics Review of prescription drug Xyzal tablets.

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Confirmatory studies

Two confirmatory efficacy studies were conducted in the clinical program of prescription drug LCTZ. 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 study treatment (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 study treatment (LCTZ 5 mg) or placebo for 6 weeks.

A total of 237 and 294 patients 12 to 71 years of age were randomized to study treatment or placebo in study A268 and A266, respectively. 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, excluded score of ocular pruritus). In study A268, the subjects were also asked how they felt over the last hour of the treatment period (instantaneous score, iT3SS) as a secondary endpoint. This was the only allergic rhinitis study that provides an assessment of the end-of-dosing interval efficacy. Table 3 below showed evidence of efficacy for LCTZ 5 mg daily dose in SAR and PAR comparing with the placebo. Study A268 also showed that LCTZ 5 mg was efficacious at the end of 24-hour dosing interval in the treatment of SAR.

Table 3 Efficacy results in studies A268 (SAR) and A266 (PAR)

Treatment	N	Baseline (SD)	*Mean Change from Baseline (SE)	Difference from Placebo		
				Estimate	95% CI	P-value
Seasonal Allergic Rhinitis (Study A268) r-T4SS						
LTCZ 5mg	118	8.40 (1.66)	5.20 (0.222)	0.89	(0.30, 1.47)	0.001
Placebo	117	8.50 (1.68)	6.09 (0.221)			
Seasonal Allergic Rhinitis (Study A268) r-T3SS						
LTCZ 5 mg	118	6.53(1.37)	4.19 (1.98)	0.69	(0.23, 1.15)	0.003
Placebo	117	6.47(1.29)	4.86 (1.94)			
Seasonal Allergic Rhinitis (Study A268) i-T3SS						
LTCZ 5mg	118	5.54(1.79)	3.56 (0.163)	0.58	(0.15, 1.01)	0.008
Placebo	117	5.60 (1.73)	4.14 (0.163)			
Perennial Allergic Rhinitis (Study A266) r-T4SS						
LTCZ 5mg	150	7.69 (1.82)	4.17 (0.176)	1.22	(0.76; 1.69)	<0.001
Placebo	142	7.44(1.80)	5.39 (0.183)			
Perennial Allergic Rhinitis (Study A266) r-T3SS						
LTCZ 5mg	150	5.98 (1.38)	3.29 (0.132)	0.99	(0.64; 1.34)	<0.001
Placebo	142	5.79 (1.41)	4.28 (0.137)			

Source: From 2.7.3 Clinical Summary of Efficacy (Allergic Rhinitis) and the Biostatistics Review of prescription drug Xyzal tablets.

Efficacy – 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 study was conducted in France and Germany. A total of 177 subjects, male or female, were randomized to receive LCTZ 5 mg or

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placebo daily 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.

Table 4 Mean rT4SS change in pediatric study A303 (SAR)

Period	Treatment	N	Baseline Mean (SD)	On-treatment Adj. Mean	Diff. vs Placebo ^(a) Adj. Mean (95% CI)	p-value
First two Treatment weeks	Placebo	87	7.67 (1.73)	6.27	1.29 (0.66; 1.92)	< 0.001
	LCTZ 5 mg	87	7.61 (1.36)	4.98		

(a) The differences are "Placebo minus LCTZ 5 mg"

Source: Table excerpted from NDA 22-064 Xyzal tablets, MO Review, Robert M. Boucher, M.D., M.P.H., 04/03/2007

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 (Table 5).

Table 5 Mean rT4SS change in pediatric study A304 (PAR)

Period	Treatment	N	Baseline Mean (SD)	On-treatment Adj. Mean	Diff. vs Placebo ^(a) Adj. Mean (95% CI)	p-value
First two Treatment weeks	Placebo	152	7.51 (1.85)	6.76	0.69 (0.27; 1.12)	0.001
	LCTZ 5 mg	154	7.53 (1.85)	6.06		

(a) The differences are "Placebo minus LCTZ 5 mg"

Source: Table excerpted from NDA 22-064 Xyzal tablets, MO Review, Robert M. Boucher, M.D., M.P.H., 04/03/2007

UCB did not conduct efficacy studies with lower doses of Xyzal. 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. Dosing recommendation based on pharmacokinetic measures for systemically active drugs for allergic rhinitis is reasonable because allergic rhinitis is the same disease in adults and children and the effect of drug on the disease is expected to be similar between adults and children. The Division had used the rationale in the past for other oral antihistamines. The two studies A303 and A304 provide ample safety data for Xyzal in the group of 6 to <12 years of age.

Efficacy – children less than 6 years of age

There were no efficacy studies in children less than 6 years of age. UCB filed a supplemental NDA (sNDA 22-064) on 02/24/2009, to extend the age range of the approved indications down to 2 years for SAR and 6 months for PAR and CIU. Efficacy studies conducted in adults and adolescents 12 years of age and older have previously demonstrated that LCTZ is effective for treatment of the symptoms of

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SAR and PAR. Efficacy for pediatric patients under 6 years of age was extrapolated from the adult and adolescent data. This is acceptable as the indicated conditions (SAR, PAR, and CIU) share the same pathophysiology and behave similarly from a clinical perspective in both children and adults. In the pediatric program, the safety and clinical pharmacology of LCTZ in children <6 years of age were evaluated. 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..

Efficacy – Onset of action, environmental exposure (EEU) studies

Onset of action was evaluated in two environmental exposure unit (EEU) studies A379 and A412. Both studies were conducted in Kingston, Ontario Canada. Both were double-blind placebo and active-controlled studies in patients with SAR. Cetirizine 10 mg tablets were used in study A379 and cetirizine 5mg (oral drops 10 mg/ml) and 10 mg tablets were used in A412 as active controls. Levocetirizine 5 mg was used in study A379 whereas LCTZ 2.5 (oral drops 5 mg/ml) and 5 mg (tablet) were used in study A412. Study A412 was conducted with the primary objective to serve as a PD link to LCTZ and cetirizine to provide data in support of the Applicant's assertion that half the dose of LCTZ had equivalent efficacy to 2x the dose of cetirizine. The assertion is based on the acknowledgement that cetirizine is a racemic mixture of R and S enantiomers and that only the R enantiomer (LCTZ) is active therefore, the efficacious dose of LCTZ should be half that of cetirizine (CTZ).

The primary objective of the study was therefore to compare the efficacy of LCTZ 2.5 mg, 5mg, and CTZ 5mg, 10 mg vs. placebo. The design of the study also allowed it to be used to support an onset and duration of action claim. Male and female patients age 16 years of age and older with a history of SAR, allergic to ragweed pollen confirmed by positive skin prick testing performed at screening or within 12 months prior to screening, were enrolled in these 2 EEU studies. Symptoms were recorded every 30 minutes during the 2 study periods. A complex of symptoms called the major symptom complex (MSC) was used as the primary efficacy variable. The MSC (Major symptom complex) consisted of 6 individual symptoms – runny nose, itchy nose, sniffles, nose blows, sneezes, and watery eyes. Four additional symptoms (itchy eyes and ears, itchy throat, cough, and postnasal drip) were combined with the MSC to form the Total Symptom Complex (TSC). In terms of severity, the individual symptoms with the exception of nose blows and sneezes were scored on a scale of 0 – 5 (0 = none, 1 = a little, 2 = moderate, 3 = quite a bit, 4 – severe, 5 = very severe). Severity of nose blows and sneezes were scored 1 -8 based on the number where 8 represents >15. The subjects also reported nasal congestion as a separate symptom using a separate severity score (0 -4).

The individual time point analyses showing the onset and duration of action for study A379 was summarized in Table 6 below. Both LCTZ and CTZ doses were statistically superior to placebo in improving allergic rhinitis symptom scores and suggested that both drugs had an onset of action within one hours and duration of effect of at least 24 hours. For study A412, UCB did not provide specific time point comparisons between LCTZ and placebo. The approved Xyzal prescription labeling (section 14.1) carries the sentence “Xyzal 5 mg was found to have an onset of action 1 hour after oral intake”.

Table 6 MSC change in EEU study A379, Onset and duration of action

Time point Treatment	N	Baseline (SD)	Adj. mean Change from Baseline (SE)	Diff. vs. Placebo Adj Mean [95% CI]
00:30min PBO LCTZ 5 mg CTZ 10 mg	95 240 235	16.68 (5.36) 15.36 (5.39) 16.00 (5.73)	1.25 (0.481) -1.08 (0.355) -0.55 (0.329)	 -2.33 (-3.52,-2.25) -1.80 (-2.9, -0.66)
01:00 hr PBO LCTZ 5 mg CTZ 10 mg	95 240 235	16.68 (5.36) 15.36 (5.39) 16.00 (5.73)	-2.93 (0.557) -5.24 (0.359) -5.34 (0.352)	 -2.31 (-3.62, -1.01) -2.41 (-3.71, -1.11)
04:00 hr PBO LCTZ 5 mg CTZ 10 mg	95 240 235	16.68 (5.36) 15.36 (5.39) 16.00 (5.73)	-5.01 (0.627) -10.23 (0.314) -10.20 (0.334)	 -5.22 (-6.60, -3.84) -5.20 (-6.60,-3.79)
24:00 hr PBO LCTZ 5 mg CTZ 10 mg	93 236 233	16.76 (5.37) 15.40(5.38) 15.96(5.74)	-1.88 (0.608) -7.05 (0.386) -7.09 (0.411)	 -5.17 (-6.59, -3.75) -5.22 (-6.66, 3.77)
29:00 hr PBO LCTZ 5 mg CTZ 10 mg	93 236 233	16.76 (5.37) 15.40(5.38) 15.96(5.74)	-3.49 (0.688) -7.30 (0.414) -7.21 (0.449)	 -3.80 (-5.38, -2.22) -3.72(-5.34, -2.10)

P < 0.001 except at 00:30min for CTZ where p < 0.002

Source: From 2.7.3 Clinical Summary of Efficacy (Allergic Rhinitis) and the Biostatistics Review of prescription drug Xyzal tablets.

7 Review of Safety

Safety Summary

The safety of levocetirizine is supported by the clinical development program (NDA 22-064) for the prescription drug product in conjunction with post-marketing experience obtained over the past 9 years. For detailed safety data review and conclusion, readers are referred to the Division of Non-prescription Drug Products (DNPD) Medical Officer Review [NDA 22-089/NDA 22-090, Medical Officer Review, Brenda S. Gierhart, M.D., 11/14/2016].

9 Appendices

9.1 Literature Review/References

A detailed review of the literature can be found in DNPD Medical Officer Review by Dr. Brenda S.

Clinical Review
Xu Wang, M.D., Ph.D.
NDA 209-089/NDA 209-090 Rx to OTC switch
Xyzal Allergy 24HR (levocetirizine dihydrochloride) tablets/solution

Gierhart.

9.2 Labeling Review

The labels for the OTC products are primarily under the review of DNNDP. The proposed LCTZ tablets and solution OTC labeling is based on the prescription labeling with appropriate editing to conform to the OTC Drug Facts Label.

9.3 Advisory Committee Meeting

There was no Advisory Committee meeting for this Rx to OTC switch NDA.

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/s/

XU WANG
12/09/2016

ANTHONY G DURMOWICZ
12/12/2016

CLINICAL SAFETY REVIEW

Application Type	Original NDA 505(b)(2) Type 8 (Partial Rx-to-OTC Switch)
Application Numbers	a) 209089 (Xyzal® Tablet) b) 209090 (Xyzal® Solution)
Priority or Standard	Standard
Submit Date	March 31, 2016
Received Date	March 31, 2016
PDUFA Goal Date	January 31, 2017
Division/Office	DNDP/ODE IV/OND
Reviewer Name	Brenda S. Gierhart, M.D.
Review Completion Date	November 14, 2016
Established Name	Levocetirizine dihydrochloride
Proposed Trade Names	a) Xyzal® Allergy 24HR b) Children's Xyzal® Allergy 24HR
Therapeutic Class	H-1 Receptor Antagonist (Antihistamine)
Applicant	UCB, Inc. (Agent: Sanofi US Services Inc.)
Formulations	a) Tablet, 5 mg b) Oral solution, 2.5 mg/5 mL
Proposed Dosing Regimen	1.25 to 5 mg once daily, depending on age and symptom severity
Indication	Uses (for both formulations) temporarily relieves these symptoms due to hay fever or other respiratory allergies: ▪ runny nose ▪ sneezing ▪ itchy, watery eyes ▪ itching of the nose or throat

Intended Populations a) Tablet: Adults and children 6-64 years of age; adults 65 years of age and older are to ask a doctor
b) Oral solution: Adults and children 2-64 years of age; adults 65 years of age and older are to ask a doctor

Template Version: March 6, 2009

Clinical Safety Review

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The sponsor provided adequate data to support the safety of its proposed Xyzal OTC line of single-ingredient levocetirizine products: tablet, 5 mg (NDA 209089) and oral solution, 2.5 mg/5 mL (NDA 209090) for the following indication:

Uses temporarily relieves these symptoms due to hay fever or other respiratory allergies: ▪ runny nose ▪ sneezing ▪ itchy, watery eyes ▪ itching of the nose or throat

Therefore, from a clinical safety perspective, this reviewer recommends approval of these two applications, as long as the sponsor incorporates the labeling recommendations for the two OTC levocetirizine drug products (see section 9.2 of this review).

1.2 Risk Benefit Assessment

The symptoms of allergic rhinitis, i.e., runny nose, sneezing, itchy, watery eyes and itching of the nose or throat, can be easily identified by the public without a learned intermediary. In the United States, the public is experienced with selecting and purchasing nonprescription drug products for allergic rhinitis because of the many years that monograph drug products for these symptoms have been available over-the-counter (OTC) and the several Rx-to-OTC switches for similar antihistamines that are currently available OTC, e.g., Zyrtec, Claritin, Allegra. It would benefit the public to have an additional oral antihistamine readily available as a nonprescription drug product. The safety of levocetirizine tablet and oral solution has been reviewed and it is the opinion of this reviewer that the significant safety issues identified for these two drug products can be adequately addressed with appropriate OTC labeling. Thus, the risk benefit assessment supports approval of these two applications, as long as the sponsor incorporates the labeling recommendations for the two levocetirizine drug products (see section 9.2 of this review).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No special risk management activities are recommended for this NDA.

1.4 Recommendations for Postmarket Requirements and Commitments

No required phase 4 commitments are recommended. No other phase 4 requests are recommended.

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2 Introduction and Regulatory Background

Rhinitis is characterized by one or more of the following symptoms: nasal congestion, rhinorrhea, sneezing, and itching.¹ Itching (pruritus) can be nasal, ocular or both. Rhinitis is generally classified as allergic, nonallergic or mixed, with allergic rhinitis being the most common (i.e., allergic rhinitis affects approximately 58 million Americans versus 19 million with nonallergic rhinitis and 26 million with mixed rhinitis).² Allergic rhinitis is a chronic, immunoglobulin E (IgE)–mediated respiratory disease, believed to occur after exposure to indoor and outdoor allergens (e.g., dust mites, insects, animal danders, molds, and pollens).³ Allergic rhinitis is traditionally subdivided into “seasonal” and “perennial” allergic rhinitis (SAR and PAR); however, allergic rhinitis has also been subdivided into “intermittent” (i.e., less than 4 days per week or for less than 4 weeks) and “persistent” (i.e., more than 4 days per week and more than 4 weeks).⁴

The diagnosis of allergic rhinitis is based upon the presence of clinical symptoms, triggers, perceived allergy, potential association with one or more seasons of the year and ruling out various types of the less common nonallergic rhinitis [e.g., drug-induced rhinitis (cocaine sniffing or aspirin intolerance), hormonal rhinitis, occupational rhinitis, skier's nose (after exposure to cold, dry air) and food-induced rhinitis (after exposure to hot spicy food)].⁵ Objective tests for the diagnosis of IgE-mediated allergy (e.g., skin prick test, serum specific IgE) can also be used. The estimated financial burden (i.e., total direct and indirect costs) for allergic rhinitis in the United States (US) for 2002 was \$11.58 billion.⁶

2.1 Product Information

Union Chimique Belge (UCB) is an international pharmaceutical company founded in 1928 and headquartered in Brussels, Belgium. In the early 1950's, UCB developed the antihistamine/tranquilizer Atarax® (hydroxyzine hydrochloride) and awarded the US

¹ Wallace DV et al; Joint Task Force on Practice; American Academy of Allergy; Asthma & Immunology; American College of Allergy; Asthma and Immunology; Asthma & Immunology; America College of Allergy; Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol.* 2008 Aug; 122 (2 Suppl); S1-84.

² Settiple RA. Rhinitis: a dose of epidemiological reality. *Allergy Asthma Proc.* 2003 May-Jun; 24 (3): 147-54.

³ Sur DK and Scandale S. Treatment of Allergic Rhinitis. *Am Fam Physician.* 2010; 81 (12): 1440-6.

⁴ Bousquet J, Van Cauwenberge P, Khaltaev N; ARIA Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol.* 2001 Nov; 108 (5 Suppl); S147-334.

⁵ *Ibid.*

⁶ Wallace DV et al; Joint Task Force on Practice; American Academy of Allergy; Asthma & Immunology; American College of Allergy; Asthma and Immunology; Asthma & Immunology; America College of Allergy; Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol.* 2008 Aug; 122 (2 Suppl); S1-84.

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distribution license for Atarax to Pfizer. In the 1980s, UCB developed the blockbuster antihistamine Zyrtec (cetirizine hydrochloride; Figure 1b), which is the main metabolite of hydroxyzine HCl (Figure 1a).^{7,8} In the 1990s, UCB developed Xyzal (levocetirizine dihydrochloride), which is the active R-enantiomer of the racemate, cetirizine HCl.⁹

In the US, UCB licensed Zyrtec to Pfizer, the first Rx Zyrtec approval in the US was in 1995 and both marketing and manufacturing of Rx Zyrtec in the US was by Pfizer. In the US, OTC Zyrtec was first approved in 2007, sponsorship was transferred from Pfizer to McNeil Consumer Healthcare in 2008 and OTC Zyrtec is currently distributed by Johnson & Johnson Consumer Inc., McNeil Consumer Healthcare Division.

Figure 1: (a) Chemical structure of hydroxyzine HCl (C₂₁H₂₇ClN₂O₂·2HCl); (b) Chemical structure of cetirizine HCl and levocetirizine diHCl (C₂₁H₂₅ClN₂O₃·2HCl)¹⁰

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⁷ [No authors listed] Cetirizine and loratadine: minimal risk of QT prolongation. *Prescrire Int.* 2010 Feb; 19 (105): 26-8.

⁸ Assouère MN et al. [Cutaneous drug eruption with two antihistaminic drugs of a same chemical family: cetirizine and hydroxyzine]. *Ann Dermatol Venereol.* 2002 Nov; 129 (11): 1295-8.

⁹ <http://www.ucb.com/our-company/history> accessed on August 10, 2016.

¹⁰ Assouère MN et al. [Cutaneous drug eruption with two antihistaminic drugs of a same chemical family: cetirizine and hydroxyzine]. *Ann Dermatol Venereol.* 2002 Nov; 129 (11): 1295-8.

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Levocetirizine dihydrochloride (also referred to as levocetirizine, LCTZ or ucb 28556 in this document) is an oral histamine H₁-receptor antagonist (antihistamine) and the active R-enantiomer of the approved racemate, cetirizine.¹¹ In 2001, levocetirizine tablets were first approved in Germany and Spain for marketing as a prescription (Rx) drug product.¹² Since that time, levocetirizine tablets and oral solution have been registered in 60 countries as an Rx drug product. Levocetirizine tablets are approved without a prescription in the following 12 countries: Armenia, Australia, Azerbaijan, Belarus, Bulgaria, Czech Republic, Georgia, Kyrgyzstan, Moldova, Russia, the Ukraine, and Uzbekistan. Levocetirizine tablets are available as a "Pharmacist Only" drug product (sold only under supervision of a pharmacist) in New Zealand, Tajikistan, and Turkmenistan. Levocetirizine oral solution is available without a prescription in Australia and the Ukraine. Levocetirizine oral drops (not registered in the US) have been registered in over 30 countries as an Rx drug product. Levocetirizine oral drops are also approved without a prescription in Australia, Bulgaria, and the Ukraine. To date, levocetirizine tablets, oral solution, and oral drops have not been withdrawn in any country due to safety reasons.

In the US, UCB submitted five meeting requests (dated April 14, 2005, September 1, 2005, January 4, 2006, March 15, 2006 and November 28, 2006) to the FDA for Rx levocetirizine and the five meetings were held under preIND 072233. On July 25, 2006, UCB submitted NDA 022064 for Rx Xyzal (levocetirizine dihydrochloride) oral tablet, 5 mg and it was approved on May 25, 2007 with pediatric studies deferred. On March 28, 2007, UCB submitted NDA 022157 for Rx Xyzal (levocetirizine dihydrochloride) oral solution, 2.5 mg/ 5 mL and it was approved on January 28, 2008. On December 14, 2007, UCB opened IND 072233 and it contained UCB's plan for levocetirizine's pediatric assessment and two protocols for pediatric safety studies. On February 3, 2009, FDA issued a pediatric Written Request containing three studies to NDAs 022064 and 022157. On February 24, 2009, study reports for the requested three pediatric studies were submitted to NDAs 022064 and 022157 and pediatric exclusivity was granted for both NDAs on August 25, 2009.

On May 29, 2015, UCB submitted two meeting requests to FDA for OTC levocetirizine (one request for the tablet and one request for the solution) and the meeting (for both formulations) was held under preINDs 126506 (oral tablet) and 126507 (oral solution). On March 31, 2016, UCB submitted NDA 202089 to support a partial Rx to over-the-counter (OTC) switch of Rx Xyzal (levocetirizine dihydrochloride oral tablet, 5 mg to OTC Xyzal Allergy 24HR (levocetirizine dihydrochloride) oral tablet, 5 mg and NDA 202090 to support a similar partial Rx-to-OTC switch of Rx Xyzal (levocetirizine

¹¹ Based upon its chemical structure, levocetirizine belongs to the **piperazine** chemical class of H₁ antihistamines, along with cetirizine, buclizine, cyclizine, hydroxyzine and meclizine [per Simons FE. Advances in H₁-antistamines. *N Eng J Med.* 2004 Nov 18; 351 (21): 2203-17.]

¹² The information provided in this sentence and in the remainder of this paragraph is from the ISS pg. 11 of 163.

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dihydrochloride) oral solution, 2.5 mg/5 mL to OTC Children's Xyzal Allergy 24HR oral solution, 2.5 mg/5 mL. For both drug products, an Rx-to-OTC switch has been requested for only two of the three currently approved Rx indications, i.e., for "relief of symptoms associated with seasonal allergic rhinitis" (SAR) and "relief of symptoms associated with perennial allergic rhinitis" (PAR). The sponsor proposes to convert these two Rx indications into the following OTC indication "temporarily relieves these symptoms due to hay fever or other respiratory allergies: ▪ runny nose ▪ sneezing ▪ itchy, watery eyes ▪ itching of the nose or throat". The third approved Rx indication, i.e., "treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria" (CIU; hives), is not being switched to OTC use at this time for either drug product and will remain under NDAs 022064 (oral tablet) and 022157 (oral solution).

For adults and adolescents 12 years of age and older, Rx Xyzal is approved at a dosage of 5 mg once daily in the evening and this recommendation is accompanied by the statement "Some patients may be adequately controlled by 2.5 mg (1/2 tablet or 1 teaspoon [5 mL] oral solution) once daily in the evening". For children 6 to 11 years of age, Rx Xyzal is approved at a dosage of 2.5 mg once daily in the evening. For children 6 months to 5 years of age, Rx Xyzal is approved at a dosage of 1.25 mg once daily in the evening.

The only clinical safety issues identified in the labeling concerned the OTC proposed dosing regimens for the two Xyzal formulations. The sponsor's proposed OTC proposed dosing regimen for Xyzal Allergy 24HR tablet, 5 mg is:

(b) (4)

Reviewer's comments:

1.

(b) (4)

All of the subjects in the pivotal Phase 3 placebo-controlled, double-blind clinical trials included in the pooled analysis of safety supporting the approval of the Rx LCTZ oral tablet NDA 022064 were dosed once daily in the evening. The safety concern is whether daytime dosing will result

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in somnolence and potential problems in maintaining alertness while driving (for adults) and in school (for younger consumers). 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).¹³ 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 or walking to school. This reviewer recommends that OTC Xyzal be dosed once daily in the evening. (b) (4)

- The sponsor proposes to split adults into two categories of "up to age 64" and "65 years and older" with different dosing recommendations for the two groups for both OTC dosage forms; 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"). This reviewer believes that the sponsor has taken this precaution for both OTC dosage forms because: a) the safety data generated in the sponsor's 62 clinical studies were minimal for subjects aged 65 years of age and older, i.e., only 221 (1.8%) of the 11,991 subjects in the safety population submitted in the sponsor's Integrated Summary of Safety (ISS) were ≥ 65 years of age, and b) the approved Rx Xyzal labeling in Section 2.1 DOSAGE AND ADMINISTRATION states: "Some patients may be adequately controlled by 2.5 mg (1/2 tablet or 1 teaspoon [5 mL] oral solution) once daily in the evening". Because so little safety data is available for the population of adults 65 years of age and older in UCB clinical studies, this reviewer concurs with the sponsor to have adults ≥ 65 years of age "ask a doctor" before taking either dosage form of OTC Xyzal. Physicians may recommend that adults ≥ 65 years of age dose with 2.5 mg LCTZ once daily in the evening, either by splitting the 5 mg tablet in half or using the oral solution.*
- The sponsor proposes that OTC Xyzal Allergy 24HR tablet, 5 mg labeling should instruct consumers to "do not use" this drug product in "children under 6 years of age" and in "consumers with kidney disease". While this reviewer believes it may be the safest course for the sponsor to contraindicate use of OTC Xyzal tablet in children under 6 years of age and contraindicate the use of either OTC Xyzal*

¹³Ferrer M. Pharmacokinetics evaluation of levocetirizine. *Expert Opin Drug Metab Toxicol*. 2011 Aug; 7 (8): 1035-47.

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formulation in consumers with kidney disease, this reviewer also notes Rx labeling for Xyzal solution provides dosing instructions for children aged ≥ 6 months, plus the dosing directions for both Rx Xyzal formulations provide clear instructions for dose adjustment in patients aged ≥ 12 years with mild, moderate or severe renal impairment and contraindicates use of LCTZ in patients with end-stage renal disease (e.g., CL_{CR} , 10 ml/min), patients undergoing hemodialysis, and in children aged 6 months to 11 years with impaired renal function. While the sponsor could revise their proposed OTC Xyzal tablet labeling to: 1) add that consumers aged ≥ 12 years with mild, moderate or severe kidney disease “ask a doctor” before using OTC Xyzal, 2) revise the “do not use” section to include consumers aged ≥ 12 years with end-stage renal disease and consumers undergoing hemodialysis, 3) revise the “do not use” section to include children under 12 years with impaired renal function, and 4) change the recommendation to “ask a doctor” for children from 6 months to under 6 years of age (because a physician would likely recommend Xyzal oral solution for the 6 months to <6 years age group), none of these revised instructions underwent testing in the sponsor’s labeling comprehension study and there may be insufficient space on the box to add all of this revised labeling. In addition, this reviewer considers the sponsor’s proposed “do not use” directions for children aged less than 6 years to be correct for the OTC Xyzal Allergy 24HR tablet, 5 mg (e.g., to avoid young children choking on the tablet and to avoid dividing the 5 mg tablet into quarters to permit the administration of 1.25 mg). Thus, without evidence that consumers would adequately understand the above rather complicated possible revisions to the OTC Xyzal tablet labeling, this reviewer accepts the sponsor’s proposed OTC Xyzal tablet labeling for “consumers with kidney disease” and “children under 6 years of age”, i.e., “do not use”. This reviewer notes that the dosing directions in the labeling for OTC Zyrtec Allergy (cetirizine HCl) tablets, 10 mg for both “children under 6 years of age” and “consumers with kidney disease” instruct consumers to “ask a doctor”. The Rx Zyrtec labeling for both formulations does not contain any contraindication pertaining to renal impairment.

The sponsor’s proposed OTC dosing regimen for Children’s Xyzal Allergy 24HR oral solution, 2.5 mg/5 mL is:

(b) (4)

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Reviewer's comments:

1. See above Reviewer's comment #1 (on pg. 11-12 of this review) for discussion of sponsor proposed dosing regimens for both OTC Xyzal formulations, i.e., dosing (b) (4) "once daily in the evening" in the approved labeling for both Rx Xyzal formulations.
2. See above Reviewer's comment #2 (on pg. 12 of this review) for discussion of sponsor proposed dosing directions for both OTC Xyzal formulations, i.e., different dosing directions for "adults and children 12-64 years of age" and "adults 65 years of age and older" versus the same dosing directions for "adults and children 12 years of age and older" in the approved labeling for both Rx Xyzal formulations.
3. The sponsor proposes that OTC Children's Xyzal Allergy 24HR oral solution, 2.5 mg/5 mL labeling should instruct consumers to "do not use" this drug product in "children under 2 years of age". However, the dosing directions for Rx Xyzal for children 6 months to 5 years of age recommend 1.25 mg (2.5 mL) oral solution once daily dosing in the evening. Because children 6 months to under 2 years of age have Rx oral solution dosing instructions, it may be less confusing to the consumer to revise the "do not use" section in the OTC oral solution labeling to "children under 6 months of age" and revise the "ask a doctor" section in the OTC oral solution labeling to "children aged 6 months to 2 years", because a physician would likely recommend dosing with 1.25 mg (2.5 mL) oral solution once daily in the evening for the 6 months to under 2 years age group (as recommended in the Rx Xyzal labeling). However, the sponsor may be taking this more conservative approach to ensure that very young children, i.e., children under 2 years of age, are not dosed with OTC Xyzal oral solution. A doctor could either provide a prescription for Rx Xyzal to the caregiver of a child between 6 months to under 2 years of age or inform the caregiver of the correct dose of OTC Xyzal oral solution for a child between 6 months to under 2 years of age. This reviewer accepts the sponsor proposal.

2.2 Tables of Currently Available Treatments for Proposed Indications

Management of allergic rhinitis includes environmental control measures for allergens, nasal saline irrigation, pharmacologic mono- or combination therapies (e.g., oral or intranasal antihistamines, oral decongestants, oral or intranasal corticosteroids, leukotriene receptor antagonists, intranasal cromolyn) and immunotherapy (i.e., "allergy shots").¹⁴ The first H₁ antihistamine, piperoxan, was reported in 1937.¹⁵ At least 11 different antihistamine active ingredients are in OTC monograph drug products currently marketed in the US (see Table 1). These OTC monograph antihistamine drug products are indicated for "the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever or other upper respiratory allergies (allergic rhinitis)".¹⁶

¹⁴ Bousquet J, Van Cauwenberge P, Khaltaev N; ARIA Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol.* 2001 Nov; 108 (5 Suppl); S147-334.

¹⁵ Parsons ME and Ganelin CR, Histamine and its receptors. *Br J Pharmacol.* 2006 Jan; 147(Suppl 1): S127-S135.

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First-generation antihistamines currently available in the US to treat the symptoms of allergic rhinitis [e.g., brompheniramine maleate, carbinoxamine maleate, chlorcyclizine hydrochloride (HCl), chlorpheniramine maleate, clemastine fumarate, cyproheptadine HCL, dexbrompheniramine, dexchlorpheniramine, diphenhydramine HCl, doxylamine succinate, pheniramine maleate, promethazine HCl, pyrilamine maleate, thonzylamine HCl and triprolidine HCl] are characterized by sedation as an adverse effect. Second-generation antihistamines currently available in the US to treat the symptoms of allergic rhinitis (e.g., acrivastine, azelastine, cetirizine HCl, desloratadine, fexofenadine, levocetirizine, loratadine and olopatadine) typically have limited penetration of the CNS and are generally associated with less or minimal sedation.

Some antihistamines currently marketed in the US as OTC drug product were initially approved as NDA drug products [e.g., cetirizine, cetirizine/pseudoephedrine (PSE), clemastine fumarate, fexofenadine HCl, fexofenadine HCl/PSE, loratadine and loratadine/PSE]. Several antihistamines are currently available in the US only by prescription (e.g., acrivastine, azelastine, carbinoxamine maleate, cyproheptadine HCl, desloratadine, levocetirizine, olopatadine HCl and promethazine HCl). The current submission concerns the partial Rx to OTC switch of levocetirizine oral tablet and oral solution for two of their three approved Rx indications.

Table 1: Antihistamine Active Ingredients in Drug Products Currently Available in the US for Symptoms of Allergic Rhinitis

	Active Ingredient (Example of Tradename)
OTC Monograph ^{17,18,19}	1) Brompheniramine maleate (Children's Dimetapp Cold & Allergy) 2) Chlorcyclizine HCl (Dallery)

¹⁶ 21 CFR 341.72(b)(2).

¹⁷ 21 CFR 341.12 lists 13 OTC monograph antihistamine active ingredients for symptoms of AR; however, only 11 are included in this table because no drug products containing diphenhydramine citrate or phenindamine tartrate appear to be currently available in the US for symptoms of allergic rhinitis. 21 CFR 341.72(b) (1) (2) lists the following indications for these 13 OTC monograph antihistamines as: (1) "Temporarily" (select one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (select one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" (which may be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)"). (2) "For the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" (which may be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)").

¹⁸ Per DailyMed and Google searches conducted by this reviewer on 8/8/16, no labeling for any drug product containing diphenhydramine citrate for symptoms of allergic rhinitis was located. All drug products located that are currently available in the US containing diphenhydramine citrate are combined with ibuprofen, naproxen or acetaminophen for use as a nighttime sleep aid and pain reliever.

¹⁹ Per DailyMed search conducted by this reviewer on 8/8/16, no labeling for any drug product containing phenindamine tartrate was located. Per Google search conducted by this reviewer on 6/30/16, it appears that drug products containing phenindamine tartrate are no longer available in the USA (e.g., Nolahist®)

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	Active Ingredient (Example of Tradename)
	3) Chlorpheniramine maleate (Chlor-Trimeton 4Hour) 4) Dexbrompheniramine maleate (Ala-Hist IR) 5) Dexchlorpheniramine maleate (Rescon) 6) Diphenhydramine HCl (Day and Night Cold) 7) Doxylamine succinate ²⁰ (Alka-Seltzer Plus Day and Night Cold) 8) Pheniramine maleate ²¹ (Care One Flu and Sore Throat) 9) Pyrilamine maleate (Capron DM) 10) Thonzylamine HCl (Poly Hist PD) 11) Triprolidine HCl (Histex)
Rx only	1) Acrivastine (Semprex-D) first approved 1994 2) Azelastine HCl (Astelin; Astepro) first approved 1996 3) Carbinoxamine maleate (generics to Clistin; Karbinal ER) first approved 1953 4) Cyproheptadine HCl (generics to Periactin) first approved 1961 5) Desloratadine (Clarinox) first approved 2001 6) Levocetirizine (Xyzal) first approved 2007 7) Olopatadine HCl (Patanase nasal spray) first approved 2008 8) Promethazine HCl (Phenergan) first approved 1951
Rx/OTC	1) Cetirizine HCl (Zyrtec) Rx first approved 1995; OTC first approved 2007 2) Clemastine Fumarate (Tavist Allergy) Rx first approved 1977; OTC first approved 1992 3) Fexofenadine HCl (Allegra) Rx first approved 1996; OTC approved 2011 4) Loratadine (Claritin, Alavert) Rx first approved 1993; OTC approved 2002

Source: Per 21 CFR 341.12 and searches conducted by this reviewer of DailyMed (U.S. National Library of Medicine Drug Labels), DARRTS, Drugs@FDA, Google and Orange Book.

For a summary of the currently available allergic rhinitis pharmacologic treatment options, see the 35-page Table 12 in Section 9.5.

2.3 Availability of Proposed Active Ingredient in the United States

Xyzal oral tablet, 5 mg (first approved in 2007 under NDA 022064) and Xyzal oral solution, 2.5 mg/5 mL (first approved in 2008 under NDA 022157) are the only two drug products containing levocetirizine dihydrochloride that are currently available in the US.

has not been available for US market since 2005 and both Amilon and Nolamine are discontinued).

²⁰ Per DailyMed search conducted by this reviewer on 8/8/16, when doxylamine succinate is the only active ingredient, use in the US is only as a "sleep aid".

²¹ Per DailyMed search conducted by this reviewer on 8/8/16, 27 drug products containing pheniramine maleate are currently used in the US for symptoms of AR and 16 drug products containing pheniramine maleate are currently used in the US to decrease eye redness and itching, e.g. Eye Allergy Relief.

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Both are currently available in the US as Rx drug products for the following three approved Rx indications:

1. **Seasonal Allergic Rhinitis:** Xyzal is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 2 years of age and older.
2. **Perennial Allergic Rhinitis:** Xyzal is indicated for the relief of symptoms associated with perennial allergic rhinitis in adults and children 6 months of age and older.
3. **Chronic Idiopathic Urticaria:** Xyzal is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 months of age and older.

2.4 Important Safety Issues With Consideration to Related Drugs

Six safety issues with consideration to related drugs are discussed in this section, i.e., QT prolongation, somnolence/sedation, urinary retention, hypersensitivity reactions (ex. urticaria, fixed drug eruptions and rash), drug-induced acute generalized exanthematous pustulosis (AGEP) and hepatotoxicity. It should be noted that while adverse drug reactions could be different between enantiomers and their racemate (explained by stereoselective metabolism), a 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 (at the daily defined dose of 10 mg) compared to the R-enantiomer levocetirizine (at the daily defined dose of 5 mg).²²

1. QT prolongation:

Antihistamines' influences on cardiac repolarization are not uniform and their risk of triggering severe ventricular arrhythmias, especially in high risk patients, differs.²³ Terfenadine (e.g., Seldane NDA 018949 approved 1985 and Seldane-D NDA 019664 approved 1991; both withdrawn 1998) and astemizole (e.g., Hismanal tablet NDA 019402 approved 1988; withdrawn 1999) are two non-sedating second-generation antihistamines with similar structures that were removed from the market due to the associated risk of causing the cardiac arrhythmia Torsades de Pointes (TdP) secondary to QT prolongation at high serum concentrations.^{24,25} The metabolism of these two

²² 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 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.

²³ Lange B, Bachel C. Adverse reaction profiles of antihistamines and their clinical relevance. *Allergologie.* 2004; 27 (2): 49-71.

²⁴ Monahan BP et al. Torsades de pointes occurring in association with terfenadine use. *JAMA.* 1990 Dec 5; 264 (21): 2788-90.

²⁵ Per Leurs R et al. H₁-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects.

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antihistamines may decrease (resulting in an increased serum concentration) when administered concomitantly with certain drugs, such as antifungals (e.g., ketoconazole and fluconazole), macrolides (e.g., erythromycin), antivirals and those with the potential to inhibit hepatic microsomal enzymes, particularly isozyme CYP3A4.²⁶ It should be noted that excessive prolongation of the QT interval in the right setting can trigger a potentially fatal ventricular tachyarrhythmia, typically of the TdP type. Since sudden unexpected deaths leave no pathological signature and TdP is, more often than not, a transient arrhythmia, its incidence in association with any drug is difficult to quantify.²⁷

Cetirizine (i.e., the racemate of levocetirizine, first marketed in France in 1988²⁸; first approved in US as Rx product in 1996 and currently marketed in US OTC as Zyrtec Allergy) has been implicated in two questionable cases of ventricular arrhythmias;

- In 2005, it was reported that a 63-year old woman had been hospitalized for cardiovascular collapse and syncope with electrocardiogram (ECG) showing a QTc interval of 580 ms and early signs of torsades de points. She had recently started taking ketoconazole 400 mg/day and cetirizine (a total of 5 doses) for a fungal skin infection. The QT interval normalized when these two drugs were withdrawn.²⁹
- In 2005, it was reported that a 55-year old patient on chronic dialysis for 3 years, who was known to have a long QT interval and intermittent hypokalemia, developed ventricular arrhythmia after taking 3 times the prescribed dose of cetirizine.^{30,31}

Clin Exp Allergy. 2002; 32: 489-98:

"Although histamine itself has important cardiovascular effects and the cardioactive properties of 'classical' antihistamines have been known for decades, it is only in the last 15 years that the issue of a possible association between the use of H₁-antihistamines and cardiac arrhythmias has received considerable attention. During this period, an increasing number of reports have shown an association between the consumption of astemizole or terfenadine, in particular, and the occurrence of prolongation of the QT interval, leading to the appearance of polymorphic ventricular arrhythmias, syncope, and even cardiac arrest. After reviewing 25 case reports of associations between cardiac arrhythmia and the use of second-generation antihistamines, the FDA in 1990 introduced labeling changes for terfenadine, and in 1992 a prominent box warning was added. In addition, to increase the level of awareness of patients and physicians about the serious and potentially fatal cardiac adverse effects associated with the inappropriate use of terfenadine, 'Dear Health Care Professional' letters were sent to physicians and pharmacists in the US in 1990, 1992 and 1996. Following these letters, the number of cases reporting potentially fatal cardiac arrhythmias in association with terfenadine and astemizole has grown to over 200. Because of continuing problems, both terfenadine and astemizole were withdrawn from the market in several countries."

²⁶ NDA 019835 Cetirizine (Zyrtec) OTC Switch Clinical Safety Review by Lolita A. Lopez, M.D. finalized in DARRTS on 10/2/07.

²⁷ Stockbridge N et al. Dealing with global safety issues: was the response to QT-liability of non-cardiac drugs well coordinated? *Drug Saf*. 2013 Mar; 36 (3): 167-82.

²⁸ [No authors listed] Levocetirizine: new preparation. Me-too: simply the active enantiomer of cetirizine. *Prescrire Int*. 2003;12 (67):171-2

²⁹ Mok NS et al. Ketoconazole induced torsades de pointes without concomitant use of QT interval-prolonging drug. *J Cardiovasc Electrophysiol*. 2005 Dec; 16 (12): 1375-7.

³⁰ Renard S et al. [Torsades de pointes caused by cetirizine overdose]. *Arch Mal Coeur Vaiss*. 2005 Feb;

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However, no QT prolongation was noted in four clinical studies of healthy males taking up to 6 times the recommended dose of cetirizine^{32,33}, cetirizine had lower reporting rates for cardiac adverse drug reactions reports from 1986 to 1996 in the WHO ADR database than four other second-generation antihistamines³⁴ and when seven antihistamines were compared in 2004, cetirizine, desloratadine and levocetirizine had the lowest risk of triggering severe ventricular arrhythmias.³⁵ 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.^{36,37}

It should be noted that cetirizine is a metabolite of the antihistamine hydroxyzine

[NOTE: hydroxyzine is not indicated for allergic rhinitis]. In the 1960s, in a study of 25 patients with psychosis taking a high dose of hydroxyzine (300 mg/day) for nine weeks, T-wave modifications were observed in 9 patients and the QT interval was also prolonged.³⁸ In 2008, one case of drug-induced long QT syndrome was reported in a

98 (2): 157-61.

³¹ [No authors listed] Cetirizine and loratadine: minimal risk of QT prolongation. *Prescrire Int.* 2010 Feb; 19 (105): 26-8.

³² 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 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."

³³ Sale ME et al. The electrocardiographic effects of cetirizine in normal subjects. *Clin Pharmacol Ther.* 1994 Sept; 56 (3): 295-301.

³⁴ 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.

³⁵ Lange B, Bacht 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.]

³⁶ 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.

³⁷ 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.

³⁸ Hollister LE. Hydroxyzine hydrochloride: possible adverse cardiac interactions. *Psychopharmacol.*

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34-year old female who experienced repetitive syncope after taking hydroxyzine 75 mg for several days.³⁹ This patient was later found to have a HERG mutation, which combined with the intake of hydroxyzine appeared to have led to syncope, probably due to torsade de pointes. The latest 2016 package insert for hydroxyzine hydrochloride oral tablet (i.e., ANDA 204279 because marketing of innovator NDA 010392 Atarax is discontinued) and the latest package insert (2016) for hydroxyzine pamoate oral capsule (NDA 011795 Vistaril) both state in the **ADVERSE REACTIONS** section: “**Cardiac System:** QT prolongation, Torsade de Pointes.”, both state in the **CONTRAINDICATIONS** section: “Hydroxyzine is contraindicated in patients with a prolonged QT interval” and both contain the following information in the **PRECAUTIONS** section:

QT Prolongation/Torsade de Pointes (TdP): Cases of QT prolongation and Torsade de Pointes have been reported during post-marketing use of hydroxyzine. The majority of reports occurred in patients with other risk factors for QT prolongation/TdP (pre-existing heart disease, electrolyte imbalances or concomitant arrhythmogenic drug use). Therefore, hydroxyzine should be used with caution in patients with risk factors for QT prolongation, congenital long QT syndrome, a family history of long QT syndrome, other conditions that predispose to QT prolongation and ventricular arrhythmia, as well as recent myocardial infarction, uncompensated heart failure, and bradyarrhythmias.

Caution is recommended during the concomitant use of drugs known to prolong the QT interval. These include Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmics, certain antipsychotics (e.g., ziprasidone, iloperidone, clozapine, quetiapine, chlorpromazine), certain antidepressants (e.g., citalopram, fluoxetine), certain antibiotics (e.g., azithromycin, erythromycin, clarithromycin, gatifloxacin, moxifloxacin); and others (e.g., pentamidine, methadone, ondansetron, droperidol).

There are three cases of asymptomatic QT prolongation associated with levocetirizine in FAERS⁴⁰, three cases of “torsadogenic signal” associated with levocetirizine in the German spontaneous reporting system⁴¹ and no reports of TdP or symptomatic QT prolongation with levocetirizine as the single suspect drug⁴². In addition, to support approval of Rx NDA 022064 (Xyzal 5 mg oral tablet):

Commun. 1975; 1 (1): 61-5.

³⁹ Sakaguchi T et al. Hydroxyzine, a first generation H₁-receptor antagonist, inhibits human ether-a-go-go-related gene (HERG) current and causes syncope in a patient with the HERG mutation. *J Pharmacol Sci.* 2008; 108: 462-71.

⁴⁰ 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.

⁴¹ 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.

⁴² Per [No authors listed] Cetirizine and loratadine: minimal risk of QT prolongation. *Prescrire Int.* 2010 Feb; 19 (105): 26-8, “Two cases of QT prolongation with cetirizine have been published, one of which

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UCB conducted a single-dose QT study in healthy subjects using 5 mg and 30 mg levocetirizine, and 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.⁴³

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 (see Figures 1 and 2).⁴⁴

Figure 2: Study A238 Mean Plasma Concentration of Levocetirizine after Single Dose of Levocetirizine Dihydrochloride (ucb 28556) 5 mg Tablet in Fed and Fasted Conditions⁴⁵

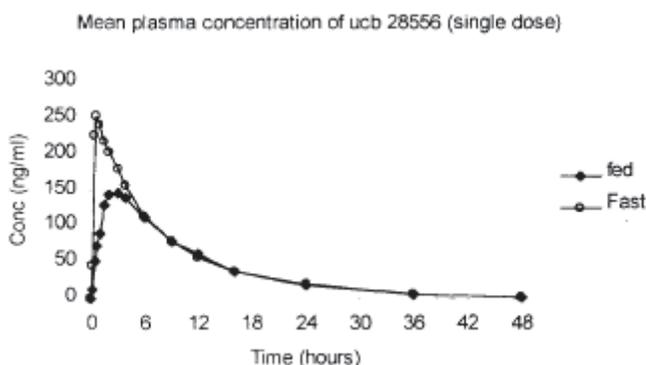


Figure 3: Study A238 Mean Plasma Concentration of Levocetirizine after 8 Daily Doses of Levocetirizine Dihydrochloride (ucb 28556) 5 mg Tablet⁴⁶

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.”

⁴³ NDA 022064 Xyzal (levocetirizine dihydrochloride) tablets Division Director Decisional Review by Badrul A. Chowdhury, MD, PhD finalized in DARRTS on 5/25/07. It was also stated in this review:

“A multi-dose QT study with levocetirizine is not necessary because levocetirizine is not expected to have a QT burden. There are QT studies with cetirizine and there is long marketing history of cetirizine without any QT prolongation reports.”

[NOTE: this review contains a typographical error in the sentence stating that the QTc change for the 30 mg single dose was 1 msec. It was actually -1 msec, per Clinical Pharmacology review of Original NDA 022064.]

⁴⁴ Per NDA 209089 Section 2.7.2 pg. 9 of 13.

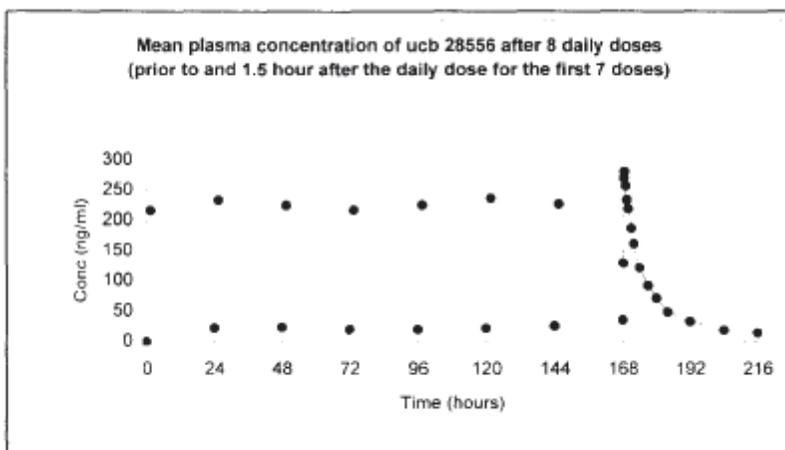
⁴⁵ NDA 022064 SDN1 CSR A238 on pg. 5 of 1127.

⁴⁶ NDA 022064 SDN1 CSR A238 on pg. 6 of 1127.

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Reviewer's comment: 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.

2. Somnolence/Sedation:

First-generation H₁-antihistamines (e.g., chlorpheniramine, diphenhydramine and hydroxyzine) are considered to have an overall unfavorable risk/benefit ratio, since they show poor selectivity and "remarkable sedative and anticholinergic effects".⁴⁷ The latest package insert (2016) for hydroxyzine hydrochloride oral tablet (i.e., ANDA 204279 because marketing of innovator NDA 010392 Atarax is discontinued) and the latest package insert (2016) for hydroxyzine pamoate oral capsule (NDA 011795 Vistaril) both state that this drug is indicated as a sedative as a premedication and following general anesthesia, both package inserts state in the **PRECAUTIONS** section:

Since drowsiness may occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery while taking hydroxyzine. Patients should also be advised against the simultaneous use of other CNS depressant drugs, and cautioned that the effects of alcohol may be increased.

and both package inserts state in the **ADVERSE REACTIONS** section:

Central Nervous System: Drowsiness is usually transitory and may disappear in a few days of continued therapy or upon reduction of dose. Involuntary motor activity including rare instances of tremor and convulsions has been reported, usually with doses considerably higher than those recommended. Clinically significant respiratory depression has not been reported at recommended doses.

⁴⁷ Bousquet J, Van Cauwenberge P, Khaltaev N; ARIA Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol.* 2001 Nov; 108 (5 Suppl); S223.

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Because second-generation H₁-antihistamines (with minimal sedative effects because of their limited penetration of the blood-brain barrier⁴⁸, higher potency and a longer duration of action) have been developed, first-generation H₁-antihistamines are no longer prescribed for the treatment of allergic rhinitis, whenever possible.^{49,50}

Despite cetirizine being a second-generation H₁-antihistamine (with a presumed decreased risk of somnolence), when seven antihistamines were compared, cetirizine, levocetirizine and mizolastine had the highest placebo-exceeding incidences in objective psychomotor and cognitive tests and cetirizine did so even below its therapeutic dosage.⁵¹ When compared to the second-generation H₁-antihistamines fexofenadine, loratadine and desloratadine, cetirizine is more sedating.⁵² 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.⁵³ 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).⁵⁴ The clinical findings of increased drowsiness or fatigue with cetirizine compared with placebo may be due to it penetrating the brain to some extent, as demonstrated in positron emission tomography (PET) scanning of the human brain after single oral doses of 10 mg and 20 mg of cetirizine.⁵⁵ However, it should be noted that “mean results” do not reveal everything as some patients may show considerable somnolence whereas others are unaffected.⁵⁶ After conducting a small study of cetirizine daytime alertness and performance in six healthy volunteers, the use of cetirizine by air personnel was not recommended.⁵⁷ The **PRECAUTIONS** section of the latest (2004) approved Rx labeling for the second-generation antihistamine Zyrtec (cetirizine) states:

⁴⁸ Church DS, Church MK. Pharmacology of antihistamines. *World Allergy Organ J.* 2011 Mar; 4 (3 Suppl): S22-7.

⁴⁹ Bousquet J, Van Cauwenberge P, Khaltaev N; ARIA Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol.* 2001 Nov; 108 (5 Suppl): S223.

⁵⁰ Brozek JL et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol.* 2010 Sep; 126 (3): 466-76.

⁵¹ 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.]

⁵² [No authors listed] Levocetirizine (Xyzal) for allergic rhinitis and urticaria. *Med Lett Drug Ther.* 2007 Dec; 3; 49 (1275): 97-9.

⁵³ Curran MP et al. Cetirizine: a review of its use in allergic disorders. *Drugs.* 2004; 64 (5): 523-61.

⁵⁴ *Ibid.*

⁵⁵ Tashiro M et al. Dose dependency of brain histamine H₁ receptor occupancy following oral administration of cetirizine hydrochloride measured using PET with [(11)C]doxepin. *Hum Psychopharmacol.* 2004; 24 (7): 540-8.

⁵⁶ Church DS, Church MK. Pharmacology of antihistamines. *World Allergy Organ J.* 2011 Mar; 4 (3 Suppl): S22-7.

⁵⁷ Nicholson AN, Turner C. Central effects of the H₁-antihistamine, cetirizine. *Aviat Space Environ Med.* 1998 Feb; 69 (2): 166-71.

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Activities Requiring Mental Alertness: In clinical trials, the occurrence of somnolence has been reported in some patients taking ZYRTEC; due caution should therefore be exercised when driving a car or operating potentially dangerous machinery. Concurrent use of ZYRTEC with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur.

The OTC (2015) labeling for Zyrtec Allergy (cetirizine) in the **Warnings** section states:

When using this product

- drowsiness may occur
- avoid alcoholic drinks
- alcohol, sedatives and tranquilizers may increase drowsiness
- be careful when driving a motor vehicle or operating machinery

Despite levocetirizine being a second-generation H₁-antihistamine (with a presumed decreased risk of somnolence), the **WARNINGS AND PRECAUTIONS** section of the latest approved (2016) Rx labeling for Xyzal (levocetirizine) oral tablet and solution states:

5.1 Somnolence: In clinical trials the occurrence of somnolence, fatigue, and asthenia has been reported in some patients under therapy with XYZAL. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness, and motor coordination such as operating machinery or driving a motor vehicle after ingestion of XYZAL. Concurrent use of XYZAL with alcohol or other central nervous system depressants should be avoided because additional reductions in alertness and additional impairment of central nervous system performance may occur.”

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).⁵⁸ After single oral doses of 5 mg levocetirizine were administered to eight healthy subjects and positron emission tomography (PET) scanning of the brain, the averaged estimated binding potential ratio (using a simplified reference tissue model method that allowed for shorter PET scanning times) did not demonstrate significant binding of levocetirizine to brain histamine H₁ receptors.⁵⁹ A randomized, double-blind trial 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.⁶⁰ In a small, three-

⁵⁸ [No authors listed] Levocetirizine (Xyzal) for allergic rhinitis and urticaria. *Med Lett Drug Ther.* 2007 Dec; 3; 49 (1275): 97-9.

⁵⁹ Hiraoka K et al. Brain histamine H₁ receptor occupancy measured by PET after oral administration of levocetirizine, a non-sedating antihistamine. *Expert Opin Drug Saf.* 2015 Feb; 14 (2): 199-206.

⁶⁰ 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.

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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.⁶¹ 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.⁶²

Reviewer's comment: *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 this review).*

3. Urinary Retention:

The **PRECAUTIONS** section of the latest approved (2004) Zyrtec (cetirizine) Rx labeling states: "ZYRTEC is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function." It should be noted that the Zyrtec Rx labeling lists "urinary retention" in the **ADVERSE REACTIONS** section and states that urinary retention was "observed infrequently (less than 2%), in either 3982 adults and children 12 years and older or in 659 pediatric patients aged 6 to 11 who received Zyrtec in U.S. trials, including an open adult study of six months duration".

The **WARNINGS AND PRECAUTIONS** section of the approved Rx labeling for both Xyzal (levocetirizine) drug products also 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."

Urinary retention is not mentioned in the latest package insert (2016) for hydroxyzine hydrochloride oral tablet (i.e., ANDA 204279 because marketing of innovator NDA 010392 Atarax is discontinued) and the latest package insert (2016) for hydroxyzine pamoate oral capsule (NDA 011795 Vistaril).

⁶¹ 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.

⁶² 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.

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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. This reviewer did not identify a safety signal for urinary retention in the scientific literature.*

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

Antihistamines are the cornerstone of allergy therapy and are not expected to cause hypersensitivity reactions; however, reported reactions to antihistamines include urticaria/angioedema, fixed drug eruption (FDE), contact dermatitis and anaphylaxis.⁶³ Almost all antihistamines have been reported as causing reactions, with cetirizine being the most common oral drug product followed by its parent drug, hydroxyzine.⁶⁴ 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.⁶⁵

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.

cetirizine=11 reports^{66,67,68,69,70,71,72,73,74,75,76}

⁶³ Shakouri AA, Bahna SL. Hypersensitivity to antihistamines. *Allergy Asthma Proc.* 2013 Nov-Dec; 34 (6): 488-96.

⁶⁴ Ibid.

⁶⁵ Ibid.

⁶⁶ Calista D et al. Urticaria induced by cetirizine. *Br J Dermatol.* 2001; 144: 196.

⁶⁷ Karamfilov T et al. Cetirizine-induced urticarial reaction. *Br J Dermatol.* 1999; 140: 979-80.

⁶⁸ Rodriguez del Rio P et al. Urticaria caused by antihistamines: report of 5 cases. *J Investig Allergol Clin Immunol.* 2009; 19 (4): 317-20. [NOTE: one of the five cases was with cetirizine.]

⁶⁹ Stingeni L et al. Maculopapular and urticarial eruption from cetirizine. *Contact Dermatitis.* 1997 Nov; 37 (5): 249-50.

⁷⁰ Tella R et al. Urticaria to cetirizine. *J Investig Allergol Clin Immunol.* 2002; 12 (2): 136-7.

⁷¹ Kranke B, Mayr-Kanhauser S. Urticarial reaction to the antihistamine levocetirizine dihydrochloride. *Dermatology.* 2005; 210 (3): 246-7.

⁷² González de Olano D et al. Urticaria induced by antihistamines. *J Investig Allergol Clin Immunol.* 2006; 16 (2): 144-6.

⁷³ Inomata N et al. Multiple H1-antihistamine-induced urticaria. *J Dermatol.* 2009 Apr; 36 (4): 224-7.

⁷⁴ Schroter S et al. Urticarial intolerance reaction to cetirizine. *Clin Exp Dermatol.* 2002 May; 27 (3): 185-7.

⁷⁵ Demoly P et al. Hypersensitivity to H₁-antihistamines. *Allergy.* 2000 Jul; 55 (7): 679-80.

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hydroxyzine=6 reports^{77,78,79,80,81}

fexofenadine=4 reports

loratadine=3 reports

ebastine=3 reports

dexchlorpheniramine=2 reports

bepotastine=1 report

diphenhydramine=1 report

levocetirizine=1 report⁸²

mizolastine=1 report

prophenyridamine=1 report

rantidine=1 report

Fixed drug reaction: at least 21 reports (with 12 associated with use of cetirizine, hydroxyzine or levocetirizine) occurring in 19 patients treated with antihistamines are in the medical literature.

cetirizine=6 reports^{83,84,85,86,87,88}

dimenhydrinate=6 reports

levocetirizine=5 reports^{89,90,91,92,93}

⁷⁶ Chang YS et al. A case of urticaria induced by both hydroxyzine and cetirizine but not by levocetirizine. *Allergy*. 2007 Jul; 62 (7): 819-21.

⁷⁷ Shakouri AA, Bahna SL. Hypersensitivity to antihistamines. *Allergy Asthma Proc*. 2013 Nov-Dec; 34 (6): 488-96.

⁷⁸ Rodriguez del Rio P et al. Urticaria caused by antihistamines: report of 5 cases. *J Investig Allergol Clin Immunol*. 2009; 19 (4): 317-20. **[NOTE: two of the five cases were with hydroxyzine.]**

⁷⁹ Inomata N et al. Multiple H1-antihistamine-induced urticaria. *J Dermatol*. 2009 Apr; 36 (4): 224-7.

⁸⁰ Demoly P et al. Hypersensitivity to H₁-antihistamines. *Allergy*. 2000 Jul; 55 (7): 679-80.

⁸¹ Chang YS et al. A case of urticaria induced by both hydroxyzine and cetirizine but not by levocetirizine. *Allergy*. 2007 Jul; 62 (7): 819-21.

⁸² Kranke B, Mayr-Kanhauser S. Urticarial reaction to the antihistamine levocetirizine dihydrochloride. *Dermatology*. 2005; 210 (3): 246-7.

⁸³ Assouère MN et al. [Cutaneous drug eruption with two antihistaminic drugs of a same chemical family: cetirizine and hydroxyzine]. *Ann Dermatol Venereol*. 2002 Nov; 129 (11): 1295-8.

⁸⁴ Inamadara AC et al. Multiple fixed drug eruptions due to cetirizine. *Br J Dermatol*. 2002; 147: 1025-6.

⁸⁵ Kranke B, Kern T. Multilocalized fixed drug eruption to the antihistamine cetirizine. *J Allergy Clin Immunol*. 2000 Nov; 106 (5): 988.

⁸⁶ Mahajan VK et al. Fixed drug eruption: a novel side effect of levocetirizine. *Int J Dermatol*. 2005 Sep; 44 (9): 796-8.

⁸⁷ Cravo M et al. Fixed drug eruption to cetirizine with positive lesional patch tests to the three piperazine derivatives. *Int J Dermatol*. 2007 Jul; 46 (7): 760-2.

⁸⁸ Gharami RC. An unusual reaction to a commonly used drug. *Indian J Dermatol Venereol Leprol*. 2001 Mar-Apr; 67 (2): 107.

⁸⁹ Mahajan VK et al. Fixed drug eruption: a novel side effect of levocetirizine. *Int J Dermatol*. 2005 Sep; 44 (9): 796-8.

⁹⁰ Kim MY et al. A case of levocetirizine-induced fixed drug eruption and cross-reaction with piperazine derivatives. *Asia Pac Allergy*. 2013 Oct; 3 (4): 281-4.

⁹¹ Gupta LK et al. Fixed drug eruption to levocetirizine and cetirizine. *Indian J Dermatol*. 2014 Jul; 59 (4): 411-3.

⁹² Guptha SD et al. Fixed drug eruption due to levocetirizine. *Indian J Dermatol Venereol Leprol*. 2005

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diphenhydramine=2 reports

hydroxyzine=1 report⁹⁴

loratadine=1 report

Generalized nonspecific rash: at least 26 reports (with 14 associated with use of cetirizine, hydroxyzine or levocetirizine) occurring in 12 patients treated with antihistamines are in the medical literature.

hydroxyzine=9 reports^{95,96,97,98,99,100}

cetirizine=4 reports^{101,102,103,104}

azelastine=1 report¹⁰⁵

desloratadine=1 report

dexchlorpheniramine=1 report

diphenhydramine=1 report

ebastine=1 report

fexofenadine=1 report

levocetirizine=1 report¹⁰⁶

loratadine=1 report

mebhydrolin=1 report

Sept-Oct; 71 (5): 361-2.

⁹³ Jhaj R et al. Fixed drug eruption due to levocetirizine. *J Pharmacol Pharmacother*. 2016 Apr-Jun; 7 (2): 109-11.

⁹⁴ Assouère MN et al. [Cutaneous drug eruption with two antihistaminic drugs of a same chemical family: cetirizine and hydroxyzine]. *Ann Dermatol Venereol*. 2002 Nov; 129 (11): 1295-8.

⁹⁵ Lew BL et al. Cutaneous drug eruption from cetirizine and hydroxyzine. *J Am Acad Dermatol*. 2004 Jun; 50 (6): 953-6.

⁹⁶ Michel M et al. Skin reactions to hydroxyzine. *Contact Dermatitis*. 1997; 36: 147-9. **[NOTE: contains reports on three different patients with generalized nonspecific rash after exposure to hydroxyzine.]**

⁹⁷ Ash S, Scheman AJ. Systemic contact dermatitis to hydroxyzine. *Am J Contact Dermat*. 1997 Mar; 8 (1): 2-5.

⁹⁸ Reid N et al. Worsening of contact dermatitis by oral hydroxyzine: a case report. *Dermatol Online J*. 2013 Feb 15; 19 (2): 4.

⁹⁹ Rodriguez del Rio P et al. Urticaria caused by antihistamines: report of 5 cases. *J Investig Allergol Clin Immunol*. 2009; 19 (4): 317-20. **[NOTE: After first exposure to hydroxyzine, Case #1 experienced urticaria and during challenge with hydroxyzine, Case #1 experienced maculopapular rash.]**

¹⁰⁰ Vinas M et al. Cutaneous drug eruption induced by antihistamines. *Clin Exp Dermatol*. 2014 Dec; 39 (8): 918-20.

¹⁰¹ Lew BL et al. Cutaneous drug eruption from cetirizine and hydroxyzine. *J Am Acad Dermatol*. 2004 Jun; 50 (6): 953-6.

¹⁰² Cusano F et al. Clinicopathologic features of systemic contact dermatitis from ethylenediamine in cetirizine and levocetirizine. *Dermatology*. 2006; 213 (4): 353-5.

¹⁰³ Vinas M et al. Cutaneous drug eruption induced by antihistamines. *Clin Exp Dermatol*. 2014 Dec; 39 (8): 918-20.

¹⁰⁴ Stingeni L et al. Maculopapular and urticarial eruption from cetirizine. *Contact Dermatitis*. 1997 Nov; 37 (5): 249-50.

¹⁰⁵ Lew BL et al. Cutaneous drug eruption from cetirizine and hydroxyzine. *J Am Acad Dermatol*. 2004 Jun; 50 (6): 953-6.

¹⁰⁶ Cusano F et al. Clinicopathologic features of systemic contact dermatitis from ethylenediamine in cetirizine and levocetirizine. *Dermatology*. 2006; 213 (4): 353-5.

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mizolastine=1 report

rantidine=1 report

rupatadine=1 report

Reviewer comment:

- 1) The **CONTRAINDICATIONS** section of the latest package insert (2016) for prescription Xyzal (levocetirizine) tablets and oral solution states:

The use of Xyzal is contraindicated in patients with known hypersensitivity to levocetirizine or any of the ingredients of XYZAL or to cetirizine. Observed reactions range from urticaria to anaphylaxis.

In Section **6.2 Post-Marketing Experience**, the latest Xyzal package insert also includes "hypersensitivity and anaphylaxis, fixed drug eruption, pruritus, rash and urticaria", i.e.:

Adverse reactions of hypersensitivity and anaphylaxis, increased appetite, angioedema, fixed drug eruption, pruritus, rash and urticaria, convulsion, paraesthesia, dizziness, tremor, dysgeusia, vertigo, movement disorders (including dystonia and oculogyric crisis), aggression and agitation, hallucinations, depression, insomnia, suicidal ideation, visual disturbances, blurred vision, palpitations, tachycardia, dyspnea, nausea, vomiting, hepatitis, dysuria, urinary retention, myalgia, arthralgia, and edema have been reported.

Besides these reactions reported under treatment with XYZAL, other potentially severe adverse events have been reported from the post-marketing experience with cetirizine.

- 2) The latest package insert for hydroxyzine hydrochloride oral tablet (i.e., ANDA 204279 because marketing of innovator NDA 010392 Atarax is discontinued) and the latest package insert for hydroxyzine pamoate oral capsule (NDA 011795 Vistaril) both state in the **ADVERSE REACTIONS** section:

Skin and Appendages: Oral hydroxyzine hydrochloride is associated with fixed drug eruptions in postmarketing reports.

...

In post-marketing experience, the following additional undesirable effects have been reported: **Body as a Whole:** allergic reaction, **Nervous System:** headache, **Psychiatric:** hallucination, **Skin and Appendages:** pruritus, rash, urticaria.

- 3) The latest package insert (2004) for prescription Zyrtec (cetirizine HCl) oral tablet and syrup does not mention "fixed drug reaction" or "fixed drug eruptions" but does already include "dermatitis", "erythematous rash", "eczema", "maculopapular rash", "rash" and "urticaria" in the **Skin** subsection of the **ADVERSE REACTIONS** section, i.e.,:

Skin: acne, alopecia, angioedema, bullous eruption, dermatitis, dry skin, eczema, erythematous rash, furunculosis, hyperkeratosis, hypertrichosis, increased sweating, maculopapular rash, photosensitivity reaction, photosensitivity toxic reaction, pruritus, purpura, rash, seborrhea, skin disorder, skin nodule, urticaria.

5. Drug-Induced Acute Generalized Exanthematous Pustulosis (AGEP):

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

On June 13, 2016, a tracked safety issue (TSI 1703) was opened in DARRTS and the above DVP I review re: AGEP was placed into this TSI. (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.

As the cetirizine Drug Facts label currently contains sufficient allergy warnings, it was determined, in conjunction with the Associate Director for Labeling, that label revisions for OTC cetirizine are not warranted at this time.¹⁰⁷

Reviewer's comment: At the current time, the DNDP decision (b) (4)

6. Hepatotoxicity:

In clinical trials, transient hepatic transaminase elevations have been observed in less than 2% of patients during cetirizine therapy¹⁰⁸ and cetirizine induced cholestasis has been reported after its prolonged use.¹⁰⁹ Levocetirizine-induced hepatotoxicity caused by an idiosyncratic reaction has been reported 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.¹¹⁰ In this case, liver enzymes gradually

¹⁰⁷ TSI Integrated Review Memorandum, DNDP re: TSI 1703 by Valerie Pratt, MD finalized on 8/4/16

¹⁰⁸ Ergun T, Kus S. Adverse systemic reactions of antihistamines: Highlights in sedating effects, cardiotoxicity and drug interactions. *Current Medicinal Chemistry: Anti-Inflammatory and Anti-Allergy Agents*. 2005; 4 (5): 507-515.

¹⁰⁹ Fong DG et al. Cetirizine-induced cholestasis. *J Clin Gastroenterol*. 2000 Oct; 31 (3): 250-3.

¹¹⁰ Ekiz F et al. Levocetirizine induced hepatotoxicity in a patient with chronic urticaria. *Ann Hepatol*. 2011

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normalized 20 days after first stopping the levocetirizine and 4 weeks after stopping the levocetirizine during the rechallenge.

Reviewer's comment: *Per the current Xyzal Rx labeling: "Elevations of blood bilirubin and transaminases were reported in <1% of patient in the clinical trials. The elevations were transient and did not lead to discontinuation in any patient" and "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".*

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Presubmission regulatory activity was conducted under the two pre-investigational new drug (preINDs) 126506 (Xyzal tablets; six submissions) and 126507 (Xyzal solution; six submissions). 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 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. Significant issues resolved during this meeting and listed in the FDA meeting minutes included:

- 1) Sanofi US Services Inc. (Sanofi US) could provide one comprehensive Summary of Clinical Efficacy (SCE) located in the tablet NDA to support the switch of both the levocetirizine tablets and the oral solution formulation.
- 2) FDA would accept a waiver of inclusion of an Integrated Summary of Efficacy (ISE) in both the NDA for the tablet and oral solution submissions.
- 3) 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.
- 4) FDA provided extensive details on the expected postmarketing safety data analyses and data to be submitted, i.e., 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.
- 5) Sanofi US would not have to submit clinical study databases (i.e., SAS datasets of the clinical data of either individual studies or pooled studies) if a listing indicating the location of the SAS datasets of the clinical data for each individual clinical study was provided. Sponsor was informed that if any SAS dataset could not be easily located, their submission may be requested.

On September 21, 2015, two separate proprietary name requests for review (i.e., Xyzal® Allergy 24HR and (b) (4) were submitted to both preINDs. On December 11, 2015, Sanofi US submitted "General Correspondence" to both preINDs

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that amended the sponsor's switch proposal for Xyzal tablets and oral solution to partially switch only two of the three approved Rx indications, i.e., SAR and PAR. On December 22, 2015, a telephone interaction was held with Sanofi US and members of the DNDP to clarify that the CIU (hives) indication would remain Rx for both drug products and no meeting minutes were issued by DNDP. On January 7, 2017, Sanofi US submitted their electronic study data standardization plan to both preINDs, which involves the submission of only one study report (i.e., consumer study "15060 Pivotal Comprehension Study – Xyzal OTC"). On March 16, 2016, the FDA notified Sanofi US that the two proposed proprietary names (i.e., Xyzal® Allergy 24HR and (b) (4) (b) (4) were both conditionally acceptable.

2.6 Other Relevant Background Information

While the labeling for both Rx Xyzal drug products states that the recommended dose should be taken "once daily in the evening", the sponsor proposes to label their two OTC Xyzal drug products (b) (4). Both Rx Xyzal drug products are labeled only for evening dosing because all of the pertinent clinical trials in the Rx tablet NDA 022064 dosed levocetirizine in the evening and sedation-related effects of daytime use were not characterized.¹¹¹ (b) (4)

Reviewer's comment: *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).¹¹² 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.* (b) (4)

This reviewer

¹¹¹ NDA 022064 Xyzal (levocetirizine dihydrochloride) Clinical Review by Robert Boucher, MD, MPH finalized in DARRTS on 4/3/07; pg. 10 of 161.

¹¹² Ferrer M. Pharmacokinetics evaluation of levocetirizine. *Expert Opin Drug Metab Toxicol.* 2011 Aug; 7 (8): 1035-47.

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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 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 and Table 11 of this review).

No new nonclinical pharmacology and toxicology, human pharmacokinetics and bioavailability, clinical pharmacology, clinical efficacy or safety studies for the intended use were conducted by the sponsor in support of these two Rx to OTC partial switch NDAs.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This is an Rx-to-OTC switch without any new clinical studies; therefore, no DSI inspection was requested.

3.2 Compliance with Good Clinical Practices

No new clinical studies were performed; therefore, no assessment was made pertaining to compliance with Good Clinical Practices. In each NDA, sponsor certified "that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application".

3.3 Financial Disclosures

No new clinical studies were performed; therefore, no new financial disclosure forms have been submitted in NDAs 209089 or 209090. The financial disclosure information for the Rx Xyzal tablet NDA 022064 (see Module 1.3.16 of Original NDA 022064 submitted on July 24, 2006 and Module 1.3.4 of the pediatric supplement to NDA 022064 submitted on February 24, 2009) has been previously reviewed. The financial disclosure information for the Rx Xyzal oral solution NDA 022157 (see Module 1.3.16 of Original NDA 022157 submitted on March 27, 2007 and Module 1.3.4 of the pediatric supplement to NDA 022064 submitted on February 24, 2009) has been previously reviewed.

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4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Per the Original NDA 209089 tablet 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 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 an administration device (dosing cup).

See Chemistry review for details.

4.2 Clinical Microbiology

Microbiology review was not necessary for these two applications.

4.3 Preclinical Pharmacology/Toxicology

No new data or toxicology information was submitted in these two NDAs. The summary of nonclinical pharmacology and toxicology, including a cross-reference to previously submitted information, is provided in Module 2.4 of both NDAs. The following information is from the June 2016 prescribing information for Xyzal (levocetirizine dihydrochloride) tablets and oral solution:

NONCLINICAL TOXICOLOGY section, Carcinogenesis, Mutagenesis, Impairment of Fertility:

No carcinogenicity studies have been performed with levocetirizine. However, evaluation of cetirizine carcinogenicity studies are relevant for determination of the carcinogenic potential of levocetirizine. In a 2-year carcinogenicity study, in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg

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(approximately 15 times the maximum recommended daily oral dose in adults, approximately 10 times the maximum recommended daily oral dose in children 6 to 11 years of age and approximately 15 times the maximum recommended daily oral dose in children 6 months to 5 years of age on a mg/m² basis). In a 2-year carcinogenicity study in mice, cetirizine caused an increased incidence of benign hepatic tumors in males at a dietary dose of 16 mg/kg (approximately 6 times the maximum recommended daily oral dose in adults, approximately 4 times the maximum recommended daily oral dose in children 6 to 11 years of age, and approximately 6 times the maximum recommended daily oral dose in children 6 months to 5 years of age on a mg/m² basis). No increased incidence of benign tumors was observed at a dietary dose of 4 mg/kg (approximately 2 times the maximum recommended daily oral dose in adults, equivalent to the maximum recommended daily oral dose in children 6 to 11 years of age and approximately 2 times the maximum recommended daily oral dose in children 6 months to 5 years of age on a mg/m² basis). The clinical significance of these findings during long-term use of XYZAL is not known.

Levocetirizine was not mutagenic in the Ames test, and not clastogenic in the human lymphocyte assay, the mouse lymphoma assay, and *in vivo* micronucleus test in mice.

In a fertility and general reproductive performance study in mice, cetirizine did not impair fertility at an oral dose of 64 mg/kg (approximately 25 times the recommended daily oral dose in adults on a mg/m² basis).

NONCLINICAL TOXICOLOGY section, **Animal Toxicology:**

Reproductive Toxicology Studies

In rats and rabbits, levocetirizine was not teratogenic at oral doses up to 200 and 120 mg/kg, respectively, (approximately 320 and 390, respectively, times the maximum recommended daily oral dose in adults on a mg/m² basis).

In mice, cetirizine caused retarded pup weight gain during lactation at an oral dose in dams of 96 mg/kg (approximately 40 times the maximum recommended daily oral dose in adults on a mg/m² basis).

4.4 Clinical Pharmacology

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. A clinical pharmacology summary, including cross-references to information previously submitted in the two Rx NDAs 022064 and 022157, is provided 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. A listing of the 31 Clinical Pharmacology studies summarized in Modules 2.7.1 and 2.7.2

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Search of the medical literature by this reviewer revealed 10 scientific publications containing data for 11 of these 31 clinical pharmacology studies. The footnotes located next to the Study code (e.g., A184) in the first column of this table link to the scientific publication about the study. This reviewer has added the pertinent safety information for each Clinical Pharmacology study to Table 2.

Table 2: Clinical Pharmacology Studies (n=31)

Study code Indication/ Type; Date; Country	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years) Male:Female Safety
A184 ¹¹⁴ PK PD WAF ADME SS DP; 1992; England, United Kingdom (UK)	Phase 1, randomized, double-blind, active-controlled, 3-way crossover, single-center; per sponsor, the type of study was pharmacokinetic (PK), pharmacodynamic (PD) wheal and flare (WAF), absorption, distribution, metabolism, elimination (ADME), steady state (SS) and dose proportionality (DP).	Total: 19 (18 completers; no premature discontinuations due to AEs) LCTZ 2.5 mg: 18 DEX 2.5 mg: 18 CTZ 5 mg: 19	Single dose (morning)/capsule	18-41 19M:0F No SAEs; 9 TEAEs (5 CTZ, 1 LCTZ, 3 DEX) in 7 subjects (4 CTZ, 1 LCTZ, 2 DEX) including 3 urticaria TEAEs (1 in CTZ subject; 2 in 1 DEX subject) and 1 headache TEAE (LCTZ)
A190 PD NPT; 1993-1994;	Phase 1, randomized, double-blind, active-	Total: 28 (24 completers; 1 prematurely	Single dose (morning)/capsule	20-40 9M:19F No SAEs; 1 TEAE

¹¹³ Per NDA 209089 Section 2.7.2 pg. 9 of 13, in addition to the 31 Clinical Pharmacology studies listed above in Table 2, the sponsor submitted three retrospective population PK analysis reports (i.e., A00422, A00422a and A00308), all with data from studies conducted in pediatric populations. Study A00422 was a supplemental retrospective population PK analysis from nine studies. Study A00422a was a supplemental retrospective population PK analysis that included data from 2 additional pediatric safety studies, along with the data analyzed in Study A00422. Study A00308 was a retrospective population PK analysis of levocetirizine in atopic infants treated with racemic cetirizine in the Early Treatment of the Atopic Child (ETAC™) study that provided additional information on the PK of levocetirizine in children. These three retrospective population PK analyses did not include any clinical or safety data; thus, they are not included in the above Table 2.

¹¹⁴ Devalia JL et al. A randomized, double-blind, crossover comparison among cetirizine, levocetirizine, and ucb 28557 on histamine-induced cutaneous responses in healthy adult volunteers. *Allergy*. 2001 Jan; 56 (1): 50-7.

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Study code Indication/ Type; Date; Country	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years) Male:Female Safety
Belgium	controlled, 4-way crossover, single-center; per sponsor this was a PD nasal provocation/ temperature (NPT) type study.	discontinued due to AE severe bronchitis LCTZ) LCTZ 5 mg: 28 DEX 5 mg: 28 CTZ 10 mg: 28 PBO: 28		severe bronchitis (LCTZ)
A221 ¹¹⁵ PK ADME SS DP; 1997; Germany	Phase 1, randomized, double-blind, active-controlled, 2-way crossover, open-label, single-center	Total: 24 (24 completers) LCTZ 10 mg: 24 CTZ 20 mg: 24	Single dose (morning)/ extemporaneous solution	20-55 12M:12F No SAEs; 29 TEAEs (14 LCTZ; 15 CTZ) in 15 subjects (6 LCTZ; 9 CTZ), including 8 tiredness (fatigue) TEAEs (6 LCTZ, 2 CTZ) , 3 headache TEAEs (2 LCTZ, 1 CTZ), 0 asthenia or somnolence TEAEs
A230 PK Safety; 1997-1998; Belgium & Czech Republic	Phase 1, not randomized, open-label, parallel- group, multicenter, special population study (conducted in renally impaired subjects and subjects with normal renal function)	Total: 18 (18 completers; 6 with normal renal function, 6 with mild renal impairment and 6 with moderate renal impairment) LCTZ 5 mg: 18	Single dose (morning)/ tablet	46-72 6M:12F No SAEs; 8 TEAEs in 4 subjects (4 headache TEAEs, 1 back pain TEAE, 1 nausea TEAE, 1 vomiting TEAE, 1 anemia TEAE)
A232 PK ADME SS DP; 1997-1998; France	Phase 1, randomized, open-label, 3-way crossover, single-center	Total: 24 (24 completers) LCTZ 5 mg: 24	Single dose x 3 (morning)/ tablet (for clinical trial, for marketing) and extemporaneous solution	20-55 12M:12F No SAEs; 22 TEAEs (including 4 somnolence, 3 fatigue, 2 malaise , 3 headache, 0 asthenia) in 14 subjects
A233 ¹¹⁶ PK ADME; 1997;	Phase 1, open-label, single-arm, single-center	Total: 4 (4 completers)	Single dose (morning, 2 hours after light	31-46 4M:0F No SAEs; 3 TEAEs

¹¹⁵ Baltés E et al. Absorption and disposition of levocetirizine, the eutomer of cetirizine, administered alone or as cetirizine to healthy volunteers. *Fundam Clin Pharmacol*. 2001 Aug; 15 (4); 269-77.

¹¹⁶ Benedetti MS et al. Absorption, distribution, metabolism and excretion of [¹⁴C]levocetirizine, the R enantiomer of cetirizine, in healthy volunteers. *Eur J Clin Pharmacol*. 2001 Oct; 57 (8); 571-82.

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Study code Indication/ Type; Date; Country	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years) Male:Female Safety
Scotland, UK		Radiolabeled LCTZ 5 mg: 4	breakfast)/capsule	(2 headache;1 mild rash) in 2 subjects
A234 PK; 1998; Belgium	Phase 1, not randomized, open- label, single-arm, single-center, special population study conducted in 5 end-stage anuric renal subjects on hemodialysis	Total: 5 (5 completers) LCTZ 5 mg: 5	Single dose (at end of 4-hour dialysis session, at noon)/ tablet	38-78 3M:2F No SAEs; 5 TEAEs (3 somnolence ; 1 hypotension, 1 thoracic pain) in 3 subjects
A238 PK ADME SS DP; 1998; France	Phase 1, open-label single-center, 2-part study: a) 2-way, crossover, randomized food effect (under fasting and nonfasting conditions) b) repeated dose PK at steady-state	Total: 21 (20 completers; no premature discontinuation due to AE) LCTZ 5 mg: 21	a) Single dose x 2 (morning)/ tablet b) QD (morning)/ 8 days, D11-D17, fasting condition/ tablet	20-37 10M:11F No SAEs; 28 TEAEs (including 6 fatigue , 5 somnolence , 5 anemia, 4 headache, 0 asthenia) in 16 subjects
A245 ¹¹⁷ SAR PD SSS VCC; 1999; Austria	Phase 2, randomized, double- blind, placebo and active-controlled, 3- way crossover, single-center; per sponsor, this was a PD SAR symptom scores (SSS) type of study conducted in a Vienna Challenge Chamber (VCC)	Total: 39 (35 completers; 2 premature discontinuations due to AEs, i.e., LCTZ dystonia; PBO asthma) LCTZ 5 mg: 38 LOR 10 mg: 37 PBO: 37	QD (morning; dosed at 10:00am, i.e., 2 hours after entering VCC at 8:00am)/ 2 days/ tablet (over encapsulated)	19-40 19M:20F No SAE; 3 TEAEs (1 LCTZ vegetative dystonia, 1 LCTZ bronchospasm, 1 PBO asthma bronchial) in 3 subjects
A246 Safety (over- the-road driving performance and psychomotor tests); 2000-2001; Netherlands	Phase 1, randomized, double- blind, placebo and active-controlled, 3- way crossover, single-center conducted in healthy volunteers aged 21- 40 years	Total: 51 ITT (48 completers; 3 subjects prematurely discontinued and were replaced; one premature discontinuation was due to AE “nervousness”)	QD (morning)/ 4 days in each of 3 periods/ tablet (over encapsulated)	21-30 25M:26F No SAEs; 809 TEAEs (393 TEAEs in 48 subjects during DIP treatment period; 236 TEAEs in 43 subjects during LCTZ treatment period; 180

¹¹⁷ Stubner P et al. A direct comparison of the efficacy of antihistamines in SAR and PAR: randomised, placebo-controlled studies with levocetirizine and loratadine using an environmental exposure unit – the Vienna Challenge Chamber (VCC). *Curr Med Res Opin.* 2004 Jun; 20 (6): 891-902.

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Study code Indication/ Type; Date; Country	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years) Male:Female Safety
		LCTZ 5 mg: 49 DIP 50 mg: 50 PBO: 48		TEAEs in 41 subjects during PBO treatment period) including 326 somnolence TEAEs (69 TEAEs in 32 PBO subjects, 93 TEAEs in 36 LCTZ subjects and 164 TEAEs in 46 DIP subjects), 79 fatigue TEAEs (11 TEAEs in 8 PBO subjects, 30 TEAEs in 19 LCTZ subjects and 38 TEAEs in 25 DIP subjects) and 38 asthenia TEAEs (13 TEAEs in 9 PBO subjects, 9 TEAEs in 9 LCTZ subjects and 16 TEAEs in 10 DIP subjects).
A252 ¹¹⁸ PD WAF; 1999; UK	Randomized, double-blind, placebo and active-controlled, 6-way crossover, single-center	Total: 19 (18 completers; no premature discontinuation due to AE) LCTZ 5 mg: 19 EBA 10 mg: 19 FEX 180 mg: 19 LOR 10 mg: 19 MIZ 10 mg: 19 PBO: 19	Single dose (morning; dosed from 8:55am to 10:25 am)/ tablet	19-51 19M:0F No SAEs; 33 TEAEs (including 3 LCTZ TEAEs: 1 fatigue, 1 dizziness, 1 rhinitis; 6 PBO TEAEs: 1 somnolence, 1 pruritus, 1 rash, 1 headache, 1 diarrhea, 1 anxiety)) in 25 subjects (3 LCTZ)
A254 PD CI; 1999-2000; France	Randomized, double-blind, placebo- controlled, 2-way crossover,	Total: 15 (15 completers) LCTZ 5 mg: 15	QD (morning)/ 6 days per period/ tablet	20-37 6M:9F No SAEs; 42 TEAEs in 15

¹¹⁸ Per Grant JA et al. A double-blind, randomized, single-dose, crossover comparison of levocetirizine with ebastine, fexofenadine, loratadine, mizolastine, and placebo: suppression of histamine-induced wheal-and-flare response during 24 hours in healthy male subjects. *Ann Allergy Asthma Immunol.* 2002 Feb; 88 (2); 190-7, dosing of subjects began at 9:00am with a 5-minute interval between dosing of individual subjects.

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Study code Indication/ Type; Date; Country	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years) Male:Female Safety
	single-center, PD cutaneous inflammation (CI)	PBO: 15		subjects (14 during PBO; 10 during LCTZ) including 25 pruritus TEAEs (15 pruritus TEAEs in 12 PBO subjects, 10 pruritus TEAEs in 7 LCTZ subjects); 0 fatigue, somnolence or asthenia TEAEs
A256 ¹¹⁹ SAR PD SSS VCC; 2000-2001; Austria	Phase 2, randomized, double- blind, placebo and active-controlled, 3- way crossover, single-center with subjects exposed for two consecutive days to grass pollen x 6 hours in VCC	Total: 73 (68 completers; no premature discontinuations due to AE) LCTZ 5 mg: 70 LOR 10 mg: 71 PBO: 69	Single dose (dosing occurred 2 hours after entering VCC; dosing occurred at approximately 10 am)/ tablet (over encapsulated)	19-34 34M:39F No SAEs; 7 TEAEs in 6 subjects (1 LCTZ TEAE: headache; 4 PBO TEAEs: inflicted injury, toothache, headache, laryngitis; 2 LOR TEAEs: allergic conjunctivitis, stomach pain)
A00260 PK Safety (effect on cognitive and psychometric function); 2000; France	Phase 1, randomized, double- blind, placebo and active-controlled, randomized, 3-way crossover, single- center	Total: 19 (18 completers; no premature discontinuation due to AE) LCTZ 5 mg: 18 DIP 50 mg: 19 PBO: 18	QD (morning)/ 5 days in each of the 3 periods / tablet (over encapsulated)	20-39 19M:0F No SAEs; 50 TEAEs (15 TEAEs in 8 LCTZ subjects, 15 TEAEs in 7 PBO subjects , 20 TEAEs in 9 DIP subjects) including 17 somnolence TEAEs (4 LCTZ, 6 PBO, 7 DIP), 11 asthenia TEAEs (4 LCTZ, 2 PBO, 5 DIP), 1 fatigue TEAE (1 DIP)
A00263 PK PD ADME SS DP Cardiac QTc; 2000;	Phase1, randomized, double- blind, placebo- controlled, 2-way crossover, single and	Total: 36 (36 completers) LCTZ 30 mg: 36 PBO: 36	QD dose of 5 mg tablet x 6 (morning)/ 6 days in each of 2 periods/ tablet	21-74 17M:19F No SAEs; 130 TEAEs (75 TEAEs in 27 LCTZ

¹¹⁹ Stubner P et al. A direct comparison of the efficacy of antihistamines in SAR and PAR: randomised, placebo-controlled studies with levocetirizine and loratadine using an environmental exposure unit – the Vienna Challenge Chamber (VCC). *Curr Med Res Opin.* 2004 Jun; 20 (6): 891-902.

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Study code Indication/ Type; Date; Country	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years) Male:Female Safety
Belgium	multiple dose, single-center [NOTE: Subject 018 ALT rose from 59 (screening) to 109; Subject 020 ALT rose from 42 to 210 and AST rose from 22 to 93; Subject 011 ALT rose from 44 to 124 and γ GT rose from 73 to 101.] [NOTE: no subject experienced a QTc prolongation higher than 60 ms when using within period baseline as reference.]			subjects; 55 TEAEs in 17 PBO subjects) including 23 somnolence TEAEs (20 in 13 LCTZ subjects, 3 in 3 PBO subjects), 14 fatigue TEAEs (11 in 9 LCTZ subjects, 3 in 3 PBO subjects), 3 hepatic function abnormal/ hepatic enzymes increased TEAEs in 3 LCTZ subjects, 12 skin reaction localized TEAEs (8 in 8 LCTZ subjects, 4 in 3 PBO subjects); 2 asthenia TEAEs (both in PBO subjects)
A00280 PD WAF; 2001; France	Phase 1, randomized, double-blind, placebo and active-controlled, 3-way crossover, single-center	Total: 18 (18 completers) LCTZ 5 mg: 18 DES 5 mg: 18 PBO: 18	Single dose (morning; dosed immediately after reading the baseline skin prick test and at least 2 hours prior to lunch)/ tablet (over encapsulated)	21-47 4M:14F No SAEs; 24 TEAEs (17 LCTZ; 6 DES; 1 PBO) in 16 subjects (15 under LCTZ; 6 under DES; 1 under PBO): 16 somnolence TEAEs (13 in 13 LCTZ subjects, 3 in 3 DES subjects), 4 fatigue TEAEs (2 in 2 LCTZ subjects, 2 in 2 DES subjects), 3 headache TEAEs (2 in 2 LCTZ subjects, 1 in 1 PBO subject); 0 asthenia TEAEs
A00297 PK; 2001;	Phase 1, randomized, open-label, 2-way	Total: 24 (23 completers; 1 premature	Single dose (morning)/ tablet and oral	18-55 12M:12F No SAEs; 13

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Study code Indication/ Type; Date; Country	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years) Male:Female Safety
Germany	crossover, single-center	discontinuation due to AE “psychic instability” LCTZ 5 mg (tablet): 24 LCTZ 5 mg (oral drops=5 mg/mL): 24	drops	TEAEs (8 TEAEs tablet; 5 TEAEs oral drops) in 3 oral drops and 6 tablet subjects; TEAEs: 5 headache, 2 fatigue (1 solution; 1 tablet), 2 dizziness, 1 muscle pain, 1 bone pain, 1 skeletal pain, 1 emotional lability, 0 somnolence, asthenia TEAEs
A00305 PD NPT; 2002; Germany	Phase 4: Part A (10 subjects) exploratory histamine dose; Part B (18 subjects) randomized, double-blind, placebo and active-controlled, 3-way crossover, single-center	Total: 19 (9 completed Parts A and B; 1 discontinued after Part A; 9 only completed Part B; no premature discontinuations due to AE) LCTZ 5 mg: 18 DES 5 mg: 18 PBO: 18	No drug administered in Part A of study; Single dose administered in each of the 3 periods in Part B (dose administered between 9:30 am to 2:30 pm)/ tablet (over encapsulated)	22-43 18M:0F No SAEs; 1 TEAE in Part B (headache PBO)
A00318 PK BE; 2002; Belgium (CSR located in Original NDA 022157)	Phase 1, randomized, single center, open-label, 2-way crossover, single-center [NOTE: supported the bioequivalence (BE) of 10 mL of the 0.5 mg/ml Xyzal oral solution with the Xyzal 5 mg oral tablet ¹²⁰].	Total: 24 (24 completers) LCTZ 5 mg (tablet): 24 LCTZ 5 mg (oral solution= 0.5 mg/mL): 24	Single dose (morning at 8 am)/ tablet and oral solution	19-54 12M:12F No SAEs; 51 TEAEs (27 solution; 24 tablet) in 16 subjects (15 with tablet; 15 with solution), including 17 somnolence TEAEs (8 LCTZ solution, 9 LCTZ tablet), 15 headache TEAEs (9 LCTZ solution, 6 LCTZ tablet), 0 asthenia or fatigue TEAEs
A00324 SAR PD SSS VCC;	Phase 4, randomized, double-blind, placebo and	Total: 94 (85 completers; four premature	Single dose (afternoon at 3:00 pm on Day 1 in	18-44 38M:56F No SAEs;

¹²⁰ NDA 209089, Section 2.7.1, pg. 7 of 9.

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Study code Indication/ Type; Date; Country	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years) Male:Female Safety
2002; Austria	active-controlled, 3-way crossover, single-center study with subjects exposed to grass pollen for 2 consecutive days (4 and 6 hours, respectively) in VCC	discontinuations due to AEs (1 PBO sinusitis, 2 PBO and 1 LCTZ nasopharyngitis, i.e., “common cold”) LCTZ 5 mg: 87 FEX 120 mg: 91 PBO: 91	each study period)/ tablet (over encapsulated)	13 TEAEs (4 PBO, 5 LCTZ, 4 FEXO) in 12 subjects (4 PBO TEAEs abdominal pain upper, sinusitis, headache, nasopharyngitis; 5 LCTZ TEAEs nausea, headache, dysmenorrhea, nasopharyngitis, pharyngitis; 4 FEX TEAEs skin fungal infection, headache, bronchospasm, nasopharyngitis)
A00331 ¹²¹ SAR PD SSS EEU; 2002; Canada	Phase 3b, randomized, double-blind, parallel, placebo and active-controlled, single center conducted with subjects exposed to pollen challenge in an environmental exposure unit (EEU)	Total: 373 randomized (362 completers; 3 discontinued prematurely due to AE: 1 DES URI, 1 DES headache. 1 PBO nausea) LCTZ 5 mg: 141 DES 5 mg: 140 PBO: 92	Single dose x 2 (one dose in Period I and one dose in Period III, both morning, 10 am)/ tablet (over encapsulated)	16-74 164M:209F No SAEs; 168 subjects (59 LCTZ, 68 DES, 41 PBO) with 258 TEAEs (87 LCTZ TEAEs) including 13 fatigue TEAEs (4 LCTZ, 7 DES, 2 PBO), 7 somnolence TEAEs (4 LCTZ, 2 DES, 1 PBO), 0 asthenia TEAEs
A00340 ^{a, 122} PK (198 pg. CSR located in NDA 209089); 2003; India	Phase 1, randomized, open-label, 2-way crossover, single-center	Total: 12 (12 completers) LCTZ 5 mg (India): 12 LCTZ 5 mg (Europe):12	Single dose (morning, at 8 am)/ tablet	25-33 12M:0F No SAEs; No AEs
A00351	Phase 4,	Total: 30 (29	Single dose	22-51

¹²¹ Day JH et al. Comparative clinical efficacy, onset and duration of action of levocetirizine and desloratadine for symptoms of seasonal allergic rhinitis in subjects evaluated in the Environmental Exposure unit (EEU). *Int J Clin Pract.* 2004 Feb; 58 (2): 109-18.

¹²² Usharani P et al. Randomized, double-blind, crossover comparison between two levocetirizine formulations on histamine-induced cutaneous response in healthy male human adult volunteers. *J Appl Res.* 2005; 5 (1): 149-59.

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Study code Indication/ Type; Date; Country	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years) Male:Female Safety
PD NPT; 2003; Germany	randomized, double-blind, placebo and active-controlled, 3-way crossover, single-center	completers; 1 prematurely discontinued due to AE acute rhinitis after period 2 FEX) LCTZ 5 mg: 30 FEX 180 mg: 30 PBO: 29	(morning, at least one hour after last food intake)/ tablet (over encapsulated)	30M:0F No SAEs; 4 TEAEs (2 URI both LCTZ, 1 fatigue LCTZ , 1 rhinitis FEX) in 3 subjects (2 LCTZ, 1 FEX)
A00373 PD WAF SSS; 2004-2005; France	Phase 1, randomized, double-blind, placebo and active-controlled, 3-way crossover, single-center	Total: 18 (18 completers) LCTZ 5 mg: 18 DES 5 mg: 18 PBO: 18	Single dose (morning approximately between 7 am and 9 am)/ tablet	18-48 9M:9F No SAEs; 12 TEAEs (1 LCTZ; 5 DES; 6 PBO) in 9 subjects (1 LCTZ, 4 PBO, 4 DES) including 6 TEAEs headache (3 DES, 3 PBO); no TEAEs somnolence, fatigue or asthenia
A00379 SAR PD SSS EEU; 2004; Canada	Phase 3b, randomized, double-blind, double-dummy, placebo and active-controlled, parallel-group, single-center in subjects exposed to ragweed pollen challenge in EEU	Total: 570 (563 completers; 5 prematurely discontinued with AE: 1 PBO (pruritus/ urticaria/ eye irritation), 2 LCTZ (1 exhaustion/sore throat; 1 migraine), 2 CTZ (1 productive cough; 1 sinus headache/ shortness of breath, anxiety/ expiratory wheeze/ dry mouth) LCTZ 5 mg: 240 CTZ 10 mg: 235 PBO: 95	Single dose (morning, at 11 am)/ tablet	16-69 233M:237F No SAEs; 133 TEAEs (44 LCTZ; 64 CTZ; 25 PBO) in 93 subjects (35 LCTZ; 43 CTZ; 15 PBO) including 31 headache TEAEs (7 PBO, 12 LCTZ, 12 CTZ) 11 fatigue TEAEs (2 PBO, 5 LCTZ, 4 CTZ), 5 somnolence TEAEs (1 PBO, 4 CTZ); 0 asthenia TEAEs
A00380 PD IT; 2004; Germany (study discontinued due to technical	Phase 4, randomized, 3-way crossover, double-blind, double dummy, placebo-controlled; per sponsor, study type was PD infrared	Total 53 (35 completers; 1 prematurely discontinued due to AE (severe migraine); 17 did not complete study due to camera	Single dose (dosing at various times throughout morning and afternoon/ tablet	19-42 53M:0F No SAEs; 24 TEAEs (9 PBO, 6 LCTZ, 9 CTZ) in 18 subjects including 5 headache TEAEs

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Study code Indication/ Type; Date; Country	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years) Male:Female Safety
problems with thermography camera)	thermography (IT).	failure) LCTZ 5 mg: 44 CTZ 10 mg: 45 PBO: 43		(2 CTZ, 3 LCTZ), 2 somnolence TEAEs (1 CTZ, 1 PBO), 1 fatigue TEAE (PBO), 0 asthenia TEAEs
A00412 SAR PD SSS EEU; 2006; Canada	Phase 2, randomized, double-blind, double-dummy, active-controlled, placebo-controlled, parallel-group, single-center in subjects exposed to ragweed pollen in EEU	Total: 551 (546 completers; 3 subjects prematurely discontinued due to AEs: 1 syncope vasovagal CTZ 10 mg, 1 conjunctivitis/ rhinorrhea LCTZ 5 mg, 1 fatigue PBO). [NOTE: AE leading to discontinuation in PBO subject occurred before treatment] LCTZ 2.5 mg (oral drops=5 mg/mL) 116 LCTZ 5 mg (tablet):119 CTZ 5 mg (oral drops=10 mg/mL): 119 CTZ 10 mg (tablet): 119 PBO: 78	Single dose (morning, at 11 am)/ tablet and oral drops	16-71 239M:312F No SAEs; 65 TEAEs (5 PBO, 18 LCTZ 2.5 mg, 13 LCTZ 5 mg, 16 CTZ 5 mg, 13 CTZ 10 mg) in 44 subjects (5 PBO, 10 LCTZ 2.5 mg, 9 LCTZ 5 mg, 13 CTZ 5 mg, 7 CTZ 10 mg) including 7 TEAEs headache (2 LCTZ 2.5 mg, 1 CTZ 5 mg, 2 CTZ 10 mg, 2 PBO), 3 TEAEs fatigue (2 LCTZ 5 mg, 1 CTZ 10 mg), 3 TEAEs somnolence (1 LCTZ 2.5 mg, 1 LCTZ 5 mg, 1 CTZ 10 mg), 3 TEAEs rash (3 LCTZ 2.5 mg), 0 asthenia TEAEs
A00414 ¹²³ SAR Efficacy EEU; 2006; Canada	Phase 3, therapeutic confirmative, randomized, double-blind, active-controlled, placebo-controlled, 3-arm, parallel-group, single-center in subjects exposed to ragweed pollen in EEU	Total: 418 ITT (411 completers; 4 prematurely discontinued due to AEs: 1 URI PBO, 1 URI LCTZ, 1 vomiting/nausea/ diarrhea MONT, 1 bacterial conjunctivitis MONT)	QD (morning, at 11 am)/ 2 days/ tablet (over encapsulated)	18-72 168M:250F No SAEs; 50 TEAEs (10 PBO, 16 LCTZ, 24 MONT) in 40 subjects (9 PBO, 13 LCTZ, 18 MONT) including 7 headache TEAEs (2 PBO, 5 MONT), 6 urticaria TEAEs

¹²³ Day JH et al. Efficacy of levocetirizine compared with montelukast in subjects with ragweed-induced seasonal allergic rhinitis in the environmental exposure unit. *Allergy Asthma Proc.* 2008 May-Jun; 29 (3): 304-12.

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Study code Indication/ Type; Date; Country	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years) Male:Female Safety
		LCTZ 5 mg: 157 MONT 10 mg: 156 PBO: 105		(1 PBO, 1 LCTZ, 4 MONT), 4 nausea TEAEs (3 MONT, 1 LTCZ), 3 somnolence TEAE (2 LCTZ, 1 MONT) 3 fatigue TEAEs (3 LCTZ), 0 asthenia TEAEs
A00415 ¹²⁴ SAR Efficacy EEC; 2006; Canada	Phase 3, therapeutic confirmatory, randomized, double-blind, active-controlled, 3-arm, placebo-controlled, parallel-group, single-center in subjects exposed to ragweed pollen in Environmental Exposure Chamber (EEC)	Total: 403 ITT (396 completers; 4 premature discontinuations due to AEs: 1 nasopharyngitis/diarrhea PBO, 2 dyspnea MONT, 1 MONT rash). NOTE: one MONT premature discontinuation due to AE dyspnea occurred pretreatment.] LCTZ 5 mg: 152 MONT 10 mg: 149 PBO: 102	QD (morning, at 11 am)/ 2 days/ tablet (over encapsulated)	18-77 168M:235F No SAEs; 94 TEAEs (33 PBO, 35 LCTZ, 26 MONT) in 63 subjects (20 PBO, 24 LCTZ, 19 MONT) including 13 TEAE headache (5 PBO, 4 LCTZ, 4 MONT), 8 TEAE abdominal pain (2 PBO, 4 LCTZ, 2 MONT); 6 TEAE fatigue (3 PBO, 3 LCTZ) , 5 TEAE rash (1 PBO, 1 LCTZ, 3 MONT), 2 TEAE somnolence (1 LCTZ, 1 MONT) , 0 asthenia TEAEs
A00419 ¹²⁵ PK PD Cardiac QTc; 2006; Belgium (CSR in NDA 022064 120 day safety update submitted 11/21/06)	Randomized, 4-way crossover, placebo- and moxifloxacin controlled study of effect of LCTZ on cardiac repolarization	Total: 52 ITT (52 completers; NOTE: 2 different subjects experienced isolated episode of non-sustained ventricular tachycardia during Holter session after more than 12 hours during 1 st treatment period ; 1 after treatment with	Single dose (morning, at 8am)/ tablet	18-46 28M:24F No SAEs; 83 TEAEs (18 LCTZ 5 mg; 28 LCTZ 30 mg; 17 PBO; 20 MOX) in 37 subjects (13 LCTZ 5 mg, 22 LCTZ 30 mg, 12 PBO, 13 MOX) including 17 somnolence TEAE

¹²⁴ Patel P, Patel D. Efficacy comparison of levocetirizine vs montelukast in ragweed sensitized patients. *Ann Allergy Asthma Immunol.* 2008 Sep; 101 (3): 287-94.

¹²⁵ Hulhoven R et al. Levocetirizine does not prolong the QT/QTc interval in healthy subjects; results from a thorough QT study. *Eur J Clin Pharmacol.* 2007 Nov; 63 (11): 1011-7.

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Study code Indication/ Type; Date; Country	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years) Male:Female Safety
		LCTZ 5 mg, 1 after treatment with LCTX 30 mg) LCTZ 5 mg (double-blind): 52 LCTZ 30 mg (double-blind): 52 MOX 400 mg (open-label): 52 PBO (double-blind): 52		(7 LCTZ 5 mg, 10 LCTZ 30 mg), 15 headache TEAE (4 LCTZ 5 mg, 2 LCTZ 30 mg, 3 MOX, 6 PBO); 10 TEAE fatigue (1 LCTZ 5 mg, 6 LCTZ 30 mg, 1 MOX, 2 PBO), 0 asthenia TEAEs
A00428 PK Safety; 2007; China	Phase 1, randomized, open-label, 2-way cross-over, single center	Total: 24 (23 completers; no premature discontinuations due to AEs) LCTZ 5 mg (tablet): 24 LCTZ 5 mg (oral drops= 5 mg/mL): 24	Single dose (morning)/ tablet and oral drops	21-39 24M:0F No SAEs; 2 TEAEs (1 diarrhea, 1 eczema) reported by 2 subjects, i.e., eczema (oral drops), diarrhea (tablet)

Source: NDA 209089 ISS pg. 18-20 of 163, with additional information from sponsor documents submitted to NDAs 209089, 022064 and 022157 for these studies added by the primary reviewer.

[NOTE: Adverse event information was manually abstracted by the primary reviewer from the sponsor submitted clinical study reports, clinical study synopses, clinical study summaries and clinical study protocols. Sponsor included two studies, i.e., A00414 (SAR/Efficacy) and A00415 (SAR/Efficacy) in their table of Clinical Pharmacology Studies that are listed in NDA 209089 under Section 5.3.5.1 as Controlled Clinical Studies; however, neither contained any PK or PD data (per search by this reviewer of both final study reports). Because each of these two studies involved administering a maximum of two doses of assigned treatment to each subject and involved testing in either an EEC or EEU, this reviewer accepts the sponsor’s decision to list these two studies in their table of Clinical Pharmacology studies.]

Abbreviations: ADME: absorption, distribution, metabolism, elimination; CI: cutaneous inflammation; CSR: Clinical Study Report; CTZ: cetirizine; DES: desloratadine; DEX: dextrocetirizine (ucb 28557); DIP: diphenhydramine; DP: dose proportionality; EBA: ebastine; EEC: environmental exposure chamber; EEU: environmental exposure unit; FEX: fexofenadine; IT: infrared thermography; LCTZ: levocetirizine (ucb 28556); LOR: loratadine; MIZ: mizolastine; MONT: montelukast; MOX: moxifloxacin; NPT: nasal provocation/temperature; PAR: perennial allergic rhinitis; PBO: placebo; QD: once a day; PD: pharmacodynamic; PK: pharmacokinetic; QTc: corrected QT interval; SAR: seasonal allergic rhinitis; SS: steady state; SSS: SAR Symptom Score; VCC: Vienna Challenge Chamber; WAF: wheal and flare
Strengths: Oral drops LCTZ = 5 mg/mL; Oral drops CTZ = 10 mg/mL; Oral solution LCTZ = 0.5 mg/mL (2.5 mg/5 mL)

a Data from Study A00340 is not included in the pool of Clinical Pharmacology studies due to unavailability of the clinical database for this study. An individual study summary of A00340 is presented separately in the ISS, Section 5.15 of NDA 209089.

b. While the sponsor included active comparators in several PK studies¹²⁶ and Phase 2-3-4 Clinical studies¹²⁷, no efficacy or safety claims based upon these comparisons have been permitted in the Xyzal Prescribing Information.

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The following information (located below in Sections 4.4.1, 4.4.2 and 4.4.3) is from the June 2016 prescribing information for Xyzal (levocetirizine dihydrochloride) tablets and oral solution:

4.4.1 Mechanism of Action

Levocetirizine, the active enantiomer of cetirizine, is an antihistamine; its principal effects are mediated via selective inhibition of H₁ receptors. The antihistaminic activity of levocetirizine has been documented in a variety of animal and human models. *In vitro* binding studies revealed that levocetirizine has an affinity for the human H₁-receptor 2-fold higher than that of cetirizine (K_i = 3 nmol/L vs. 6 nmol/L, respectively). The clinical relevance of this finding is unknown.

4.4.2 Pharmacodynamics (PD)

Studies in adult healthy subjects showed that levocetirizine at doses of 2.5 mg and 5 mg inhibited the skin wheal and flare caused by the intradermal injection of histamine. In contrast, dexroctirizine exhibited no clear change in the inhibition of the wheal and flare reaction. Levocetirizine at a dose of 5 mg inhibited the wheal and flare caused by intradermal injection of histamine in 14 pediatric subjects (aged 6 to 11 years) and the activity persisted for at least 24 hours. The clinical relevance of histamine wheal skin testing is unknown.

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 cetirizine and the long post-marketing history of cetirizine without significant reports of QT prolongation.

4.4.3 Pharmacokinetics (PK)

Levocetirizine exhibited linear pharmacokinetics over the therapeutic dose range in adult healthy subjects.

Absorption

¹²⁶ e.g., in A184, comparing LCTZ 2.5 mg to DEX 2.5 mg and CTZ 5 mg; in A190, comparing LCTZ 5 mg to DEX 5 mg and CTZ 10 mg; in A221, comparing LCTZ 10 mg to CTZ 20 mg; in A245, comparing LCTZ 5 mg to LOR 10 mg; in A246, comparing LCTZ 5 mg to DIP 50 mg; in A252 comparing LCTZ 5 mg to EBA 10 mg, FEX 180 mg, LOR 10 mg and MIZ 10 mg; and in A00260, comparing LCTZ 5 mg to DIP 50 mg.

¹²⁷ e.g., in A222, comparing LCTZ 5 mg to CTZ 10 mg; in A00299, A00334, A00348 and A00349, comparing LCTZ 5 mg to LOR 10 mg; and in A00391, A00394 and A00401 comparing LCTZ 5 mg to DES 5 mg, with only two of these clinical studies including a placebo comparator.

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

A dose of 5 mg (10 mL) of XYZAL oral solution is bioequivalent to a 5 mg dose of XYZAL tablets. Following oral administration of a 5 mg dose of XYZAL oral solution to healthy adult subjects, the mean peak plasma concentrations were achieved approximately 0.5 hour post-dose.

Distribution

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

Metabolism

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

Elimination

The plasma half-life in adult healthy subjects was about 8 to 9 hours after administration of oral tablets and oral solution, and the mean oral total body clearance for levocetirizine was approximately 0.63 mL/kg/min. The major route of excretion of levocetirizine and its metabolites is via urine, accounting for a mean of 85.4% of the dose. Excretion via feces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion. Renal clearance of levocetirizine correlates with that of creatinine clearance. In patients with renal impairment the clearance of levocetirizine is reduced [see *Dosage and Administration* (2.3)].

Drug Interaction Studies

In vitro data on metabolite interaction indicate that levocetirizine is unlikely to produce, or be subject to metabolic interactions. Levocetirizine at concentrations well above C_{max} level achieved within the therapeutic dose ranges is not an inhibitor of CYP isoenzymes

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1A2, 2C9, 2C19, 2A1, 2D6, 2E1, and 3A4, and is not an inducer of UGT1A or CYP isoenzymes 1A2, 2C9 and 3A4.

No formal *in vivo* drug interaction studies have been performed with levocetirizine. Studies have been performed with the racemic cetirizine [see *Drug Interactions* (7)].

Pediatric Patients

Data from a pediatric pharmacokinetic study with oral administration of a single dose of 5 mg levocetirizine in 14 children age 6 to 11 years with body weight ranging between 20 and 40 kg show that C_{max} and AUC values are about 2-fold greater than that reported in healthy adult subjects in a cross-study comparison. The mean C_{max} was 450 ng/mL, occurring at a mean time of 1.2 hours, weight-normalized, total body clearance was 30% greater, and the elimination half-life 24% shorter in this pediatric population than in adults.

Dedicated pharmacokinetic studies have not been conducted in pediatric patients younger than 6 years of age. A retrospective population pharmacokinetic analysis was conducted in 323 subjects (181 children 1 to 5 years of age, 18 children 6 to 11 years of age, and 124 adults 18 to 55 years of age) who received single or multiple doses of levocetirizine ranging from 1.25 mg to 30 mg. Data generated from this analysis indicated that administration of 1.25 mg once daily to children 6 months to 5 years of age results in plasma concentrations similar to those of adults receiving 5 mg once daily.

Geriatric Patients

Limited pharmacokinetic data are available in elderly subjects. Following once daily repeat oral administration of 30 mg levocetirizine for 6 days in 9 elderly subjects (65–74 years of age), the total body clearance was approximately 33% lower compared to that in younger adults. The disposition of racemic cetirizine has been shown to be dependent on renal function rather than on age. This finding would also be applicable for levocetirizine, as levocetirizine and cetirizine are both predominantly excreted in urine. Therefore, the XYZAL dose should be adjusted in accordance with renal function in elderly patients [see *Dosage and Administration* (2)].

Gender

Pharmacokinetic results for 77 patients (40 men, 37 women) were evaluated for potential effect of gender. The half-life was slightly shorter in women (7.08 ± 1.72 hr) than in men (8.62 ± 1.84 hr); however, the body weight-adjusted oral clearance in women (0.67 ± 0.16 mL/min/kg) appears to be comparable to that in men (0.59 ± 0.12 mL/min/kg). The same daily doses and dosing intervals are applicable for men and women with normal renal function.

Race

The effect of race on levocetirizine has not been studied. As levocetirizine is primarily renally excreted, and there are no important racial differences in creatinine clearance, pharmacokinetic characteristics of levocetirizine are not expected to be different across

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racemic cetirizine have been observed.

Renal Impairment

Levocetirizine exposure (AUC) exhibited 1.8-, 3.2-, 4.3-, and 5.7-fold increase in mild, moderate, severe, renal impaired, and end-stage renal disease patients, respectively, compared to healthy subjects. The corresponding increases of half-life estimates were 1.4-, 2.0-, 2.9-, and 4-fold, respectively.

The total body clearance of levocetirizine after oral dosing was correlated to the creatinine clearance and was progressively reduced based on severity of renal impairment. Therefore, it is recommended to adjust the dose and dosing intervals of levocetirizine based on creatinine clearance in patients with mild, moderate, or severe renal impairment. In end-stage renal disease patients ($CL_{CR} < 10$ mL/min) levocetirizine is contraindicated. The amount of levocetirizine removed during a standard 4-hour hemodialysis procedure was <10%.

The dosage of XYZAL should be reduced in patients with mild renal impairment. Both the dosage and frequency of administration should be reduced in patients with moderate or severe renal impairment [see *Dosage and Administration (2.4)*].

Hepatic Impairment

XYZAL has not been studied in patients with hepatic impairment. The non-renal clearance (indicative of hepatic contribution) was found to constitute about 28% of the total body clearance in healthy adult subjects after oral administration.

As levocetirizine is mainly excreted unchanged by the kidney, it is unlikely that the clearance of levocetirizine is significantly decreased in patients with solely hepatic impairment [see *Dosage and Administration (2)*].

5 Sources of Clinical Data

No new clinical studies were conducted by the sponsor to support the two NDA applications under review. IN the current submission under review, the safety data from 59 of the 62 studies conducted by UCB were integrated into one pooled safety database consisting of 11991 safety evaluable subjects.¹²⁸ Two studies (i.e., Studies A00340 and A00410) were excluded from the pooled safety database because their clinical databases were not available and only limited safety data (where available) was integrated into the pooled safety data for Study A00420, because it was a Phase 4, postmarketing, non-interventional retrospective observational study. The Integrated Review of Safety supporting the approval of NDA 022064 for LCTZ tablet included data from 54 clinical studies¹²⁹ (44 of which had been pooled for analysis).¹³⁰ The Integrated

¹²⁸ Per NDA 209089 Section 2.7.4 Summary of Clinical Safety (Allergic Rhinitis) pg. 12 of 65.

¹²⁹ The **27 Clinical Pharmacology** studies A184, A190, A221, A230, A232, A233, A234, A238, A245, A246, A252, A254, A256, A00260, A00263, A00280, A00297, A00305, A00318, A00324, A00331,

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Review of Safety supporting the approval of NDA 022157 for LCTZ oral solution included data from one additional clinical study (A00318).¹³¹ The Integrated Review of Safety supporting the approval of efficacy supplement-17 submitted to NDA 022157 on 2/25/09 for LCTZ tablet and efficacy supplement-3 to NDA 022157 for LCTZ oral solution included data from two additional clinical studies, A00423 and A00426.¹³² The remaining five studies included in the currently submitted polled safety database were the three Clinical Pharmacology Studies A00414, A00415, and A00428 and the two Clinical Studies A00430 and A00431.

The clinical data utilized in this review include summaries of efficacy and safety data from clinical trials conducted to support the approval of the original Rx levocetirizine applications: NDAs 022064 (Xyzal tablet) and 022157 (Xyzal oral solution) and worldwide postmarketing safety data. The ISS information for the two levocetirizine products submitted by the sponsor is essentially identical. The sponsor refers to their approved Rx applications for information on chemistry, nonclinical, human pharmacokinetics and bioavailability.

5.1 Tables of Studies/Clinical Trials

Table 3: Categorization of Study Groups (n=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, A00340 ^{a b} , A00351, A00373, A00379, A00380, A00412 ^b , A00414 ^b , A00415 ^b , A00419 ^b , A00428 ^b
Studies in special populations (n=2)	A230, A234
Phase 2-3-4 studies in adults 12 years old and older (n=22)	
	A217, A219, A222, A00265, A00266, A00268, A00269, A00270, A00299,

A00340, A00351, A00373, A00379, A00380, A00412 and the **27 Clinical studies** A217, A219, A222, A00264, A00265, A00266, A00268, A00269, A00270, A00299, A00303, A00304, A00306, A00309, A00315, A00333, A00334, A00348, A00349, A00384, A00385, A00391, A00392, A00394, A00401, A00410, A00419.

¹³⁰ NDA 022064 Levocetirizine Dihydrochloride Tablet Clinical Review by Robert M. Boucher, MD, MPH finalized in DARRTS on 4/3/07 on pg. 51-52.

¹³¹ NDA 022157 Levocetirizine Dihydrochloride Oral Solution Clinical Review by Robert M. Boucher, MD, MPH finalized in DARRTS on 10/8/09 on pg. 11.

¹³² NDA 022064 S017 Levocetirizine Dihydrochloride Tablet Clinical Review by Xuemeng Han Sarro, MD finalized in DARRTS on 5/5/09 on pg. 9.

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Study group	Study numbers
Short-term studies (≤ 12 weeks; n=19)	A00333, A00334, A00348, A00349, A00391 ^b , A00394 ^b , A00401 ^b , A00410 ^{a b} , A00430 ^b , A00431 ^b ,
Long-term studies (4-18 months; n=3)	A00264, A00306, A00392 ^b
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, A00423 ^b , A00426 ^b
Long-term studies (4-18 months; n=2)	A00309 ^b , A00384 ^b
Other studies (n=1)	
Non-interventional, retrospective data collection study in children 2 to 12 years of age	A00420 ^{b c}
Special groups (subset of studies listed above) (n=12)	
Dose ranging studies (n=4)	A217, A219, A00265, A00270
Special CTZ Comparison studies (n=8)	A184, A190, A221, A222, A00379, A00380, A00410 ^{a b} , A00412 ^b

Source: NDA 20989 ISS pg. 14 of 163.

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.

Search of the medical literature by this reviewer revealed eight scientific publications containing data for six of the following 22 Phase 2-3-4 clinical studies in adults/adolescents ≥ 12 years of age. The footnotes located next to the Study code (e.g., A217) in the first column of this table link to the scientific publication about the study. This reviewer has added the pertinent safety information for each Clinical study to Tables 4 and 5.

Table 4: Phase 2-3-4 Studies in Adults/Adolescents Aged ≥ 12 Years (n=22)

Study code/ Indication/ Type	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years)/ Male:Female
Short-term studies (≤ 12 weeks treatment duration; n=19)				
A217 ¹³³ SAR Efficacy; 1996; France, Germany	Phase 2, 4- arm, dose ranging, randomized, double-blind, placebo- controlled, parallel group,	Total: 470 ITT [405 completers; 8 prematurely discontinued due to AEs: 3 PBO (1 coughing, 1 asthenia, 1 pruritus/ nausea/ psychophysiologic disorder), 2 LCTZ 5 mg (1 pregnancy, 1 headache); 3	QD (evening)/ 2 weeks/ tablet	17-72 235M:235F No deaths, 1 SAE (LCTZ 10 mg elevated LFTs/overdosage- took 10 tablets within 7 days); 271

¹³³ Leynadier F et al. Efficacy and safety of levocetirizine in seasonal allergic rhinitis. *Acta Otorhinolaryngol Belg.* 2001; 55 (4): 305-12.

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Study code/ Indication/ Type	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years)/ Male:Female
	multicenter	<p>LCTZ 10 mg (3 somnolence)]</p> <p>LCTZ 2.5 mg: 117 LCTZ 5 mg: 116 LCTZ 10 mg:118 PBO: 119</p> <p>[NOTE: no safety information was located in study report for TEAEs; only available safety information was for AEs.]</p>		<p>AEs (70 PBO, 56 LCTZ 2.5 mg, 51 LCTZ 5 mg, 94 LCTZ 10 mg) in 164 subjects (39 PBO, 35 LCTZ 2.5 mg, 37 LCTZ 5 mg, 53 LCTZ 10 mg) including 48 AE headache (19 PBO, 8 LCTZ 2.5 mg, 10 LCTZ 5 mg, 11 LCTZ 10 mg), 17 AE somnolence (3 LCTZ 2.5 mg, 2 LCTZ 5 mg, 12 LCTZ 10 mg), 16 AEs fatigue (2 PBO, 1 LCTZ 2.5 mg, 6 LCTZ 5 mg, 7 LCTZ 10 mg), 11 AEs increased LFT (2 PBO, 3 LCTZ 2.5 mg, 2 LCTZ 5 mg, 4 LCTZ 10 mg) and 7 AEs asthenia (3 PBO, 1 LCTZ 2.5 mg, 1 LCTZ 5 mg, 2 LCTZ 10 mg)</p>
A219 PAR Efficacy; 1996-1997; France	Phase 2, 4- arm, randomized, double-blind, placebo- controlled, parallel group, multicenter	<p>Total: 421 ITT [386 completers; 7 prematurely discontinued due to AEs (2 PBO: 1 somnolence, 1 myalgia/ abdominal pain/back pain/gastritis/ laryngitis; 2 LCTZ 2.5 mg: 1 asthma , 1 somnolence/ gastroenteritis; 2 LCTZ 5 mg: 1 cholecystitis, 1 malaise/elevated hepatic enzyme; 1 LCTZ 10 mg sciatic nerve palsy)]</p> <p>LCTZ 2.5 mg: 105 LCTZ 5 mg: 103 LCTZ 10 mg: 109 PBO: 104</p>	QD (evening)/ 4 weeks/ tablet	<p>12-66 205M:216F No deaths, 1 SAE (LCTZ 5 mg hospitalized cholecystitis) 270 TEAEs (62 PBO, 71 LCTZ 2.5 mg, 66 LCTZ 5 mg, 71 LCTZ 10 mg) in 173 subjects (42 PBO, 47 LCTZ 2.5 mg, 40 LCTZ 5 mg; 44 LCTZ 10 mg) including 36 headache TEAEs (9 PBO, 10 LCTZ 2.5 mg, 10 LCTZ 5 mg, 7 LCTZ 10 mg) ; 28 rhinitis TEAEs (2 PBO, 11 LCTZ 2.5 mg, 11 LCTZ 5 mg, 4 LCTZ 10 mg), 15</p>

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Study code/ Indication/ Type	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years)/ Male:Female
				<p>somnolence TEAEs (1 PBO, 7 LCTZ 2.5 mg, 4 LCTZ 5 mg, 3 LCTZ 10 mg), 6 asthenia TEAEs (1 PBO, 1 LCTZ 2.5 mg, 4 LCTZ 10 mg) and 2 fatigue (1 PBO, 1 LCTZ 5 mg)</p>
<p>A222 SAR Efficacy; 1997; France</p>	<p>Phase 3, 3-arm, randomized, double-blind, placebo and active-controlled, parallel group, multicenter</p>	<p>Total: 797 ITT [763 completers; 5 prematurely discontinued due to AEs: 1 PBO asthma, 2 LCTZ (1 asthma, 1 heartburn), 2 CTZ (1 elevated bilirubin, 1 asthenia)]</p> <p>LCTZ 5 mg: 319 CTZ 10 mg: 318 PBO: 160</p>	<p>QD (evening)/ 1 week/ tablet</p>	<p>12-66 401M:396F No SAEs; 797 TEAEs (160 PBO, 319 LCTZ, 318 CTZ) in 242 subjects (49 PBO, 96 LCTZ, 97 CTZ) including 69 TEAEs headache (11 PBO, 25 LCTZ, 33 CTZ), 53 somnolence TEAEs (5 PBO, 28 LCTZ, 20 CTZ); 20 abnormal LFTs TEAEs (4 PBO, 7 LCTZ, 9 CTZ- including one “jaundice”); 18 asthenia TEAEs (3 PBO, 7 LCTZ, 8 CTZ); 11 fatigue TEAEs (1 PBO, 8 LCTZ, 2 CTZ)</p>
<p>A00265 PAR Efficacy; 2000-2001; France, Germany</p>	<p>Phase 2, therapeutic exploratory, 3-arm, randomized, double-blind, placebo-controlled, parallel group, multicenter</p>	<p>Total: 519 ITT [482 completers; 13 premature discontinuations due to AEs (5 PBO: 1 rhinopharyngitis/ cough, 1 otitis media, 1 bronchitis, 1 fainting, 1 tachyarrhythmia/left bundle branch block; 4 LCTZ 2.5 mg: 2 somnolence, 1 pharyngitis, 1 metrorrhagia resulting in hysterectomy; 2 LCTZ 5 mg: 1 somnolence, 1 tiredness; 2 LCTZ 10 mg: 2 somnolence)]</p>	<p>QD (evening)/ 4 weeks/ tablet</p>	<p>12-74 206M:313F No deaths; 3 SAEs (1 LCTZ appendicitis, 2 PBO: 1 tachyarrhythmia/ left bundle branch block, 1 left ureter lithiasis); 507 TEAEs (168 PBO, 183 LCTZ 2.5 mg, 165 LCTZ 5 mg, 159 LCTZ 10 mg) reported in 254 subjects; including 64 headache TEAEs (14 PBO, 19 LCTZ 2.5 mg, 13 LCTZ 5</p>

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Study code/ Indication/ Type	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years)/ Male:Female
		LCTZ 2.5 mg: 133 LCTZ 5 mg: 128 LCTZ 10 mg: 130 PBO: 128		mg, 18 LCTZ 10 mg); 47 pharyngitis TEAEs (15 PBO, 16 LCTZ 2.5 mg, 8 LCTZ 5 mg, 8 LCTZ 10 mg), 28 somnolence TEAEs (2 PBO, 7 LCTZ 2.5, 7 LCTZ 5 mg), 12 LCTZ 10), 25 fatigue TEAEs (8 PBO, 3 LCTZ 2.5 mg, 11 LCTZ 5 mg, 3 LCTZ 10 mg), 10 asthenia TEAEs (4 LCTZ 2.5 mg, 1 LCTZ 5 mg, 5 LCTZ 10 mg)
A00266 ¹³⁴ PAR Efficacy; 2000; South Africa	Phase 3, 2- arm, randomized, double-blind, placebo- controlled, parallel group, multicenter	Total: 294 ITT (276 completers; 2 premature discontinuations due to AEs, both PBO: 1 URI/ bronchospasm, 1 nausea/pruritus/ shortness of breath/ dizziness) LCTZ 5 mg: 150 PBO: 144	QD (bedtime)/ 6 weeks/ tablet	12-71 126M:168F No deaths; 3 SAEs (all PBO : 1 torsion ovarian cyst, 1 cholecystitis, 1 pregnancy- termination); 772 TEAEs (338 PBO; 384 LCTZ) in 188 subjects (98 PBO, 90 LCTZ) including 165 headache TEAEs (79 PBO, 86 LCTZ), 13 somnolence TEAEs (4 PBO, 9 LCTZ), 11 fatigue TEAEs (4 PBO, 7 LCTZ), 2 rash TEAEs (2 LCTZ) and 1 asthenia TEAE (1 LCTZ)
A00268 SAR Efficacy; 2000-2001; South Africa	Phase 3, 2- arm, randomized, double-blind, placebo- controlled,	Total: 236 ITT [232 completers; 2 prematurely discontinued due to AE : 1 PBO (severe headache), 1 LCTZ (severe somnolence)]	QD (evening)/ 2 weeks/ tablet	12-71 89M:147F No deaths, 1 SAE (hospitalized for infected sebaceous cyst; PBO during

¹³⁴ Potter PC et al. Levocetirizine is effective for symptom relief including nasal congestion in adolescent and adult (PAR) sensitized to house dust mites. *Allergy*. 2003 Sep; 58 (9): 893-9.

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Study code/ Indication/ Type	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years)/ Male:Female
	parallel group, multicenter	LCTZ 5 mg: 119 PBO: 117		pretreatment); 289 TEAEs (126 PBO; 163 LCTZ) in 112 subjects (52 PBO; 60 LCTZ) including 56 headache TEAEs (29 PBO, 27 LCTZ); 8 somnolence TEAEs (1 PBO, 7 LCTZ); 7 fatigue TEAEs (3 PBO; 4 LCTZ); 0 asthenia
A00269 CIU Efficacy; 2001; Germany, Switzerland	Phase 3, 2- arm, randomized, double-blind, placebo- controlled, parallel group, multicenter	Total: 166 ITT (124 completers; no premature discontinuations due to AEs) LCTZ 5 mg: 81 PBO: 85	QD (evening)/ 4 weeks/ tablet	18-79 68M:98F No deaths; 1 SAE (larynx edema, pretreatment PBO); 138 TEAEs (49 PBO; 89 LCTZ) reported in 53 subjects (22 PBO, 31 LTCZ) including 15 headache TEAEs (4 PBO, 11 LCTZ); 11 fatigue TEAEs (1 PBO, 10 LCTZ); 2 asthenia TEAEs (1 PBO, 1 LTCZ), 0 somnolence
A00270 CIU Efficacy; 2001-2002; France	Phase 2, dose ranging, 4- arm, randomized, double-blind, placebo- controlled, parallel group, multicenter	Total: 257 ITT (202 completers; 10 premature discontinuations due to AEs : 2 PBO: 1 angioedema, 1 dizziness; 2 LCTZ 2.5 mg: 1 pregnancy unintended , 1 photosensitivity reaction; 1 LCTZ 5 mg: ankle fracture; 5 LCTZ 10 mg: 2 somnolence , 1 agitation, 1 insomnia, 1 pregnancy unintended) LCTZ 2.5 mg: 70 LCTZ 5 mg: 65 LCTZ 10 mg: 59 PBO: 63	QD (evening)/ 4 weeks/ tablet	18-85 71M:186F No deaths; 4 SAEs (2 PBO: 1 worsening urticaria, 1 angioedema; 1 LCTZ 5 mg: ankle fracture; 1 LCTZ 10 mg: peritonitis); 344 TEAEs (81 PBO, 71 LCTZ 2.5 mg, 92 LCTZ 5 mg, 100 LCTZ 10 mg) in 130 subjects (30 PBO, 30 LCTZ 2.5 mg, 39 LCTZ 5 mg, 31 LCTZ 10 mg) including 32 headache TEAEs (8 PBO, 6 LCTZ 2.5 mg, 9 LCTZ 5 mg, 9 LCTZ

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Study code/ Indication/ Type	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years)/ Male:Female
				10 mg), 27 somnolence TEAEs (3 PBO, 5 LCTZ 2.5 mg, 8 LCTZ 5 mg, 11 LCTZ 10 mg); 6 fatigue TEAEs (1 PBO, 4 LCTZ 5 mg, 1 LCTZ 10 mg), 5 asthenia TEAEs (5 LCTZ 10 mg)
A00299 PAR Efficacy; 2001-2002; Taiwan	Randomized, double-blind, active-controlled, parallel group, single center (no phase listed)	Total: 62 ITT (57 completers; 1 LOR premature discontinuation due to 2 AEs: dizziness, alopecia) LCTZ 5 mg: 30 LOR 10 mg: 32	QD ("bedtime")/ 2 weeks/ tablet (both identically encapsulated)	18-58 11M:51F No SAEs; 29 TEAEs (12 LCTZ, 17 LOR) in 20 subjects (7 LCTZ, 13 LOR) including 5 dry mouth TEAEs (4 LOR, 1 LCTZ), 4 rhinitis TEAEs (2 LCTZ, 2 LOR), 4 somnolence TEAEs (4 LOR, 0 LCTZ); 0 fatigue or asthenia TEAEs
A00333 PAR Efficacy; 2002-2003; France	Phase 4, randomized, double-blind, placebo-controlled, parallel group, multicenter	Total: 453 ITT [368 completers; 16 subjects prematurely discontinued due to AEs: 10 LCTZ (1 somnolence/asthenia, 1 somnolence/headache, 2 somnolence, 1 headache, 1 pruritus, 1 rhinitis/pharyngolaryngeal pain, 1 pharyngitis/nasal congestion, 1 abdominal pain, 1 influenza); 6 PBO (1 somnolence, 1 pruritus, 1 migraine/ insomnia/ irritability, 1 urinary tract infection, 1 sinusitis, 1 nasopharyngitis)] LCTZ 5 mg: 226 PBO: 227	QD (evening)/ 30 days/ tablet	12-79 167M:286F No deaths; Two SAEs (1 LCTZ cranial impact; 1 PBO retrosternal thoracic pain); 292 TEAEs (127 PBO; 165 LCTZ) in 179 subjects (85 PBO; 94 LCTZ) including 48 TEAEs headache (20 PBO, 28 LCTZ), 20 somnolence TEAEs (2 PBO, 18 LCTZ), 9 asthenia TEAEs (3 PBO, 6 LCTZ), 7 fatigue TEAEs (1 PBO, 6 LCTZ)
A00334 CIU Efficacy; 2003-2004; China (no CSR)	Phase 3, randomized, investigator-blind, active-controlled,	Total: 134 [124 completers; one subject prematurely discontinued due to AE (LCTZ); no information located re: specific AE	QD (morning)/ 2 weeks/ tablet	18-58 47M:87F No SAEs; 27 TEAEs (21 LCTZ, 6 LOR) in 17

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Study code/ Indication/ Type	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years)/ Male:Female
available; 53-pg submission to NDA 209089 on 9/16/16 contained 1-pg title page, 6-pg synopsis, 1-pg table of contents; 2-pg clinical study summary and 43-pg protocol)	parallel-group, multicenter	resulting in the premature discontinuation due to AE] LCTZ 5 mg: 67 LOR 10 mg: 67		subjects (12 LCTZ, 5 LOR); 6 subjects reported at least one TEAE “nervous system disorders” (4 LCTZ, 2 LOR) and 5 subjects reported at least one TEAE “gastrointestinal disorders” (4 LCTZ, 1 LOR) [NOTE: No additional safety data was located.]
A00348 SAR Efficacy; 2003; China (no CSR available; 59-pg submission to NDA 209089 on 9/16/16 contained 1-pg title page, 6-pg synopsis, 1-pg table of contents, 2-pg clinical study summary and 49-pg protocol)	Phase 3, randomized, investigator-blind, active-controlled, parallel-group, multicenter	Total: 67 [66 completers; one subject prematurely discontinued due to AE (LCTZ; pregnancy)] LCTZ 5 mg: 34 LOR 10 mg: 33	QD (morning)/ 2 weeks/ tablet	18-60 40M:27F No SAEs; 15 TEAEs (10 LCTZ; 5 LOR) in 9 subjects (7 LCTZ; 2 LOR); 4 subjects reported at least one TEAE “nervous system disorders” (3 LCTZ, 1 LOR), 3 subjects reported TEAE “gastrointestinal disorders” (2 LCTZ, 1 LOR), 2 subjects reported TEAE “infections and infestations” (2 LCTZ) [NOTE: No additional safety data was located.]
A00349 PAR Efficacy; 2003-2004; China (no CSR available; 64-pg submission to NDA 209089 on 9/16/16 contained 1-pg title page, 6-pg	Phase 3, randomized, investigator-blind, active-controlled, parallel-group, multicenter	Total: 71 (66 completers; no premature discontinuation due to AE) LCTZ 5 mg: 35 LOR 10 mg: 36	QD (morning)/ 2 weeks/ tablet	17-60 28M:43F No SAEs; 14 AEs (7 LCTZ, 7 LOR) in 9 subjects (7 LCTZ, 2 LOR); 6 subjects reported at least one TEAE “nervous system disorders” (4 LCTZ, 2 LOR) [NOTE: No additional safety data was located.]

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Study code/ Indication/ Type	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years)/ Male:Female
synopsis, 1- pg table of contents, 2-pg clinical study summary and 54-pg protocol)				
A00391 SAR Efficacy; 2005; Germany	Phase 4, exploratory, randomized, double-blind, active- controlled, parallel group, single center, with a switch to other treatment allowed after first week of treatment (i.e., switch could occur at Visit 3)	Total: 200 ITT (196 completers; no premature discontinuation due to AE) LCTZ 5 mg: 100 DES 5 mg: 100	QD (morning)/ 3 weeks/ tablet	19-66 103M:97F No deaths; 1 pretreatment SAE (joint ligament rupture); 193 TEAEs (85 DES; 108 LCTZ) in 115 subjects (51 when treated with DES, 64 when treated with LCTZ); 80 TEAE headache (32 DES, 48 LCTZ), 29 TEAE fatigue (13 DES, 16 LCTZ); 10 of the 12 LCTZ subjects who opted to switch to DES due to side effects had fatigue , while 3 of the 4 DES subjects who opted to switch to LCTZ due to side effects had fatigue; 0 somnolence or asthenia TEAEs
A00394 CIU Efficacy; 2005-2007; 7 countries (135 sites) in Europe, South Africa and UK	Phase 4, randomized, double-blind, active- controlled, parallel group, multicenter	Total: 886 ITT (832 completers; 7 premature discontinuations due to AEs (4 LCTZ: 1 somnolence, 1 dizziness , 2 urticaria; 3 DES: 2 urticaria, 1 diabetes mellitus) LCTZ 5 mg:438 DES 5 mg: 448	QD (morning)/ 4 weeks/ tablet (over encapsulated)	18-81 296M:590F One death (DES); 2 SAEs (1 diabetes- DES; 1 myocardial infarction resulting in death-DES) 541 TEAEs (284 LCTZ; 257 DES) in 279 subjects (148 LCTZ; 131 DES) including 99 headache TEAEs (41 LCTZ; 58 DES) in 83 subjects (35 LCTZ,

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Study code/ Indication/ Type	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years)/ Male:Female
				48 DES), 53 somnolence TEAEs (36 LCTZ, 17 DES) in 45 subjects (31 LCTZ, 14 DES), 33 fatigue TEAEs (19 LCTZ, 14 DES) in 33 subjects with TEAE (19 LCTZ, 14 DES), 4 asthenia TEAEs (2 LCTZ; 2 DES) in 4 subjects (2 LCTZ; 2 DES)
A00401 AR Efficacy; 2005; France, Italy, Germany	Phase 4, randomized 4:4:1, double- blind, placebo and active- controlled, parallel group, multicenter	Total: 765 ITT (705 completers; 7 prematurely discontinued due to AEs , i.e., 3 DES (1 gastroenteritis, 1 dyspnea, 1 rhinitis); 4 LCTZ (1 somnolence , 1 pruritus, 1 tachycardia/ high blood pressure, 1 rhinitis) [NOTE: DES premature discontinuation due to gastroenteritis occurred in pre-treatment period] LCTZ 5 mg: 342 DES 5 mg: 335 PBO: 88	QD (morning)/ 2 weeks/ tablet (over encapsulated)	18-77 334M:431F No deaths, 1 SAE (hospitalized tachycardia/high blood pressure LCTZ); 197 TEAEs (12 PBO, 93 LCTZ, 92 DES) in 142 subjects (11 PBO, 67 LCTZ, 64 DES) including 71 headache TEAE (7 PBO, 23 LCTZ; 41 DES), 21 somnolence TEAE (13 LCTZ; 8 DES), 15 fatigue TEAE (7 LCTZ, 8 DES), 10 asthenia TEAE (8 LCTZ; 2 DES)
A00410a Atopic Dermatitis Eczema Efficacy; 2005-2006; Korea	Phase 3, randomized, double-blind, double- dummy, active- controlled, parallel group, multicenter (with placebo- run in for 3 days after screening); all subjects used standard	Total: 464 ITT (423 completers; safety group=423; modified ITT for efficacy=340 due to study drug packing error that excluded 99 subjects from efficacy analysis; 3 premature discontinuations due to AE all CTZ: 1 urticaria, 1 pruritus, 1 rhinitis) LCTZ 5 mg: 231 CTZ 10 mg: 233	QD (bedtime)/ 2 weeks/ tablet [NOTE: for first 3 days after screening, all subjects were administered before bedtime: 1) placebo for Xyzal, 2) placebo for Zyrtec, and 3) standard topical steroid] 1%	15-69 107M:233F No deaths; 1 SAE (acute leukemia LCTZ) In the safety cohort, 37 TEAEs (12 LCTZ, 25 CTZ) occurred in 27 subjects (11 LCTZ; 16 CTZ) including 4 somnolence TEAEs (2 LCTZ, 2 CTZ), 3 SGOT/SGPT increase (3 CTZ), 1

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Study code/ Indication/ Type	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years)/ Male:Female
	topical steroid before bedtime during treatment phase		hydrocortisone ointment.]	rash TEAE (1 CTZ),
A00430 ^{135,136} SAR Efficacy; 2008; United States (US) [CSR located in NDA 209089 submitted 9/22/16]	Phase 4, randomized, double-blind, placebo- controlled, parallel group, multicenter	Total: 596 ITT [580 completers; 6 subjects prematurely discontinued due to AEs: 4 PBO (1 URI, 1 pharyngitis, 1 fatigue , 1 hypokalemia/depression/ delirium/ mental status changes/suicide attempt), 2 LCTZ (1 overdose study drug, 1 conjunctivitis allergic/ eye irritation/dry eye/eye redness)] LCTZ 5 mg: 301 PBO: 295	QD (evening)/ 2 weeks/ tablet	18-64 191M:405F No deaths; 2 SAEs (1 PBO suicide attempt, 1 PBO atypical noncardiac chest pain/ gastroesophageal reflux disease); 246 TEAEs (126 PBO; 120 LCTZ) in 144 subjects (72 PBO; 72 LCTZ) including 42 headache TEAEs (29 PBO; 13 LCTZ), 20 somnolence TEAE (8 PBO, 12 LCTZ), 17 fatigue TEAE (8 PBO, 9 LCTZ), 0 asthenia
A00431 ¹³⁷ SAR Efficacy; 2008; US [CSR located in NDA 209089 submitted 9/22/16]	Phase 4, randomized, double-blind, placebo- controlled, parallel group, multicenter	Total: 580 ITT [566 completers; 3 subjects prematurely discontinued due to AEs: 2 PBO (1 nasal dryness; 1 nasopharyngitis), 1 LCTZ severe cellulitis] LCTZ 5 mg: 287 PBO: 293	QD (evening)/ 2 weeks/ tablet	18-65 229M:351F No deaths; 1 SAE (LCTZ severe cellulitis); 166 TEAEs (84 PBO, 82 LCTZ) in 95 subjects (54 PBO, 41 LCTZ) including 31 headache TEAEs (16 PBO, 15 LCTZ), 5 somnolence TEAEs (3 PBO, 2 LCTZ), 5 fatigue TEAEs (5 LCTZ), 0 asthenia
Long-term studies (4-18 months treatment duration; n=3)				

¹³⁵ Segall N et al. Efficacy and safety of levocetirizine in improving symptoms and health-related quality of life in US adults with seasonal allergic rhinitis: a randomized, placebo-controlled study. *Ann Allergy Asthma Immunol.* 2010 Mar; 104 (3): 259-67.

¹³⁶ Mansfield LE et al. Study of levocetirizine in seasonal allergic rhinitis. *Curr Med Res Opin.* 2010 Jun; 26 (6): 1269-75.

¹³⁷ Gawchik S et al. Randomized, placebo-controlled, multicenter trial evaluating the effects of

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Study code/ Indication/ Type	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years)/ Male:Female
A00264 ^{138,139} PAR Efficacy; 2001-2002; Belgium, Germany, Spain, Italy, France	Phase 2, 2- arm, randomized, double-blind, placebo- controlled, parallel group, multicenter, exploratory QOL	Total: 551 ITT [421 completers; 19 prematurely discontinued treatment due to AEs (8 PBO, 11 LCTZ; including 5 LCTZ due to somnolence, 4 LCTZ and 1 PBO due to tiredness), of which 5 prematurely discontinued from the study (3 pregnancy :1 PBO, 2 LCTZ; 1 gastroenteritis PBO, 1 LCTZ somnolence)] LCTZ 5 mg: 278 PBO: 273	QD (evening)/ 6 months/ tablet	18-70 241M:310F 8 SAEs (6 LCTZ- abdominal pain, pregnancy, migraine, appendectomy x 2, car accident, 2 PBO- knee surgery, seizure); 166 subjects with at least 1 TEAE (80 PBO, 86 LCTZ); 1919 TEAEs (995 LCTZ; 924 PBO) including 177 headache TEAEs (86 PBO, 91 LCTZ), 52 fatigue TEAEs (32 LCTZ , 20 PBO), 25 somnolence TEAEs (20 LCTZ , 5 PBO), 7 asthenia TEAEs (5 LCTZ ; 2 PBO)
A00306 SAR Asthma Efficacy; 2004; France, Italy, Belgium	Phase 2, randomized, 3-arm, double- blind, placebo- controlled, parallel group, multicenter	Total: 459 ITT [391 completers; 19 discontinued prematurely due to AE (5 PBO/PBO : 1 asthma, 1 bronchitis, 1 fatigue , 1 pruritus, 1 urticaria; 9 LCTZ/LCTZ : 1 nausea/abdominal pain, 1 somnolence / depression, 1 asthenia / dry mouth, 1 rash, 2 headache, 1 sinusitis, 1 ear infection, 1 sedation ; 5 PBO/LCTZ: 1 headache, 1 asthma, 1 bronchitis, 1 depression, 1 vertigo/dyspnea)] LCTZ 5 mg /LCTZ 5 mg: 150	QD (evening)/ 8 weeks before and 8 weeks after anticipated onset of grass pollen season/ tablet	12-68 203M-256F No deaths; 3 SAEs (1 inguinal hernia LCTZ/LCTZ; 1 torsion testicular cord LCTZ/LCTZ; 1 severe asthma PBO/LCTZ with SAE reported during PBO period); 604 TEAEs (180 PBO/PBO, 217 LCTZ/LCTZ, 207 PBO/LCTZ) in 250 subjects (83 PBO/PBO, 90 LCTZ/LCTZ, 77 PBO/LCTZ) including 87 headache TEAEs

levocetirizine on symptoms, work productivity, and daytime sleepiness in US adults with seasonal allergic rhinitis. *Allergy Asthma Proc.* 2009 (Mar-Apr); 30 (2): 210.

¹³⁸ Canonica GW et al. Levocetirizine improves health-related quality of life and health status in persistent allergic rhinitis. *Respir Med.* 2006 Oct; 100 (10); 1706-15.

¹³⁹ Bachert C et al. Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis. *J Allergy Clin Immunol.* 2004 Oct; 114 (4): 838-44.

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Study code/ Indication/ Type	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years)/ Male:Female
		PBO/LCTZ 5 mg: 153 (i.e., treated with PBO weeks 1-8, then treated with LCTZ weeks 9-18) PBO/PBO: 156		(22 PBO/PBO, 30 LCTZ/LCTZ, 35 PBO/LCTZ); 21 fatigue TEAEs (6 PBO/PBO, 12 LCTZ/LCTZ, 3 PBO/LCTZ); 11 TEAEs somnolence (4 PBO/PBO, 5 LCTZ/LCTZ, 2 PBO/LCTZ); 9 asthenia TEAEs (3 PBO/PBO, 3 LCTZ/LCTZ, 3 PBO/LCTZ); 1 sedation TEAE (1 LCTZ/LCTZ)
A00392 ¹⁴⁰ PER Efficacy; 2005-2006; Italy	Phase 4, pilot, randomized, open-label, parallel group, single center	Total: 62 ITT (40 completers; one premature discontinuation due to AE (LCTZ “on demand” group somnolence) LCTZ 5 mg (continuous): 31 LCTZ 5 mg (on demand): 31	QD (continuous group dosed in morning; on demand group dosed whenever needed)/ 24 weeks/ tablet	18-68 19M:43F No SAEs; 24 TEAEs (4 LCTZ continuous; 20 LCTZ on demand) in 14 subjects (4 LCTZ continuous; 10 LCTZ on demand”) including 4 TEAE somnolence (1 continuous, 3 on demand) ; 4 TEAE headache (1 continuous, 3 on demand) , 0 fatigue or asthenia TEAEs

Source: NDA 209089 ISS pg. 15-16 of 163 with the adverse event information manually abstracted (by the primary reviewer of this document) from the submitted clinical study reports, clinical study synopses, clinical study summaries and clinical study protocols.

Abbreviations: abnl: abnormal; AR: allergic rhinitis; CIU: chronic idiopathic urticaria; CTZ: cetirizine; DES: desloratadine; LCTZ: levocetirizine; LOR: loratadine; ITT: intention-to-treat (population); LFT: liver function tests; mITT: modified intention to treat (population); PAR: perennial allergic rhinitis; PBO: placebo; PER: persistent allergic rhinitis; QD: once a day; QOL: quality of life; SAR: seasonal allergic rhinitis
a Data from Study A00410 is not included in the pool of Phase 2 to 4 studies conducted in adults/adolescents due to the unavailability of the clinical database for this study. The sponsor presented an individual study summary separately for this study in the ISS, Section 5.15 of NDA 209089.

¹⁴⁰ Canonica GW et al. Levocetirizine in persistent allergic rhinitis: continuous or on-demand use? A pilot study. *Curr Med Res Opin.* 2008 Oct; 24 (10): 2829-39.

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Search of the medical literature by this reviewer revealed seven scientific publications containing data for six of the following eight Phase 2-3-4 clinical studies conducted in children (6 months to 12 years old). The footnotes located next to the Study code (e.g., A00303) in the first column of this table link to the scientific publication about the study.

Table 5: Phase 2-3-4 Studies in Children (Aged 6 Months to 12 Years) (n=8)

Study code/ Indication/ Type	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years)/ Male:Female
Short-term studies (≤ 12 weeks treatment duration; n=6)				
A00303 ¹⁴¹ SAR Efficacy; 2002; France, Germany	Phase 4, 2-arm, randomized, double- blind, placebo- controlled, parallel group, multicenter	Total: 177 (145 completers; 1 prematurely discontinued due to AE: PBO asthma) LCTZ 5 mg: 89 PBO: 88	QD (evening)/ 6 weeks/ tablet	6-13 117M:60F No SAEs; 90 TEAEs (45 LCTZ; 45 PBO) in 57 subjects (30 LCTZ; 27 PBO); 18 headache TEAEs (13 PBO, 5 LCTZ) including 5 asthenia TEAEs (3 PBO, 2 LCTZ); 1 fatigue TEAE (LCTZ), 1 somnolence TEAE (LCTZ)
A00304 ¹⁴² PAR Efficacy; 2002; South Africa	Phase 3, randomized, 2-arm, double-blind, placebo- controlled, parallel group, multicenter	Total: 306 ITT [297 completers; 4 prematurely discontinued due to AEs: 2 PBO (1 sinusitis-bronchitis; 1 asthma aggravated) , 2 LCTZ (1 URI; 1 otitis media)] LCTZ 5 mg: 154 PBO: 152	QD (evening)/ 4 weeks/ tablet	6-13 186M:120F Two SAEs in non- randomized subjects (1 epididymitis; 1 ingestion of study medication by subject’s sister); 300 TEAEs (150 LCTZ; 150 PBO) in 165 subjects (85 LCTZ; 80 PBO) including 42 headache TEAEs (22 LCTZ; 20 PBO), 7 somnolence TEAEs 6 LCTZ; 1 PBO), 3 fatigue TEAEs (3 LCTZ), 0 asthenia TEAEs [NOTE: one 16 year old subject died accidentally after the

¹⁴¹ de Blic J et al. Levocetirizine in children: evidenced efficacy and safety in a 6-week randomized seasonal allergic rhinitis trial. *Pediatric Allergy Immunology*. 2005 May; 16 (3): 267-75.

¹⁴² Potter PC, Paediatric Levocetirizine Study Group. Efficacy and safety of levocetirizine on symptoms and health-related quality of life of children with perennial allergic rhinitis: a double-blind, placebo-controlled randomized clinical trial. *Ann Allergy Asthma Immunol*. 2005 Aug; 95 (2):175-80.

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Study code/ Indication/ Type	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years)/ Male:Female
				end of the study due to an electrocution]
A00315 ¹⁴³ Asthma PK Safety; 2001-2003; Australia, Czech Republic (CSR in NDA 022064 Efficacy Supplement submitted 2/24/09)	Phase 2, pilot, open-label, non-controlled, single-arm, multicenter study treating recurrent cough associated with other allergic symptoms, e.g., wheezing	Total: 15 ITT (one premature discontinuation due to AE: marked increase of alkaline phosphatase, i.e., 2215 IU/L) LCTZ 0.125 mg/kg (oral drops= 5 mg/mL): 15	BID/ 90 days/ oral drops	1-2 11M:4F No deaths; 1 SAE (hospitalized pneumonia); 36 TEAEs in 7 subjects, including 9 URI TEAEs in 4 subjects and 2 elevated ALP TEAEs in 2 subjects (investigator thought possibly due to benign transient hyperphosphatasemia of infancy and early childhood)
A00385 PAR SAR Safety; 2004; France (CSR in NDA 022064 Efficacy Supplement submitted 2/24/09)	Phase 2, open-label, single-arm, multicenter	Total: 30 (29 completers; no premature discontinuations due to AEs) LCTZ 1.25 mg (oral solution = 0.5 mg/mL): 30	BID (morning and evening)/ 4 weeks/ oral solution	2-6 15M:15F No SAEs; 36 TEAEs in 19 subjects (most common TEAEs were respiratory infections: 5 subjects with TEAE bronchitis, 3 subjects with TEAE pharyngitis, 4 subjects with URI) [NOTE: 1 fatigue TEAE, no somnolence or asthenia TEAEs]
A00423 ^{144,145} SAR PAR CIU Safety; 2008; USA (CSR in NDA 022064 Efficacy	Phase 3, randomized, double-blind, placebo-controlled, parallel group, multicenter	Total: 69 (65 completers; 3 subjects prematurely discontinued due to AEs (3 LCTZ subjects: 1 skin infection, 1	QD (morning)/ 2 weeks/ oral drops (5 drops = 1.25 mg)	6-11 months 39M:30F No deaths; 2 SAEs (Both LCTZ: 1 MRSA skin colonization; 1 URI with otitis media); 88 TEAEs (54 LCTZ; 34 PBO) in 46 subjects

¹⁴³ Cranswick N et al. Levocetirizine in 1-2 year old children: pharmacokinetic and pharmacodynamic profile. *Int J Clin Pharmacol Ther.* 2005 Apr; 43 (4): 172-7.

¹⁴⁴ Hampel F et al. Safety and tolerability of levocetirizine dihydrochloride in infants and children with allergic rhinitis or chronic urticaria. *Allergy Asthma Proc.* 2010 Jul-Aug; 31 (4): 290-5.

¹⁴⁵ Meloy LD et al. The safety and tolerability of levocetirizine dihydrochloride in infants 6-11 months with allergic rhinitis or chronic idiopathic urticaria. *Allergy Asthma Proc.* 2009 (Mar-Apr); 30 (2): 210.

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Study code/ Indication/ Type	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years)/ Male:Female
Supplement submitted 2/24/09)		diarrhea/rash, 1 URI) LCTZ 1.25 mg (oral drops = 5 mg/mL): 45 (treated) PBO: 24 (treated) [NOTE: above numbers include 1 subject randomized to LCTZ (who received PBO by error) in PBO group]		(29 LCTZ, 17 PBO) including 11 pyrexia TEAEs (7 LCTZ; 4 PBO), 7 diarrhea TEAEs (6 LCTZ, 1 PBO), 6 otitis media TEAEs (3 LCTZ; 3 PBO), 4 constipation TEAEs (3 LCTZ, 1 PBO) [NOTE: 3 somnolence TEAES (2 LCTZ, 1 PBO), 0 fatigue or asthenia TEAEs]
A00426 ¹⁴⁶ SAR PAR CIU Safety; 2008; USA (CSR in NDA 022064 Efficacy Supplement submitted 2/24/09)	Phase 3, randomized, double-blind, placebo- controlled, parallel group, multicenter	Total: 173 ITT (169 completers; no premature discontinuations due to AE) LCTZ 1.25 mg (oral drops = 5 mg/mL): 114 PBO: 59	BID (morning and evening)/ 2 weeks/ oral drops	1-5 101M:72F No deaths; 1 SAE (LCTZ pyrexia); 103 TEAEs (60 LCTZ; 43 PBO) in 61 subjects (40 LCTZ, 21 PBO) including 6 pyrexia TEAEs (5 LCTZ, 1 PBO), 3 somnolence TEAEs (1 LCTZ, 2 PBO), 2 fatigue TEAEs (1 LCTZ, 1 PBO), 0 asthenia TEAEs
Long-term studies (4-18 months treatment duration; n=2)				
A00309 ¹⁴⁷ Asthma Efficacy Safety; 2002-2006; 12 countries in Europe, Australia, UK and South Africa (87 sites) [CSR located in NDA 022064	Phase 3, 1:1 randomized, 2-arm, double-blind, placebo- controlled, parallel group, multicenter	Total: 510 ITT (434 completers; 9 premature discontinuations, due to AEs: 6 LCTZ: 2 hypersensitivity, 1 SAE severe weight gain, 1 SAE tonsillitis, 1 SAE acute leukemia, 1 failure to thrive; 3 PBO: 1 varicella, 1 atopic dermatitis, 1 hepatic enzyme	BID (morning and evening)/ 18 months/ oral drops (dosed at 0.125 mg/kg body weight twice daily)	12-26 months 319M:195F No deaths; 131 SAEs in 68 subjects (37 PBO, 31 LCTZ) with most common treatment- emergent SAE category "respiratory, thoracic and mediastinal disorders" in 19 PBO subjects and 12 LCTZ subjects; 4893 AEs reported (2422 PBO; 2471

¹⁴⁶ Hampel F et al. Safety and tolerability of levocetirizine dihydrochloride in infants and children with allergic rhinitis or chronic urticaria. *Allergy Asthma Proc.* 2010 Jul-Aug; 31 (4): 290-5.

¹⁴⁷ Simons FE. Safety of levocetirizine treatment in young atopic children: an 18-month study. *Pediatr Allergy Immunol.* 2007 Sep; 18 (6): 535-42.

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Study code/ Indication/ Type	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years)/ Male:Female
Supplement-17 Efficacy submitted 2/25/09]		increased) LCTZ 0.125 mg/kg (oral drops = 5 mg/mL): 255 PBO: 255		LCTZ) in 491 subjects (244 PBO; 247 LCTZ); most TEAEs were attributed to “infections and infestations” (479 subjects), “gastrointestinal disorders” (210 subjects) and “respiratory, thoracic and mediastinal disorders” (193 subjects) including 5 malaise TEAEs (3 LCTZ; 2 PBO), 1 somnolence TEAE (PBO); 0 asthenia TEAE; 0 fatigue TEAE
A00384 Asthma Efficacy Safety; 2004-2006; 10 countries in Europe Australia, UK and South Africa (54 sites) [CSR located in NDA 022064 Supplement-17 Efficacy submitted 2/25/09]	Phase 3, randomized, double-blind, placebo-controlled, parallel group, multicenter (prolongation of Study A00309 at sites having randomized at least 2 subjects in Study A00309)	Total: 207 (21 completers; 186 prematurely discontinued, of which, 3 were due to AEs: 1 LCTZ-LCTZ rhinitis allergic, 1 LCTZ-PBO hypersensitivity, 1 PBO-PBO worsening dermatitis atopic) LCTZ-LCTZ ¹⁴⁸ : 59 LCTZ-PBO ¹⁴⁹ : 47 PBO-PBO ¹⁵⁰ : 101 (LCTZ dosed 0.125 mg/kg BID; oral drops = 5 mg/mL)	BID (morning and evening)/ 18 months [NOTE: study initiated June 2004; study discontinued January 2006 (last subject completed March 2006) because primary efficacy endpoint was not met in predecessor study A00309]/ oral drops	29-45 months 121M:86F No deaths; 18 SAEs in 11 subjects (3 PBO-PBO: 1 gastroenteritis, 1 bronchopneumonia/atelectasis, 1 dyspnea/wheezing; 3 LCTZ-PBO: 1 vomiting/urticaria, 1 pneumonia, 1 femur fracture; 5 LCTZ-LCTZ: 3 wheezing, 1 dermatitis atopic, 1 strangulated inguinal hernia); 1005 TEAEs (458 TEAEs in 81 PBO-PBO subjects; 243 TEAEs in 38 LCTZ-PBO subjects; 304 TEAEs in 53 LCTZ-LCTZ subjects); most common system organ class “infections and infestations” TEAEs were reported in 154 subjects (73 PBO-PBO,

¹⁴⁸ LCTZ-LCTZ treatment group was allocated to LCTZ in both Study A00309 and Study A00384.

¹⁴⁹ LCTZ-PBO treatment group was allocated to LCTZ in Study A00309 and PBO in Study A00384.

¹⁵⁰ PBO-PBO treatment group was allocated to PBO in both Study A00309 and Study A00384.

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Study code/ Indication/ Type	Study design	Treatment group: N subjects (ITT)	Treatment regimen/ Duration/ Formulation	Age range (years)/ Male:Female
				35 LCTZ-PBO, 46 LCTZ-LCTZ) [NOTE: no somnolence, fatigue or asthenia TEAEs]

Source: NDA 209089 ISS pg.17 of 163 with the adverse event information manually abstracted (by the primary reviewer of this document) from the submitted clinical study reports, clinical study synopses, clinical study summaries and clinical study protocols.

Abbreviations: BID: twice a day; CIU: chronic idiopathic urticaria; LCTZ: levocetirizine m-ITT: modified intention-to-treat population; PAR: perennial allergic rhinitis; PBO: placebo; QD: once a day; SAR: seasonal allergic rhinitis.

Strength: Oral drops LCTZ = 5 mg/mL; Oral solution LCTZ = 0.5 mg/mL (2.5 mg/5 mL)

5.2 Review Strategy

Submissions SDN2, SDN9, SDN10 and SDN 11 to NDA 209089 have been reviewed in detail. Submissions to NDA 209090 do not provide any additional clinical information and simply refer the reviewer back to the relevant NDA 209089 submissions. The cut-off date for data included in the sponsor's clinical studies summaries was October 31, 2015. The sponsor's Summary of Clinical Safety (SCS) includes the safety information obtained from the 62 clinical studies conducted by UCB with levocetirizine formulations in the range from 1.25 mg/day to 30 mg/day.¹⁵¹ Complete Study Reports or Synopses for all 62 of these clinical studies to support the Rx-to-OTC switch of levocetirizine have been previously submitted for review by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). It has been previously determined that these two drug products are safe and effective as prescription drugs for their respective indications. The efficacy of the two Rx-to-OTC switch NDAs will be evaluated by DPARP.

This review will evaluate the safety of levocetirizine for OTC use, focusing primarily on the new information accumulated since the initial approval of the Xyzal oral tablet NDA 022064 in 2007 and include an analysis of all postmarketing serious adverse events (SAEs), including information from:

- UCB's Drug Safety Database
- FDA Adverse Event Reporting System (FAERS)

¹⁵¹ Cross comparison was made by this reviewer between the 62 clinical studies included in the sponsor's SCS and the 26 studies listed at ClinicalTrials.gov with "UCB Pharma" as sponsor. One of these 26 studies at ClinicalTrials.gov was not included in the 62 studies included in the sponsor's SCS (i.e., NCT00598780 = **A00421** "Long-term Evaluation of Safety and Treatment Satisfaction With Levocetirizine in Routine Clinical Practice in the Czech and Slovak Republics - Non-interventional Study"; completed 9/07; n=7870 patients). This reviewer accepts deletion of this study from the sponsor's SCS because it was a non-interventional study. This reviewer notes that UCB sponsored an additional non-interventional study conducted in 7272 patients treated with an oral antihistamine in nine European countries [see De Vos C et al. Non-interventional study comparing treatment satisfaction in patients treated with antihistamines. *Clin Drug Investig.* 2008; 28 (4): 221-30.]

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- World Health Organization (WHO) VigiBase
- National Poison Data System (NPDS) from the American Association of Poison Control Centers (AAPCC)
- Drug Abuse Warning Network (DAWN)
- Medical literature

An Interdisciplinary Scientist (IDS) reviewer from the Division of Nonprescription Drug Products (DNPD) will be reviewing the OTC label in detail.

5.3 Discussion of Individual Studies/Clinical Trials

Per NDA 209089 Section 2.7.4 Summary of Clinical Safety (Allergic Rhinitis) pg. 12 of 65, the safety data from 59 of the 62 studies conducted by UCB are integrated into one pooled safety database consisting of 11991 safety evaluable subjects. Two studies (i.e., Studies A00340 and A00410) were excluded from the pooled safety database because their clinical databases were not available. Only limited data was integrated for Study A00420 because it was a non-interventional, retrospective, observational study that collected data on antihistamine treatment satisfaction. Safety data summaries from the individual clinical study reports (CSRs) for Studies A00340, A00410, and A00420 are presented separately in the ISS, Section 5.15 of NDA 209089.

Per NDA 209089 Section 2.7.4 Summary of Clinical Safety (Allergic Rhinitis) pg. 11 of 65, all 62 clinical study reports (complete study reports or synopses) were previously submitted as part of NDA 022064 (for 5 mg tablets), NDA 022157 (for oral solution), the pediatric supplements to both NDAs, 120-day safety updates, IND 072233 (Phase 4 studies), or annual reports. Among the 62 studies conducted in UCB's clinical program, 44 studies were previously pooled for the prescription NDA 022064 oral tablet registration.

Per the request of this reviewer, the sponsor submitted additional Final Clinical Study Reports and additional clinical study information to NDA 209089, as follows:

- On 9/16/16 in SDN 10, the sponsor submitted Final Clinical Study Reports for nine clinical pharmacology studies (i.e., A00245, A00252, A00256, A00280, A00305, A00324, A00331, A00351, and A00373) and one clinical study (A00299) and all available information for the clinical studies A00334, A00348, and A00349, which included synopses, clinical study summaries and protocols along with amendments.
- On 9/22/16 in SDN 11, the sponsor submitted Final Clinical Study Reports for two clinical studies A00430 and A00431.

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6 Review of Efficacy

Efficacy Summary

No new indications are being proposed for these two single-ingredient levocetirizine products; therefore, no additional clinical efficacy studies were submitted in these two applications. Data from clinical studies submitted in the two Rx NDAs were referenced to support the efficacy of levocetirizine in the treatment of symptoms of allergic rhinitis.

DNNDP defers to Division of Pulmonary, Allergy, and Rheumatology Products (DPAAP) for the review and conclusions pertaining to the efficacy of these two drug products. See the Clinical efficacy Review from the DPAAP.

7 Review of Safety

Safety Summary

The sponsor has conducted 62 clinical studies in a total of 11991 safety evaluable subjects [6685 took at least one dose of levocetirizine (at doses ranging from 1.25 mg to 30 mg daily), 3963 subjects took at least one dose of placebo and 2808 subjects took at least one dose of an active comparator]. A total of 232 subjects were exposed to levocetirizine for at least 365 days and 247 subjects were exposed to placebo for at least 365 days. It should be noted that safety data were analyzed according to the treatment actually received. Only four subjects were identified as receiving treatment that differed from the randomized treatment.

7.1 Methods

This review evaluates the safety of levocetirizine for OTC use, including an analysis of safety information and all known postmarketing adverse events (AEs) and serious adverse events (SAEs) obtained from:

- UCB's safety data from all of their 62 levocetirizine dihydrochloride clinical studies up to the cut-off date October 31, 2015, including those clinical studies conducted for the chronic idiopathic urticaria (CIU) indication¹⁵²
- UCB's internal pharmacovigilance database¹⁵³
- FDA Adverse Event Reporting System (FAERS)¹⁵⁴

¹⁵² The safety data from all of UCB's 62 levocetirizine dihydrochloride clinical studies were submitted in Original NDA 209089. No UCB levocetirizine clinical studies were initiated, ongoing or completed during the time period covered by the 120 Day Safety Report, i.e., from November 1, 2015 through March 31, 2016.

¹⁵³ The results of an accumulative search of UCB's internal pharmacovigilance database containing spontaneously reported safety data through the cut-off data of October 31, 2015 were submitted in Original NDA 209089 in the ISS. The results of a second search of this internal pharmacovigilance database covering the time period of November 1, 2015 to March 31, 2016 were submitted to NDA 209089 in the 120 Day Safety Update on July 29, 2016.

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- World Health Organization (WHO) VigiBase from 2001 to June 2015¹⁵⁵
- National Poison Data System (NPDS) from the American Association of Poison Control Centers (AAPCC) from 2007 through 2015¹⁵⁶
- Drug Abuse Warning Network (DAWN) from 2007 through 2011¹⁵⁷
- Medical literature¹⁵⁸

Specifically regarding information from the medical literature, the sponsor submitted a 108-page "ISS - Tabular summary of medical literature" pertaining to levocetirizine in Original NDA 209089 Section 5.3.5.3. The summaries of the 283 literature references contained in this document were reviewed, 65 of these literature references were determined by this reviewer to be potentially relevant to the safety of levocetirizine and all 65 of these references were obtained, reviewed in detail and included in the reference listing located in Section 9.1 of this review. The 78 literature references provided in Original NDA 209089 Section 5.4 were reviewed, 41 of these literature references were determined by this reviewer to be potentially relevant to the safety of levocetirizine and all 41 of these references were obtained, reviewed in detail and included in the reference listing located in Section 9.1 of this review. A separate PubMed search of "levocetirizine" was conducted by this reviewer and of the 348 listed references, six additional literature references were considered by this reviewer to be potentially relevant to the safety of levocetirizine and all six of these references were obtained, reviewed in detail and included in the reference listing located in Section 9.1 of this review. In addition, a separate EMBASE search of "levocetirizine AND safety" was conducted by this reviewer and of the 340 listed references, five additional literature references were considered by this reviewer to be potentially relevant to the

¹⁵⁴ The results of accumulative search of adverse events reported in the FDA FAERS database through the cut-off date of December 2014 (through 2014Q4) were submitted in Original NDA 0209089 in the ISS. The results of a second search of this database covering the time period of 2015Q1 to 2015Q4 were submitted to NDA 209089 as the 120 Day Safety Update on July 29, 2016.

¹⁵⁵ The results of a search of adverse events reported in the WHO Vigibase database from of 2001 (i.e., when levocetirizine was first approved, in Germany and Spain) to April 2015 (second quarter of 2015, i.e., 2015Q2) were submitted in Original NDA 0209089 in the ISS. The results of a second search of this database covering the time period of 2015Q3 to 2016Q1 were submitted to NDA 209089 as the 120 Day Safety Update on July 29, 2016.

¹⁵⁶ The results of a search of adverse events reported in the NPDS database from 2007 (i.e., when levocetirizine was first approved in the US) to 2015 were submitted in Original NDA 0209089 in the ISS. The results of a second search of this database covering the time period of October 1, 2015 to April 1, 2016 were submitted to NDA 209089 as the 120 Day Safety Update on July 29, 2016.

¹⁵⁷ DAWN collected US hospital emergency room data through the end of the calendar year 2011; however, Xyzal (levocetirizine) was first approved in the US on May 25, 2007. Thus, the results of a search of the DAWN database pertaining to levocetirizine covering the time period of 2007 through the closing of this network at the end of the calendar year 2011 were submitted in Original NDA 0209089 in the ISS.

¹⁵⁸ The results of a literature review up to a cut-off data of October 31, 2015 were submitted in Original NDA 0209089 in the ISS. The results of a second search of the medical literature covering the time period of November 1, 2015 to March 31, 2016 were submitted to NDA 209089 as the 120 Day Safety Update on July 29, 2016.

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safety of levocetirizine and all five of these references were obtained, reviewed in detail and included in the reference listing located in Section 9.1 of this review.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The cut-off date for data included in the sponsor's clinical studies summaries was October 31, 2015. The sponsor's Summary of Clinical Safety (SCS) includes the safety information obtained from the 62 clinical studies conducted by UCB with levocetirizine formulations in the range from 1.25 mg/day to 30 mg/day. Complete Study Reports (n=49) or Synopses (n=13) for all 62 of these clinical studies to support the Rx-to-OTC switch of levocetirizine have been previously submitted for review by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). It has been previously determined that these two drug products are safe and effective as prescription drugs for their respective indications.

Reviewer's comments:

- 1. On September 1, 2016, a clinical information request was sent to the sponsor requesting final clinical study reports (CSRs) for the 13 (of the 62) studies with only a synopsis available. Specifically, final study reports were requested for nine clinical pharmacology studies (i.e., A245, A252, A256, A00280, A00305, A00324, A00331, A00351 and A00373) and four clinical studies (i.e., A00299, A00334, A00348 and A00349). On September 16, 2016, the sponsor submitted final CSRs for all nine of the requested clinical pharmacology studies and for the clinical study A00299. In the cover letter, the sponsor stated that Studies A00334, A00348 and A00349 were clinical studies conducted in China in 2003 and 2004 for local registration purposes and full study reports were not available for these three studies. However, the sponsor submitted all available information for these three studies consisting of synopses, clinical study summaries and protocols (along with amendments). All of the CSRs and additional clinical information submitted by the sponsor was reviewed and pertinent details pertaining to study design and safety abstracted from these documents were added to Tables 2, 4, and 5 in this review.*
- 2. On September 16, 2016, a clinical information request was sent to the sponsor requesting final CSRs for two clinical studies (i.e., A00430 and A00431) that were apparently omitted from their submission. On September 22, 2016, the sponsor submitted final CSRs for these two clinical studies and they were reviewed. Pertinent details pertaining to study design and safety of these two clinical studies were added to Table 4 in this review.*

7.1.2 Categorization of Adverse Events

Per the sponsor, adverse events were collected at every visit by asking subjects if they noticed anything unusual about their health since the last visit.¹⁵⁹ Pre-treatment and

¹⁵⁹ NDA 029089 SCS Section 2.1.2.3.

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treatment-emergent adverse events (TEAEs) were defined as AEs that developed or worsened during the screening and TEAE periods, respectively. If an AE date of onset (occurrence, worsening, or becoming serious) was incomplete, an imputation algorithm was used to classify the AE as pre-treatment or treatment-emergent.

Serious adverse events were all AEs that fulfilled at least one of the following International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) seriousness criteria, irrespective of whether or not they were considered treatment-emergent or their causal relationship with the drug product:

- Resulted in death
- Was life threatening (an immediate risk of death)
- Resulted in persistent or significant disability/incapacity (any severe or long-lasting inability to carry out normal work or normal activities)
- Required in-patient hospitalization or prolongation of existing hospitalization
- Was a congenital anomaly/birth defect (in a child of a subject who took the study investigational product, especially of a mother who was pregnant during the study)
- Was an important medical event that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety data from 59 of the 62 studies conducted by UCB are integrated into one pooled safety database.¹⁶⁰ Safety data summaries from the three excluded individual clinical study reports (CSRs) for Studies A00340, A00410, and A00420 are presented separately by the sponsor in the ISS, Section 5.15 of NDA 209089. Two studies (i.e., Studies A00340 and A00410) were excluded from the pooled safety database because their clinical databases were not available and they are summarized as follows:

- In Study **A00340** (randomized, 2-way crossover, open label, single dose, comparative PK study conducted in 2003 at one center in India), 12 subjects were randomized and 12 subjects were treated with two single doses of LCTZ 5 mg oral tablet (one tablet was produced in India by UCB India Private Limited and the reference tablet was manufactured in Switzerland by UCB Farchim S.A.). None of the 12 subjects reported any adverse reactions during the study. None of the subjects discontinued treatment prematurely.
- In Study **A00410** (Phase 3, randomized, multicenter, double-blind, double-dummy, randomized, active-controlled, parallel-group efficacy and safety study

¹⁶⁰ Per NDA 209089 Section 2.7.4 Summary of Clinical Safety (Allergic Rhinitis) pg. 12 of 65.

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conducted at six centers in Korea in 2005-2006), 466 subjects with atopic dermatitis and eczema aged at least 15 years were randomized (232 to LCTZ 5 mg once daily at bedtime and 234 to CTZ 10 mg once daily at bedtime) and 464 subjects were treated. Treatment duration was 2 weeks, 423 subjects were included in the safety cohort (209 treated with LCTZ and 214 treated with CTZ) and 340 subjects were included in the mITT cohort. No deaths and one SAE was reported (acute leukemia in the LCTZ group; considered unrelated to drug product). Three subjects treated with CTZ discontinued prematurely from the study due to an AE. Eleven subjects (5.26%) in the LCTZ group and 16 subjects (7.48) in the CTZ group experienced a TEAE. There was no significant change from baseline in laboratory values or vital signs.

For Study **A00420**, only limited safety data (where available) was integrated into the pooled safety data because it was a Phase 4, postmarketing, non-interventional, retrospective, observational study that collected data from 4581 subjects on antihistamine treatment satisfaction conducted in 2006-2008 in seven countries (i.e., Bulgaria, Spain, Romania, Russia, Portugal, India and South Korea).¹⁶¹ A total of 424 physicians located at 424 centers participated in the study. No deaths or SAEs were reported. Overall, 175 adverse events were reported by 159 (3.5%) subjects [**NOTE:** 46 subjects treated with LCTZ and 45 subjects treated with CTX reported at least one AE]. Subjects treated with second-generation antihistamines reported fewer AEs compared to first-generation antihistamines. The proportion of subjects with AEs after treatment with second-generation antihistamines was cetirizine (4.7%), loratadine (2.5%), fexofenadine (2.4%), levocetirizine (2.0%) and desloratadine (1.8%). Overall, the most commonly reported primary system organ class was "nervous system disorders" [reported by 125 (2.7%) subjects and the most commonly reported AE by preferred term was "somnolence" [reported by 116 (2.5%) subjects]. Psychiatric disorders were reported by 4 subjects (0.1% of subjects).

Reviewer's comment: *No safety signal was noted in Study A00340. It is the opinion of this reviewer that no new safety findings related to the safety of levocetirizine were reported in Study A00410 or Study A00420.*

7.2 Adequacy of Safety Assessments

¹⁶¹ Ferrer M et al. Evaluation of treatment satisfaction in children with allergic disease treated with an antihistamine; An international, non-interventional, retrospective study. *Clin Drug Investig.* 2010; 30 (1): 15-34.

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7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 6: Number of Subjects by Study Group and Treatment Group in Safety Population

Study Group	Placebo	Levocetirizine						Comparator (a) [Cetirizine]	All
		1.25 mg	2.5 mg	5 mg	10 mg	30 mg	Combined		
Clinical Pharmacology Studies									
Clinical Pharmacology	960	0	134	1371	24	88	1565	1382 [589]	2835
PK studies in special population	0	0	0	17	0	0	17	0	17
Phase 2-3-4 studies age ≥ 12 years									
Short-term studies (b)	1813	0	421	2979	414	0	3801	1426 [318]	6869
Long-term studies (c)	580	0	0	622	0	0	622	0	1068
Phase 2-3-4 studies age 6 months to 12 years									
Short-term studies	323	45	159 (d)	243	0	0	447	0	770
Long-term studies	302	0	256 (e)	0	0	0	256	0	510
ALL STUDIES	3963 (f)	45	970	5221	438	88	6685 (g)	2808 [907]	11991 (h)

Source: NDA 209089 Section 2.7.4 pg. 14 of 65.

Safety population = all randomized subjects who took at least one dose of investigational medicinal product

[NOTE: A subject may be counted once in several study or treatment groups, but will only be counted once in the total of all studies in each study or treatment group.]

(a) **Comparators:** cetirizine 5 mg, 10 mg and 20 mg, desloratadine 5 mg, diphenhydramine 50 mg, ebastine 10 mg, fexofenadine 120 mg and 180 mg, loratadine 10 mg, mizolastine 10 mg, ucb 28557 2.5 mg and 5 mg, montelukast 10 mg, moxifloxacin 400 mg.

(b) Short-term studies are less than or equal to 12 weeks (84 days) in duration.

(c) Long-term studies are 4-18 months in duration.

(d) Dose received: 0.125 mg/kg BID for study A00315 and 1.25 mg BID for study A00385.

(e) Dose received: 0.125 mg/kg BID for studies A00309 and A00384.

(f) 247 of these 3963 subjects (6.2%) were exposed to placebo for at least 365 days (per NDA 209089 SCS Section 2.2).

(g) 232 of these 6685 subjects (3.5%) were exposed to levocetirizine for at least 365 days (per NDA 209089 SCS Section 2.2).

(h) Total number of subjects in safety population.

Reviewer’s comment: *In the ISS submitted in NDA 209089, the sponsor provided safety information for 6685 subjects dosed with levocetirizine, 2808 subjects dosed with at least one active comparator and 3963 subjects dosed with placebo (total = 11,991 subjects in 62 studies). It should be noted that if the subjects enrolled in four open label, uncontrolled, clinical practice studies (located by this reviewer in the medical*

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literature) had been included, there would have been safety data for an additional 19,261 subjects dosed with levocetirizine.^{162,163,164,165}

Table 7: Demographics

Study Group (Number of Subject in Safety Population)	Placebo (N=3963)	Combined Levocetirizine (N=6685)	Active Comparator (a) (N=2808)	All (N=11991)
Clinical Pharmacology Studies				
Clinical Pharmacology	N=960	N=1565 (2.5, 5, 10 or 30 mg)	N=1382	N=2835
Age in Years Mean (range)	31.5 (16.8-74.1)	32.4 (16.1-74.6)	31.7 (16.2-77.2)	33.0 (16.1-77.2)
Gender M, F	M 48.9% F 51.1%	M 48.8% F 51.2%	M 48.5% F 51.5%	M 46.2% F 53.8%
Region E=Europe, A=Asia, NA=North America	E= 51.5% A= 0 NA=48.5%	E= 40.8% A= 1.5% NA=57.6%	E= 35.6% A= 0 NA=64.4%	E= 23.2% A= 0.8% NA=75.9%
Race W=White, B=Black or African American, A=Asian, O=Other	W=90.3% B= 3.6% A= 4.6% O= 1.5%	W=90.9% B= 3.0% A= 4.7% O= 1.5%	W=91.0% B= 4.1% A= 3.8% O= 1.0%	W=89.0% B= 4.6% A= 4.7% O= 1.7%
PK studies in special population	N=0	N=17 (all dosed with 5 mg)	N=0	N=17
Age in Years Mean (range)		57.4 (38.9-78.1)		57.4 (38.9-78.1)
Gender M, F		M 41.2% F 58.8%		M 41.2% F 58.8%
Region E=Europe		E=100%		E=100%
Race W=White, B=Black or African American		W=94.1% B= 5.9%		W=94.1% B= 5.9%
Phase 2-3-4 studies age ≥ 12 years				
Short-term studies ≤12 weeks (84 days) in duration	N=1813	N=3801 (2.5, 5 or 10 mg)	N=1426	N=6869
Age in Years Mean (range)	33.5 (12.1-76.5)	34.8 (12.0-85.1)	36.2 (12.2-81.3)	34.8 (b) (12.0-85.1)
Gender	M 40.8%	M 41.1%	M 40.7%	M 40.8%

¹⁶² Fang SY et al. An open-label, multicentre study of levocetirizine for the treatment of allergic rhinitis and urticaria in Taiwanese patients. *Chin J Physiol.* 2010 Aug 31; 53 (4); 199-207. [NOTE: n=333 patients treated with levocetirizine tablet 5 mg once daily for 2-6 weeks]

¹⁶³ Jorissen M et al. Levocetirizine as treatment for symptoms of seasonal allergic rhinitis. *B-ENT.* 2006; 2 (2): 55-62. [NOTE: n=1290 patients treated with levocetirizine tablet 5 mg once daily for 4 weeks]

¹⁶⁴ Klimek L, Hundorf I. Levocetirizine in allergic diseases – an open multicenter practice study on efficacy and safety. *Allergologie.* 2002; 25 (1): S1-S7. [NOTE: n=17,638 patients treated with levocetirizine tablet 5 mg once daily for 4-6 weeks (mean duration 32 days)]

¹⁶⁵ Pfaar O et al. Levocetirizine in patients with chronic idiopathic urticaria: results of a multicenter clinical practice study. *Int J Clin Pharmacol Ther.* 2006 Apr; 44 (4): 191-2. [NOTE: sub-analysis of 2707 patients from above Klimek study treated with levocetirizine tablet 5 mg once daily for 4-6 weeks (mean duration 37.4 days)]

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Study Group (Number of Subject in Safety Population)	Placebo (N=3963)	Combined Levocetirizine (N=6685)	Active Comparator (a) (N=2808)	All (N=11991)
M, F	F 59.2%	F 58.9%	F 59.3%	F 59.2%
Region E=Europe, As=Asia, NA=North America, Af=Africa	E= 53.4% As= 0 NA=32.4% Af= 14.1%	E= 71.2% As= 5.6% NA=15.4% Af= 7.9%	E= 83.0% As=14.9% NA= 0 Af= 2.1%	E= 68.3% As= 6.2% NA=17.1% Af= 8.4%
Race W=White, B=Black or African American, A=Asian, O=Other, U=Unknown	W=65.1% B= 7.0% A= 4.0% O= 3.6% U= 20.4%	W=60.9% B= 4.2% A= 7.8% O= 2.2% U= 24.9%	W=59.7% B= 1.1% A= 16.6% O= 1.3% U= 21.3%	W=61.2% B= 4.4% A= 8.8% O= 2.4% U= 23.2%
Long-term studies 4-18 months in duration	N=580	N=622 (all dosed with 5 mg)	N=0	N=1068
Age in Years Mean (range)	30.5 (11.0-70.3)	31.1 (11.0-68.7)		30.8 (11.0-70.3)
Gender M, F	M 43.8% F 56.2%	M 41.8% F 58.2%		M 43.4% F 56.6%
Region E=Europe	E=100%	E=100%		E=100%
Race W=White, B=Black or African American, A=Asian, O=Other	W=96.7% B= 2.2% A= 0.7% O= 0.3%	W=95.7% B= 2.1% A= 1.1% O= 1.1%		W=96.3% B= 2.0% A= 0.9% O= 0.8%
Phase 2-3-4 studies age 6 months to 12 years				
Short-term studies ≤12 weeks (84 days) in duration	N=323	N=447 (1.25, 2.5, 5 mg)	N=0	N=770
Age in Years Mean (range)	8.1 (0.5-13.0)	6.8 (0.5-12.9)		8.2 (0.5-13.0)
Gender M, F	M 58.2% F 41.8%	M 62.9% F 37.1%		M 60.9% F 39.1%
Region E=Europe, NA=North America, O=Oceania, Af=Africa	E= 27.2% NA=25.7% O= 0 Af= 47.1%	E= 28.6% NA=35.6% O= 1.3% Af= 34.5%		E= 28.1% NA=31.4% O= 0.8% Af= 39.7%
Race W=White, B=Black or African American, A=Asian, O=Other,	W=56.0% B= 10.5% A= 9.3% O=24.1%	W=59.7% B= 11.2% A= 9.2% O=19.9%		W=58.2% B= 10.9% A= 9.2% O=21.7%
Long-term studies 4-18 months in duration	N=302	N=256 (all dosed with 2.5 mg)	N=0	N=510
Age in Years Mean (range)	1.6 (1.0-2.2)	1.6 (1.0-2.2)		1.6 (1.0-2.2)
Gender M, F	M 61.6% F 38.4%	M 60.5% F 39.5%		M 62.5% F 37.5%
Region E=Europe, O=Oceania, Af=Africa	E= 69.5% O= 16.6% Af=13.9%	E= 69.5% O= 18.8% Af=11.7%		E= 69.2% O= 18.6% Af=12.2%
Race W=White, B=Black or African American, A=Asian, O=Other,	W=85.8% B= 3.3% A= 3.3%	W=88.3% B= 2.0% A= 3.5%		W=86.7% B= 2.4% A= 3.7%

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Study Group (Number of Subject in Safety Population)	Placebo (N=3963)	Combined Levocetirizine (N=6685)	Active Comparator (a) (N=2808)	All (N=11991)
	O= 7.6%	O= 6.3%		O= 7.3%

Sources: ISS Tables 16 (pg. 38-9), 17 (pg. 40-1), 18 (pg. 43-44), 19 (pg. 45-6), 20 (pg. 47-8), 21 (pg. 49) and NDA 209089 Section 2.7.4 pg. 14 of 65.

NOTE: a subject may be counted once in several study or treatment groups, but will only be counted once in the total of all studies in each study or treatment group. A total of 171 subjects (2.5%) were ≥ 65 years of age.

Comparators: cetirizine 5 mg, 10 mg and 20 mg, desloratadine 5 mg, diphenhydramine 50 mg, ebastine 10 mg, fexofenadine 120 mg and 180 mg, loratadine 10 mg, mizolastine 10 mg, ucb 28557 2.5 mg and 5 mg, montelukast 10 mg, moxifloxacin 400 mg.

Reviewer's comment: *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.¹⁶⁶ Per the ISS Tables and Listing submission, 38 of the 171 subjects aged ≥ 65 years of age in the Phase 2-3-4 short-terms studies reported at least one TEAE, including 8 subjects with headache, 7 subjects with somnolence, 3 subjects with fatigue and 2 subjects with asthenia.¹⁶⁷ Thus, only limited clinical study data is available pertaining to the safety of levocetirizine HCl in geriatric patients.*

7.2.2 Explorations for Dose Response

No explorations for dose response were submitted in NDAs 209089 or 209090.

7.2.3 Special Animal and/or In Vitro Testing

No results of new special animal and/or in vitro testing were submitted in NDAs 209089 or 209090.

7.2.4 Routine Clinical Testing

The specific safety assessments performed in the clinical studies varied, as demonstrated in the following table of the safety assessment performed in the 12 clinical studies individually reviewed in the Clinical Review for Original NDA 022064 (Rx Xyzal):¹⁶⁸

¹⁶⁶ 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.

¹⁶⁷ 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).

¹⁶⁸ NDA 022064 Xyzal (levocetirizine dihydrochloride) Clinical Review by Robert Boucher, MD, MPH finalized in DARRTS on 4/3/07; pg. 52-3 of 161.

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Study Number	N exposed To LCTZ	AE	VS	PE	Pregnancy test	CBC	Alkaline phosphatase	SGOT/SGPT	Total bilirubin	Direct bilirubin	Urea	Creatinine
A00268	119	√	√	√	√	√		√	√	√	√	√
A00266	150	√	√	√	√	√		√	√	√	√	√
A00303	89	√	√	√								
A00304	154	√	√	√								
A00269	81	√	√	√	√	√	√	√	√	√	√	√
A00270	194	√	√	√	√	√	√	√	√	√	√	√
A00412	235	√	√	√	√							
A00373	18	√	√	√	√							
A217	349	√	√	√	√	√	√	√	√		√	√
A00379	240	√	√	√	√							
A00265	391	√	√	√	√	√		√	√	√	√	√
A00264	278	√	√	√	√	√		√	√	√	√	√
Total	2,298											

7.2.5 Metabolic, Clearance, and Interaction Workup

No results of new metabolic, clearance or interaction workups were submitted in NDAs 209089 or 209090

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See Section 2.4 of this review.

7.3 Major Safety Results

It should first be noted that in general, data on the long term safety of antihistamines is limited¹⁶⁹ and specifically, clinical study data pertaining to the safety of levocetirizine in the geriatric population is quite limited.

7.3.1 Deaths

In the 62 UCB-sponsored clinical studies, no deaths were reported in any levocetirizine-treated subjects; however, one 63-year-old white male subject randomized to an active-control desloratadine group in Study A00394 died due to myocardial infarction after 31 days of treatment. It is also noted that one 12-year old subject randomized to placebo in Study A00304 died due to accidental electrocution three days after completing treatment. There were no deaths associated with levocetirizine reported in the National

¹⁶⁹ Ergun T, Kus S. Adverse systemic reactions of antihistamines: Highlights in sedating effects, cardiotoxicity and drug interactions. *Current Medicinal Chemistry: Anti-Inflammatory and Anti-Allergy Agents*. 2005; 4 (5): 507-515.

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Poison Control Centers database from 2007-2015 or in the DAWN database during the study period of 2007-2011.

The following 32 fatal postmarketing cases¹⁷⁰ have been reported in patients who died after being treated with LCTZ:

1. **Manufacturer's report number UCBSA-1004911:** AE "death" occurred (b) (6); 60 year old female in Germany with T-cell non-Hodgkins lymphoma first diagnosed in 2000 was treated with LCTZ starting 2/25/02 for pruritus related to the malignancy; concomitant medications also included chemotherapy with bendamustine from about October 2001 to January 2002 and prophylactic heparin; on 2/27/02 patient developed significant decrease in thrombocytes down to 10,000/ul; no autopsy results were reported. Initial reporter's occupation: physician.
2. **Manufacturer's report number UCBSA-8005176:** AE "death" occurred on (b) (6); 71 year old male on LCTZ for allergic conjunctivitis from 9/17/02 to 5/19/03; experienced unexpected, fatal cerebrovascular accident; concomitant medications included Betnesol (betamethasone) nasal TID, salmeterol xinafoate 2 puffs daily, and fluticasone propionate 2 puffs daily from 5/28/03; no significant medical history (i.e., nonsmoker, not diabetic, normotensive); Initial reporter's occupation: physician; reported to British Health Authorities.
3. **Manufacturer's report number UCBSA-8012508 (associated case UCBSA-8012506 for mother):** AE "elective termination" occurred in "May 2005" after a fetal malformation (not specified) was confirmed after an amniocentesis was performed during 4th month of pregnancy; 30 year old female in Greece took LCTZ 5 mg TID and Medrol (methylprednisolone) during "January 2005" (specific dates not provided) for wheals and itching and stopped both medications during the second week of treatment when she realized she was pregnant.
4. **FAERS Case 8396167 (version 1); Pfizer Manufacturer's report number 2005135511:** AE "death" occurred on (b) (6) (cause "infarction"; per physician reporter, patient was feeling well prior to death); 48 year old female in Germany on LCTZ (unknown dose, unknown start and stop dates); also taking Lyrica 300 mg for "ill-defined disorder", Beloc and Nexium; medical history included sinus tachycardia; minimal information provided; Initial reporter's occupation: physician.
5. **FAERS Case 6075455 (version 2); Manufacturer's report number FR-GLAXOSMITHKLINE0B0429234A:** AE "death: occurred on (b) (6); 75-year old female in France on LCTZ (dose and length of treatment not reported) and 10

¹⁷⁰ 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 this reviewer revealed eight additional postmarketing death reports that listed LCTZ. None of these eight additional reports were submitted by UCB.

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additional concomitant medications including Cartrex (aceclonfenac, Zofenil (zofenopril) and Toplexil (oxomemazine) developed hepatitis on 5/25/06 leading to death from hepatic failure; medical history included chronic cystitis, hypertension arterial and thyroid nodules; laboratory tests for auto-immune tests, hepatitis A, B all negative; Initial reporter's occupation: physician. [NOTE: duplicate report for this same death by UCB in **UCBSA-8017683**.]

6. **FAERS Case 6162626 (version 2); Celgene Manufacturer's report number 062-C5013-06091079:** AE "death" occurred on (b) (6); 66 year old female in Germany on LCTZ unknown dose for pruritus (unknown frequency, start and stop times); hospitalized on (b) (6) for cough, fever and low white blood cell, red blood cell and platelet counts; developed sepsis, multiple embolism arterial and complete bone marrow aplasia (failure); medical history of myelodysplastic syndrome, arterial hypertension and hemolysis; also taking lenalidomide 15 mg qd from (b) (6), omeprazole, deferoxamine mesylate, and tramado; enrolled in open-label named patient CC-5013 program; Initial reporter's occupation: physician.
7. **FAERS Case 6563017 (version 1); Manufacturer's report number UCBSA-8029691 (associated case UCBSA-8023420 for mother):** AE "elective pregnancy termination" occurred in "2007" after fetal malformation "Tetralogy of Fallot" diagnosed in "July 2007" during echography at 22 weeks gestation; fetal karyotype indicated 22Q deletion; 34 year old female G1P0000 in France with no relevant medical history took 4 or 5 tablets of LCTZ in early pregnancy before she realized that she was pregnant (exposure to LCTZ occurred at 1.5 months of pregnancy); Initial reporter's occupation: physician.
8. **FAERS Case 6411761 (version 2); Manufacturer's report numbers UCBSA-003298 and GlaxoSmithKline B0623770A:** AE "death" occurred on (b) (6) due to dyspnea; 89 year old male in Korea on LCTZ from (b) (6) who experienced "compression fracture" due to accident on (u) (u) and was hospitalized; during the hospitalization, he developed pneumonia on (b) (6); also took 14 concomitant medications, including prednisolone, salbutamol inhaler and ketoprofen patch.
9. **FAERS Case 6781776 (version 1); Manufacturer's report numbers UCBSA-8037110:** AE "death" occurred (b) (6); 69 year old male in Austria treated with LCTZ 5 mg qd for eczema from 8/15/08 to unknown date who developed jaundice on 8/19/08 and probably died on (b) (6) (not confirmed on report); also taking Diclofenac 25 mg (frequency and indication unknown) from 8/15/08 to unknown date; minimal information provided on this 1-page report; Initial reporter's occupation: physician.
10. **FAERS Case 7380487 (version 1); Manufacturer's report number DE-PFIZERINC-2010052089:** AE "death" occurred (b) (6); 47 year old female in Germany on 28 concomitant medications including one dose of LCTZ 5 mg on 11/25/08 for hypersensitivity developed Steven's Johnson syndrome after treatment for cystitis from 11/10/08 to 11/12/08 and from 11/15/08 to 11/25/08, treatment for recurrent thrombosis from 1/1/08 to 11/7/08 and from 11/29/08 to

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12/2/08, treatment for metabolic acidosis from 1/1/08 to unknown date, treatment of lumbar spine syndrome from 1/1/08 to unknown date, treatment of sleeping disorder from 11/11/08 to 11/12/08, treatment of hypotension from 11/18/08-11/19/08; medical history included edema and urosepsis diagnosed on 11/10/08; Initial reporter's occupation: physician.

11. **FAERS Case 6970504 (no Manufacturer's report number):** AE "death" apparently in 2009 (FDA received report on 4/6/09); 68 year old male in US on LCTZ 5 mg "for a bad cold" on unknown dates; limited information was provided by patient's sister; two days after starting LCTZ, he was hospitalized for jaundice, liver biopsy demonstrated toxicity, went into renal failure, put on dialysis and eventually on a respirator; he did not recover and died approximately one week later; his sister stated: "The doctor who headed the transplant team saw him at this hospitalization and thought the reaction to the Xyzal "os" (sic was) what caused my brother's death"; medical history: liver transplant 7 years prior to his death and cardiovascular disease; also taking immunosuppressant drugs because of the transplant. Initial reporter's occupation: not a health care profession.
12. **FAERS Case # 7067016 (version 1); Manufacturer's report number UCBSA-8049388 (associated case UCBSA-8049402 for mother; same case also reported by AstraZeneca FR-ASTRAZENECA-2009SE05569):** AE "elective pregnancy termination" occurred on 4/15/09 at 15.5 weeks gestation after fetal malformation "spina bifida; lumbo-sacral lumbo-myelo-meningocele" was diagnosed on 3/23/09 during echography at 12 weeks gestation; 25 year old female G1P0000 in France with history of multiple allergies took LCTZ tablets once daily in early pregnancy until 2/14/09, when she was 7.5 weeks pregnant; also took Rhinocort (nasal budesonide dosed every other day) and Mucohime (nasal homeopathy drug dosed every other day) until 2/14/09; Initial reporter's occupation: physician.
13. **FAERS Case 7058391 (version 3 received 8/28/09; version 1 received 7/6/09); Manufacturer's report number UCBSA-8048317:** AE "death" occurred (b) (6); 70 year old female in Taiwan treated with LCTZ strength unknown qd for allergic rhinitis from 12/2/08 to 12/16/08 and 12/31/08-1/14/09; on 1/19/09, she was diagnosed with acute myeloid leukemia; on (b) (6), she developed pneumonia, left hospital against medical advice on (b) (6) and died at home later that day; also took diclofenac potassium (six courses between 3/26/07 and 1/9/09), diclofenac sodium (5/7/08-5/14/08), clindamycin (12/25/08), erythromycin (12/30/08-1/2/09), chlorpheniramine (3/26/07-4/23/07 and 1/6/09-1/13/09), fexofenadine (11/29/08-12/6/08), and cephalexin (9/22/07-9/26/07) and received one dose of blinded influenza virus vaccine on 1/19/09; medical illnesses included obstructive pulmonary disease; no autopsy; Initial reporter's occupation: physician.
14. **FAERS Case 7768389 (version 1); Manufacturer's report number UCBSA-023801:** AE "death" due to "medical termination of pregnancy" occurred on 8/26/09 in France at 36 weeks and 3 days gestation after major congenital hydrocephalus of 4 ventricles with necrotic mass in parietal foramen ("central nervous system necrosis") was diagnosed by ultrasonography on 8/18/09; mother took LCTZ at an unknown dose, unknown frequency and for an unknown indication until 36 weeks

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and 3 days gestation; mother also took Celestamine (betamethasone; chlorphenamin), Spasfon (phloroglucinol, trimethylphloroglucinol) and Doliprane (paracetamol) during the pregnancy; Initial reporter's occupation: physician.

15. **FAERS Case 7607649 (version 1); Manufacturer's report number Schering Plough 2010SP046932:** AE "death" occurred on (b) (6) 34 year old female in US on LCTZ (unknown dose, unknown start and end dates) found dead on her couch; cause of death was reported as an asthma attack; unknown if autopsy was performed; 3 weeks before her death, she had been hospitalized due to asthma and pneumonia; medical history included hypertension; 12 concomitant medications were metoprolol, spironolactone, lisinoprel, aspirin, omeprazole, tessalon (benzolonatate), singulair (montelukast), spriva (tiotropium bromide), astelin (azelastine hydrochloride), veramyst (fluticasone), proair (fluticasone propionate) and xyzal; Initial reporter's occupation: nurse.
16. **FAERS Case 7934020 (version 1); Manufacturer's report number UCBSA-031989:** AE "death" occurred (b) (6); 53 year old male in France treated with LCTZ for unknown indication on unknown dates who was hospitalized on (b) (6) for vomiting believed due to be due to initiation of everolimus 3 tablets daily on 1/3/11; everolimus was stopped on 1/11/11, nausea and vomiting occurred on 1/12/11 and was treated with Zophren (ondansetrom) 4 mg daily with improvement in vomiting, then confusional syndrome began with sudden dyspnea and desaturation; angio-scanner showed left pulmonary embolism and large intestine perforation; antibiotics were started; general status worsened quickly and palliative symptomatic care was given; relevant history included resected hepatocellular carcinoma complicated by peritoneal metastases, alcoholic cirrhosis, alcoholism and tobacco use; Initial reporter's occupation: physician. **[NOTE:** same case also submitted by ORTHO as **FAERS Case 79349020 (version 1); Manufacturer's report number FR-JNJFOC-20110412155** and by UCB as **FAERS Case 7970233 (version 1); Manufacturer's report UCBSA-031989]**
17. **FAERS Case 7970097 (version 1); Manufacturer's report number UCBSA-032063:** AEs "sudden death" and "sudden cardiorespiratory arrest" occurred on (b) (6); 73 year old female in France treated with LCTZ 10 mg ("overdose") from unknown starting date to (b) (6); hospitalized on (b) (6) for total knee prosthesis under general anesthesia; on (b) (6), new AE "anemia" (Hgb 9.6 g/dL); on (b) (6), echodoppler demonstrated permeability of deep and superficial venous system of right lower limb; on (b) (6) worsening anemia (Hgb 8.6 g/dL) noted; discharged to reeducation home on (b) (6) at 11am and arrested at 1:10pm; no autopsy performed; 16 concomitant medications including Lovenox and Lasilix retard; Initial reporter's occupation: physician. **[NOTE:** same case submitted by Aventis as **FAERS Case 7928297 (version 1)** with **Manufacturer's report number FR-SANOFI-AVENTIS-2011SA026307**, by Pfizer as **FAERS Case 7929084 (version 4)** with **Manufacturer's report number FR-PFIZERINC-2011091298**, by Cadence as **FAERS Case 7966372 (version 1)** with **Manufacturer's report number 2011CP000076**, by Boehringer Ingelheim as **FAERS Case 7862754 (version 5)** with **Manufacturer's report number FR-**

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B.I.PHARMACEUTICALS,INC./RIDGEFIELD-2011-FF-00257FF and twice by Novartis as **FAERS Case 7940197 (version 3)** with **Manufacturer's report number PHHY2011FR38238** and as **FAERS Case 8515423 (version 1)** with **Manufacturer's report number PHHY2011FR40654.**]

18. **FAERS Case 8011503 (version 1); Manufacturer's report number FR-UCBSA-035460:** AE "death" occurred on (b) (6); 72 year old female (also) in France treated with LCTZ "3 units daily" (considered by reporter to be an overdose) for unknown indication starting on 5/1/11; medical history included Alzheimer's disease; hospitalized on unknown date because of impairment of general state; on 4/27/11, treatment with memantine, haloperidol, lorazepam, lipido-sterol extract of Florida palm and amoxicillin with clavulanic acid began; on 5/5/11, pancytopenia diagnosed and treatment with memantine, haloperidol, LCTZ and amoxicillin with clavulanic acid stopped; on 5/5/11, treatment with lipido-sterol extract of Florida palm stopped; on (b) (6) patients died (no cause identified; no biological workup provided); Initial reporter's occupation: physician. [**NOTE:** same case submitted by Janssen as **FAERS Case 8001726 (version 2)** with **Manufacturer's report number FR-JNJFOC-20110606988** (in this report, subject reported to be a male, which sponsor stated they had previously reported as a female) and twice by Forest as **FAERS Case 8033378 (version 1)** and as **FAERS Case 9482192 (version 2)** both with **Manufacturer's report number 1000021701**]
19. **FAERS Case 7995064 (version 4); MedWatch SAE 7705809-4; UCB Manufacturer's report number JP-UCBSA-030303:** AE "death" occurred on (b) (6) due to pneumonia aspiration; male aged 63 years in Japan on oral LCTZ 5 mg tablet **BID** (off label dose in Japan) from 3/11/11 to 3/27/11 for pruritus; date AEs occurred or began 3/1/11; date FDA received initial report 8/24/11; date UCB received initial report 8/10/11; he developed infection at puncture site of dialysis shunt, pyrexia and was hospitalized with bacteremia; AEs: death, neutropenia, sepsis, white blood cell count decreased, pneumonia, aspiration; also taking oral Maintate (bisopropol fumarate; hypertension), oral Adalat-CR (nifedipine; hypertension); oral equa (vildagliptin; diabetes mellitus), oral Zyrtec (cetirizine; hypersensitivity) and oral Olmetec (olmesartan medoxomil; hypertension); medical history included pruritus, type II diabetes mellitus, chronic renal failure and hemodialysis; Initial reporter's occupation: physician.
20. **FAERS Case 8311734 (version 5); UCB Manufacturer's report JP-UCBSA-047993:** AE "death" occurred (b) (6) due to allergic drug-induced hepatitis; female aged 81 years on oral LCTZ 5 mg once daily from 11/10/11 to 11/13/11 for erythema, xeroderma and pruritus; she developed liver disorder on 11/15/11; was hospitalized on (b) (6) for jaundice and malaise; developed ascites, hepatic atrophy, oliguria and abnormal liver function, abnormal PTT and fibrinogen tests; also took Celestamine (betamethasone; d-chlorphenamin maleate qd) and Allelock OD (olopatadine hydrochloride 5 mg qd); Initial reporter's occupation: physician. [**NOTE:** same case also submitted by Pfizer as **FAERS Case 8352025 (version 5)**, **Manufacturer's report number JP-PFIZERINC-2011314731**]

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21. **FAERS Case 10022177 (version 1) and 10081603 (version 2); Manufacturer's report number FR-UCBSA-114568:** AE "death" occurred on (b) (6); female aged 86 years in France on LCTZ from 1/27/14 to 1/30/14 for unknown indication; (b) (6) hospitalized for desaturation and management of bronchial infection; on 1/29/14, edematous erythema on the ankle and face ("dry rash face" appeared and treatment initiated with hydroxyzine and Polaramine (dexchlorpheniramine); on next day 1/30/14, patient died due to her respiratory infection; past medical history included atrial fibrillation, cardiac arrhythmia caused by atrial fibrillation, arterial hypertension, cranial arteritis, hypothyroidism, adrenal insufficiency, ischemic stroke, vascular dementia, osteoporosis, bronchitis; seven concomitant medications included amiodarone 200 mg qd and Eupantol 40 mg (pantoprazole intravenous injection) qd.
22. **FAERS Case 9062117 (version 1); Manufacturer's report number PHHY2013US006739;** AE "death" (date not specified; presumed to be 2011) of 46 year old female due to intentional suspected suicide with autopsy work-up showing bupropion at 3.4 mcg/mL in whole blood; Literature report¹⁷¹ from Table no. 21, Patient No. 1263ph in the 2011 Annual Report of the American Association of Poison Controls Centers, National Poison Data System (NPDS); concomitant medications included LCTZ (dose unknown; start and stop dates unknown), temazepam, clonazepam, hydrochloride thiazide, bupropion, and thyroid preparation; Initial reporter's occupation: health professional.
23. **FAERS Case 10141575 (version 4); Manufacturer's report number JP-GLAXOSMITHKLINE-B0988801A;** AE "death" occurred in March 2014 from interstitial lung disease; male aged 66 years in Japan on LCTZ 5 mg QD from 1/4/14/ to 1/28/14 for eczema and from 1/28/14-3/28/14 for drug eruption due to a contrast medium; it is unknown whether an autopsy was performed; past medical history included systemic lupus erythematosus; concurrent medical conditions were interstitial lung disease and oxygen supplementation; patient had enrolled in atovaquone study and took atovaquone 1500 mg oral bid from 12/14/13 to 1/21/14 as pneumocystis jiroveci pneumonia; atovaquone was stopped due to hospitalization for liver disorder starting on (b) (6).
24. **FAERS Case 10227030 (Manufacturer's report number JP-UCBSA-2014001099):** AE "death" occurred (b) (6) of unknown cause; female aged 11 months in Japan on LCTZ 2.5 mL syrup qd starting 5/14/14 for rhinorrhea with unknown stop date; date FDA received initial report 6/10/14 and second report 6/26/16; date UCB received initial report 5/26/14; medical history: infection, rhinorrhea, pyrexia, cough and otitis media; also taking oral epcalol (procatamol hydrochloride) for cough starting 5/14/14 with unknown stop date and oral pasetocin (amoxicillin) for otitis media starting 5/14/14 with unknown stop date; sponsor stated in ISS that "procatamol (associated with QT prolongation) could have contributed to the patient's death"; Initial reporter's occupation: physician.

¹⁷¹ Bronstein A et al. 2011 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th Annual Report. *Clinical Toxicology*. 2012; 50: 911-1164.

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25. **FAERS Case 10844421 (version 2); Manufacturer's report number JP-UCBSA-2015004816:** AE "sudden infant death syndrome; SIDS" occurred (b) (6); female aged 9 months in Japan on LCTZ 2.5 mg oral solution qd for rhinitis allergic and Sawacillin (amoxicillin trihydrate) 300 mg qd for pharyngitis, both from 2/3/15 to unknown date; post-death (b) (6) "full-body computed tomographic scans revealed an intracardiac, intrahepatic (vascular endothelium) air image only, which was probably due to resuscitation; no pathologic abnormality was indicated. External examination showed no clear traumatic abnormality"; Also taking Onon (pranlukast) 60 mg qd begun 2/3/15, Asverin (tipecidine hiberzate) 2 mL qd begun 1/5/15, Meptin (procaterol hydrochloride) 3 mL qd begun 2/3/15, Mucosolvan (ambroxol hydrochloride 2 mL qd and Mucodyne (carbocisteine) 4.8 mL qd begun 1/5/15, all for asthma; autopsy was performed (results unknown); Initial reporter's occupation: physician.
26. **FAERS Case 10876652 (version 2); Manufacturer's report number JP-UCBSA-2015005081:** AE "death" occurred (b) (6) due to subarachnoid hemorrhage; female aged 87 years in Japan on LCTZ 5 mg qd from 1/26/15-2/2/15 for generalized itching; LCTZ was stopped on 2/2/15 due to involuntary "jerking" movements (dyskinesia); developed subarachnoid hemorrhage on (b) (6); also taking Plavix (clopidogrel bisulfate), Amlodipine (amlodipine maleate), Onealfa (alfacalcidol), Olmetec (olmesartna medoxomil) and Luprac (torasemide); past medical history included carotid artery aneurysm, hypertension and anemia chronic renal failure, dialysis, hypertension and anemia; Initial reporter's occupation: pharmacist.
27. **FAERS Case 1120510 (version 1); Manufacturer's report number US-UCBSA-2015014698:** AE "death" occurred in "April 2015"; female aged 62 years in US on LCTZ unknown dose, for unknown duration, for unknown indication; Medical history included metastatic breast cancer under treatment with chemotherapy; in "April 2015", patient went to ER for fatigue and abdominal pain and was admitted to the ICU because she was pancytopenic and had right lower lobe pneumonia, acute renal failure and atrial fibrillation; two days later she became septic and died. Initial reporter's occupation: physician. **[NOTE: duplicate report for same subject death submitted by a different manufacturer report number US-MYLANLABS-2015M1017572 and FAERS Case 11173319 (version 3).]**
28. **FAERS Case 11101193 (version 1); Manufacturer's report number OM-UCBSA-2015014317:** AE "death" from cardiac arrest with date unknown; report was received on 4/26/15 by GSK; female aged 39 years from Oman on LCTZ 5 mg qd for urticaria (dates of treatment are unknown); also taking dexamethasone injection and Atarax (hydroxyzine hydrochloride) 10 mg tablet qd; Patient did not suffer from a history of cardiac diseases and was not diabetic or hypertensive; unknown if autopsy performed; Initial reporter's occupation: physician.
29. **FAERS Case 11349256 (version 1); Manufacturer's report number US-GLENMARKGENERICSEUROPE)LTD-2015GMKO18665:** AE "death" occurred on (b) (6) by suicide with a gunshot wound to the head; male aged 24 years on LCTZ 5 mg qd from 7/23/15 to 7/27/15; also taking permethrin cream and

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triamcinolone 0.1% cream for a rash from 7/23/15 to 7/27/15; subject reported feeling weird ('feeling abnormal') to his girlfriend on 7/26/15, which he believed that the LCTZ tablets "were making him crazy"; autopsy was performed but results not known; Initial reporter's occupation: nurse **[NOTE: duplicate report of same subject death submitted as FAERS Case 1343725 (version 1).]**

30. **FAERS Case 11564102 (version 1); Manufacturer's report number ID-UCBSA-2015030529:** AE "death" occurred (b) (6); reported cause of death was COPD acute exacerbation and pneumonia; male aged 90 years from Indonesia on LCTZ 5 mg once daily from 8/8/15-8/9/15 for unknown indication; AE severe somnolence "hypersomnia" started 8/8/15, followed by AEs coma (began 8/9/15) and vocal cord edema; also taking cetirizine and Depressan, which were both stopped on 8/9/15; medical history included fall, fractured hip, hip surgery on (b) (6), lung neoplasm, vertigo; autopsy was not performed; Initial reporter's occupation: physician.
31. **FAERS Case 12094175 (version 1); Manufacturer's report number FR-UCBSA-2016006121;** AE "death" occurred on (b) (6) with cause of death listed as SAE "diabetic ketoacidotic hyperglycemic coma"; male aged 86 years in France on LCTZ 5 mg qd from 11/8/15 to 11/12/15 for unknown indication; hospitalized on (b) (6) for the rare and life-threatening delayed drug hypersensitivity reaction known as DRESS (drug rash with eosinophilia and systemic symptoms) syndrome treated with IV steroids; on (b) (6), patient developed hyperosmolar coma, acidocetosis and aspiration (after vomiting); on (b) (6), he developed hypovolemic shock and acute renal failure; he temporarily improved but developed sepsis on (b) (6) and died on (b) (6); it was unknown whether an autopsy was performed; ; Initial reporter's occupation: "other health professional"
32. **FAERS Case 12098408 (version 1); Manufacturer's report number JP-UCBSA-2016005847:** AE "death" occurred on (b) (6) in association with the SAE "somnolence/sedation"; male aged 79 years in Japan on LCTZ 5 mg qd from 2/5/16 to 2/10/16 for "itchy skin"; he had known hypertension and chronic renal impairment (2/5/16 creatinine clearance 20; BUN 33.1 mg/dL) and received a higher than appropriate dose of LCTZ for someone with renal impairment (i.e., 5 mg once daily); he was hospitalized on (b) (6) for urinary retention, somnolence and worsening renal impairment (2/9/16 creatinine clearance 6.8; (b) (6) BUN 12.95 mg/dL); he began dialysis on (b) (6), his clinical condition worsened gradually and he died on (b) (6) of "renal function aggravated, electrolyte abnormality and under nutrition"; it is unknown whether an autopsy was performed; Initial reporter's occupation: pharmacist.

Reviewer's comment: *It is the opinion of this reviewer that two of the above 32 deaths are potentially concerning (i.e., UCBSA-2015014317: 39 year old healthy female from Oman who died from cardiac arrest and UCBSA-2014001099: 11 month old female with apparent mild URI) because each of them could have experienced QT prolongation and torsades de pointes. However, 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*

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(hydroxyzine hydrochloride) and LCTZ, with Atarax generally considered to be a more frequent cause of QT prolongation than LCTZ [NOTE: see Section 2.4 of this review pg. 21 for additional information pertaining to hydroxyzine and QT prolongation] and the 11 month old female was concomitantly taking both procaterol hydrochloride and LCTZ. The antiasthmatic procaterol is listed as having been associated with QT prolongation (with no mention of TdP or tachyarrhythmias) in clinical studies.¹⁷²

7.3.2 Nonfatal Serious Adverse Events

In the clinical studies, 54 subjects (0.8%) in the levocetirizine group, 2 subjects (<0.1%) in the active comparator group, and 57 subjects (1.4%) in the placebo group experienced at least one treatment-emergent serious adverse event (SAE).¹⁷³ Within the levocetirizine group, the most frequently reported treatment-emergent SAE was wheezing, which occurred in 15 (all <6 years of age) of the 6685 subjects (0.2%) treated with levocetirizine, compared to twenty (all <6 years of age) of the 3963 subjects (0.5%) treated with placebo and none of the 2808 subjects treated with an active comparator. The next most frequently reported treatment-emergent SAEs in the levocetirizine group were bronchopneumonia (n=4), febrile convulsion (n=4), cough (n=4) and dermatitis atopic (n=4), which again occurred exclusively in subjects <6 years of age.

In UCB's internal post marketing safety database, a total of 955 serious events for LCTZ 5 mg oral tablets were reported in 459 cases, with the ten most common serious events MedDRA preferred terms being suicide attempt (n=22), seizure (n=22), dyspnea (n=18), somnolence (n=18), loss of consciousness (n=16), angioedema (n=14), malaise (n=13), intentional overdose (n=12), urticaria (n=12), anaphylactic shock (n=11). In UCB's internal post marketing safety database, a total of 710 serious events for LCTZ oral drops and LCTZ formulation unknown were reported in 359 cases, with ten most common serious events MedDRA preferred terms being exposure during pregnancy (n=28), abortion spontaneous (n=24), angioedema (n=23), urticaria (n=20), somnolence (n=16), seizure (n=14), overdose (n=13), abortion induced (n=11), dyspnea (n=9) and hepatitis n=9. In UCB's internal post marketing safety database, a total of 56 serious events for LCTZ oral solution were reported in 25 cases, with only six serious events MedDRA preferred terms occurring more often than once, i.e., overdose (n=4), anaphylactic reaction (n=3), rash (n=3), dizziness (n=2), seizure (n=2) and somnolence (n=2).

7.3.3 Dropouts and/or Discontinuations

In the clinical studies, 77 subjects (1.2%) in the levocetirizine group, 9 subjects (0.3%) in the active comparator group, and 64 subjects (1.6%) in the placebo group

¹⁷² De Ponti F et al. Non-antiarrhythmic drugs prolonging the QT interval: considerable use in seven countries. *Br J Clin Pharmacol*. 2002 Aug; 54 (2): 171-177.

¹⁷³ NDA 209089 Module 2.7.4 Summary of Clinical Safety, Table 11, pg. 39.

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prematurely discontinued treatment due to a treatment emergent adverse event (TEAE).¹⁷⁴

Of the 77 subjects in the levocetirizine group who discontinued treatment due to a TEAE, 21 subjects discontinued due to somnolence, seven due to headache, four due to fatigue, four due to asthenia and 4 due to pregnancy.

7.3.4 Significant Adverse Events

The sponsor considered **sedation** [preferred terms (PT): lethargy, neonatal oversedation, sedation, somnolence, somnolence neonatal, sopor, stupor and lower level term (LLT): narcosis], **urinary retention** (PT: urinary retention postoperative, bladder discomfort, bladder pain, bladder spasm, incontinence, micturition disorder, micturition frequency decreased, micturition urgency, pollakiuria, stangury, stress urinary incontinence) and **torsade de pointes/QT prolongation** (PT: electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged, long QT syndrome, Torsade de pointes, ventricular tachycardia) to be adverse events of special interest (AESI). This reviewer agrees with the three above sponsor AESIs and also considers **fatigue** and **asthenia** to be AESIs. From the medical literature, three additional significant adverse events were: **hepatotoxicity**, **drug-induced lung injury** and **iridocyclitis**.

Regarding **sedation**, 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 (see Section 7.5.2 of this review for additional details). 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. It should be noted that sedation impairs driving ability, work and school performance and comprises various conditions including somnolence, impairment in learning ability, concentration and cognitive functions (e.g., psychomotor performance, memory, attention and coordination, sedation).¹⁷⁵ There has been no standardized approach to assess the effects of sedation by psychometric measurements¹⁷⁶; however, a draft guidance providing recommendations on the evaluating of drug effects on the ability to operate a motor vehicle has been posted.¹⁷⁷ Subjective assessment of somnolence

¹⁷⁴ NDA 209089 Module 2.7.4 Summary of Clinical Safety, pg. 41.

¹⁷⁵ Ergun T, Kus S. Adverse systemic reactions of antihistamines: Highlights in sedating effects, cardiotoxicity and drug interactions. *Current Medicinal Chemistry: Anti-Inflammatory and Anti-Allergy Agents*. 2005; 4 (5): 507-515.

¹⁷⁶ Ergun T, Kus S. Adverse systemic reactions of antihistamines: Highlights in sedating effects, cardiotoxicity and drug interactions. *Current Medicinal Chemistry: Anti-Inflammatory and Anti-Allergy Agents*. 2005; 4 (5): 507-515.

¹⁷⁷ U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Draft Guidance *Evaluating Drug Effects on the Ability to Operate a Motor Vehicle*. January 2015, available at:

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does not correlate with objective measures on psychomotor skills and thus, may be unreliable.¹⁷⁸ In a simulated car-driving 4-way crossover study evaluating the effects on driving of single doses of levocetirizine 5 mg, fexofenadine 60 mg, diphenhydramine 50 mg and placebo in 20 healthy volunteers, levocetirizine and fexofenadine did not impair simple brake reaction time, choice break reaction test, lateral tracking and a multiple task, while diphenhydramine did.¹⁷⁹ In a one-year duration Prescription-Event Monitoring (PEM) study conducted in England and initiated soon after levocetirizine was launched onto the United Kingdom (UK) market in September 2001, drowsiness/sedation was more frequently reported for the whole cohort (n=12,367 subjects) in the first month after starting treatment with levocetirizine (46 events) than the second month (4 events).¹⁸⁰ When the results of this PEM study was compared to a similar PEM study evaluating desloratadine (also launched in UK in 2001), more first reports of drowsiness/sedation occurred in the first month after starting treatment with levocetirizine (46 events) than with desloratadine (9 events).¹⁸¹

Regarding **urinary retention**, two (<0.1%) of the 6685 subjects exposed to levocetirizine reported at least one TEAE of urinary retention (both pollakiuria “frequent urge to urinate”), compared to none (0%) of the 3963 subjects exposed to placebo and compared to two (<0.1%) of the 2808 subjects exposed to an active comparator (both “urinary frequency”).¹⁸²

Reviewer’s comment: *It is the opinion of this reviewer that because the number of urinary retention TEAEs reported during the sponsor’s 62 clinical trials were so few, it is not anticipated to be a significant problem if LCTZ is approved for OTC switch.*

Regarding **torsade de pointes/QT prolongation**, 2 (<0.1%) of the 6685 subjects exposed to levocetirizine reported at least one event of one torsade de pointes/QT prolongation-related TEAE, compared to none (0%) of the 3963 subjects exposed to placebo and one (<0.1%) of the 2808 subjects exposed to an active comparator. All three subjects experienced this TEAE during the QT study A00419 with the two subjects in the levocetirizine group (one dosed with 5 mg and one dosed with 30 mg) each

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm430374.pdf>

¹⁷⁸ Ergun T, Kus S. Adverse systemic reactions of antihistamines: Highlights in sedating effects, cardiotoxicity and drug interactions. *Current Medicinal Chemistry: Anti-Inflammatory and Anti-Allergy Agents*. 2005; 4 (5): 507-515.

¹⁷⁹ Inami A et al. A simulated car-driving study on the effects of acute administration of levocetirizine, fexofenadine, and diphenhydramine in healthy Japanese volunteers. *Hum Psychopharmacol*. 2016 May; 31 (3) 167-77.

¹⁸⁰ Layton D et al. Examining the utilization and tolerability of the non-sedating antihistamine levocetirizine in England using prescription-event monitoring data. *Drug Saf*. 2011; 34 (12): 1177-89.

¹⁸¹ Layton D et al. Comparison of the risk of drowsiness and sedation between levocetirizine and desloratadine: a prescription-event monitoring study in England. *Drug Saf*. 2006; 29 (10): 897-909.

¹⁸² Subjects A00333/086-1030 treated with LCTZ 5 mg and A00384/075-0941 treated with LCTZ 2.5 mg both reported the TEAE “pollakiuria”. Subjects A00394/140-02698 treated with desloratadine 5 mg and A00414/001-0215 treated with montelukast 10 mg both reported the TEAE “urinary frequency”.

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experiencing an isolated episode of non-sustained ventricular tachycardia during Holter monitoring (Subject 419-001-00108 treated with 5 mg experienced 7 ventricular complexes and Subject 419-001-00110 treated with 30 mg experienced 9 ventricular complexes) and both occurred more than 12 hours after single dosing. The subject treated with moxifloxacin 400 mg [Subject A00419/001-0041] experienced the TEAE "electrocardiogram QT prolonged/Long QTC".

Reviewer's comment: *It is the opinion of this reviewer that because the number of QT prolonged TEAEs reported during the sponsor's QT study are so few, it is not anticipated to be a significant problem if LCTZ is approved for OTC switch*

Regarding **fatigue**, 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.

Regarding **asthenia**, 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 cumulative 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.

Regarding **hepatotoxicity**, 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.¹⁸³ In this case, liver enzymes gradually normalized 20 days after first stopping the levocetirizine and 4 weeks after stopping the levocetirizine during the rechallenge.

Regarding **drug-induced lung injury**, one report in the medical literature linked a three-month exposure to levocetirizine in a nonsmoking woman in her 60s who developed a nonproductive cough, shortness of breath, non-specific interstitial pneumonia that improved following withdrawal of levocetirizine.¹⁸⁴ A drug lymphocyte

¹⁸³ Ekiz F et al. Levocetirizine induced hepatotoxicity in a patient with chronic urticaria. *Ann Hepatol.* 2011 Apr-Jun; 10 (2): 237-8.

¹⁸⁴ Endo S et al. Histamine H₁ antagonist levocetirizine as a potential cause of lung injury. *Respirol Case Repo.* 2015 Jun; 3 (2): 64-7.

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stimulation test was positive for levocetirizine and her illness did not recur under steroid therapy and the discontinuation of levocetirizine; thus, the authors considered this to be the first reported case of levocetirizine-induced lung injury.

Regarding **iritidocyclitis**, there is one report in the medical literature of levocetirizine-induced iridocyclitis in a patient with allergic rhinitis, which recurred upon rechallenge of only one dose of levocetirizine.¹⁸⁵

7.3.5 Submission Specific Primary Safety Concerns

The primary safety concern noted in this submission is sedation (PT: lethargy, neonatal oversedation, sedation, somnolence, somnolence neonatal, sopor, stupor; LLT: narcosis) and whether somnolence adverse events would be more frequent if once daily LCTZ was no longer dosed once daily in the evening (b) (4)

It should be noted that the adverse event term "somnolence" appeared to overlap with "fatigue" and "asthenia".

7.4 Supportive Safety Results

(b) (4)

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 different in the incidence of the TEAE somnolence in these two groups.¹⁸⁷ 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 bedtime¹⁸⁸; thus, the Rx labeling for once daily LCTZ tablet and solution instructs the patient to dose once daily in the evening.

Reviewer's comment: *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*

¹⁸⁵ Konstantinou GN et al. Levocetirizine-induced iridocyclitis in a patient with allergic rhinitis. *J Investig Allergol Clin Immunol.* 2010; 20 (1): 90-1.

¹⁸⁶ Original NDA 209089 Section 2.7.4 on pg. 32 of 65.

¹⁸⁷ 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.

¹⁸⁸ Per the sponsor; see Original NDA 209089 Section 2.7.4 Summary of Clinical Safety on pg. 32 of 65.

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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.

7.4.1 Common Adverse Events

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

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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.

See Section 7.5.2 of this review for a discussion of time dependency of the common adverse events "somnolence" and "fatigue".

7.4.2 Laboratory Findings

No pertinent laboratory findings have been noted with LCTZ. Elevations of blood bilirubin and transaminases were reported in $<1\%$ of subjects enrolled in clinical studies in which laboratory data were collected. The elevations were transient and did not lead to discontinuation in any subject.

7.4.3 Vital Signs

Analyses of vital signs data (blood pressure and heart rate) from studies in which the data were collected did not reveal any significant changes in vital signs values in adult/adolescent or pediatric populations.

7.4.4 Electrocardiograms (ECGs)

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

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ECGs measured at controlled time points in a large double-blind, placebo-controlled efficacy study.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The incidence of sedation-related TEAEs tended to increase with increasing dose of levocetirizine, although there is limited safety data available for doses greater than the highest approved dose, which is 5 mg. The incidence of torsade de pointes/QTc-related TEAEs do not appear to increase with increasing dose of levocetirizine (i.e., in the QTc study A00419, there was one ventricular tachycardia TEAE on LCTZ 5 mg and one ventricular tachycardia TEAE on LCTZ 30 mg).

7.5.2 Time Dependency for Adverse Events

Because [REDACTED] (b) (4) it is particularly important to assess time dependency for adverse events that would be less acceptable if reported more frequently when Xyzal was dosed in the morning compared to dosing in the evening (i.e., near bedtime). [REDACTED] (b) (4)

[REDACTED] . All eleven of these UCB studies had been previously submitted in Original NDA 022064 to support the approval of LCTZ tablet.¹⁸⁹

Table 8: Three Levocetirizine Only-Morning Dosing Studies (per Sponsor and Reviewer)

¹⁸⁹ The safety data from all 11 of these studies was previously reviewed by Robert M. Boucher, MD in his Clinical Review of Original NDA 022064 finalized in DARRTS on 4/3/07, which included the statement (on pg. 10) "since all of the pertinent clinical trials in the NDA dose levocetirizine in the evening, and sedation-related effects of daytime use are not characterized in the application, the label recommendation should be for evening dosing only".

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Study Number	LCTZ 5 mg # Dosed Subjects	LCTZ 5 mg # Somnolence/ Sedation TEAEs	LCTZ 5 mg # Fatigue TEAEs	LCTZ 5 mg # Asthenia TEAEs
A00391 ; Phase 4 single center, no placebo; active-controlled; switch to other active treatment allowed after first week	100	0 (10 of the 12 LCTZ subjects who opted to switch to DES due to side effects reported fatigue; 3 of 4 DES subjects who opted to switch due to side effects reported fatigue)	16	0
A00394 ; Phase 4 no placebo; active controlled	438	36 (includes 2 “sedation”; 1 LCTZ subject prematurely discontinued due to somnolence)	19	2
A00401 ; Phase 4 4:4:1 randomized; PBO and active-controlled	342	13 (1 LCTZ subject prematurely discontinued due to somnolence)	7	8
Total	880 (935 per sponsor¹⁹⁰)	49 (46 per sponsor¹⁹¹)	42 (37 per sponsor)	10

Source: Original NDA 209089 Section 2.7.4 Tables 9 and 10 on pg. 34-35 of 65 and Reviewer analysis of Tables of Individual TEAEs in Final Study Reports.

Table 9: Eight Levocetirizine Only-Evening Dosing Studies (per Sponsor and Reviewer)

Study Number	LCTZ 2.5 mg # Dosed Subjects	LCTZ 5 mg # Dosed Subjects	LCTZ 10 mg # Dosed Subjects	LCTZ 2.5 mg # Somnolence TEAEs	LCTZ 5 mg # Somnolence TEAEs	LCTZ 10 mg # Somnolence TEAEs
A217 Phase 2 PBO-controlled	117	116	118	3	2	12 (of which, 4 prematurely withdrew due to severe somnolence)
A219 Phase 2 PBO-controlled	105	103	109	7	4	3
A222 Phase 3 active & PBO-controlled	0	319	0	N/A	28 (1 prematurely withdrew due to moderate somnolence)	N/A
A00265 Phase 2 PBO-controlled	133	128	130	7	7	12

¹⁹⁰ Per Original NDA 209089 Section 2.7.4 Table 9 on pg. 34 of 65.

¹⁹¹ Per Original NDA 209089 Section 2.7.4 Note for “Table 9 – Treatment emergent adverse events in morning compared to evening dosing studies” and for “Table 10 – Sedation related treatment-emergent adverse events in morning compared to evening dosing studies” (i.e., “NOTE: Subject are counted only once per preferred term as well as per system organ class”) on pg. 34 and 35 of 65. Thus, it appears to this reviewer that sponsor provided the number of subjects with at least one TEAE in Tables 9 and 10, rather than the number of TEAEs.

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Study Number	LCTZ 2.5 mg # Dosed Subjects	LCTZ 5 mg # Dosed Subjects	LCTZ 10 mg # Dosed Subjects	LCTZ 2.5 mg # Somnolence TEAEs	LCTZ 5 mg # Somnolence TEAEs	LCTZ 10 mg # Somnolence TEAEs
A00266 Phase 3 PBO-controlled	0	150	0	N/A	9	N/A
A00268 Phase 3 PBO-controlled	0	119	0	N/A	7	N/A
A00269 Phase 3 PBO-controlled	0	81	0	N/A	0	N/A
A00270 Phase 2 PBO-controlled	70	65	59	5	8	11
Total	425 (421 per sponsor)	1081 (1070 per sponsor)	416 (414 per sponsor)	22 /425 5.2%	65 (61 per sponsor) /1081 6%	38/416 9.1%

Study Number	LCTZ 2.5 mg # Fatigue TEAEs	LCTZ 5 mg # Fatigue TEAEs	LCTZ 10 mg # Fatigue TEAEs	LCTZ 2.5 mg # Asthenia TEAEs	LCTZ 5 mg # Asthenia TEAEs	LCTZ 10 mg # Asthenia TEAEs
A217; Phase 2; PBO-controlled	1	6	7	1	1	2
A219	0	1	0	1	0	4
A222	N/A	8	N/A	N/A	6	N/A
A00265	3	11	3	4	1	5
A00266	N/A	7	N/A	N/A	1	N/A
A00268	N/A	4	N/A	N/A	0	N/A
A00269	N/A	10	N/A	N/A	1	N/A
A00270	0	4	1	0	0	5
Total	4 (5 per sponsor)	51 (46 per sponsor)	11 (10 per sponsor)	6	10	16

This reviewer then evaluated all 62 UCB clinical studies to determine which studies dosed only in the evening bedtime and only in the AM. Per Table 10 (see below), the 2496 subjects dosed with LCTZ only in the morning reported a total of 395 LCTZ somnolence/sedation, fatigue and asthenia TEAEs, which accounted for 29.9% of the total number of LCTZ TEAEs (i.e., 1319) reported in these 32 studies. When the 60 subjects only administered LCTZ > 5 mg (i.e., 10 mg or 30 mg) in the morning and the 117 TEAEs (including 31 somnolence, 23 fatigue and 0 asthenia TEAEs) reported by a subject after administered LCTZ > 5 mg (i.e., 10 mg or 30 mg) only in the morning were removed from this table, the remaining 2436 subjects dosed with LCTZ ≤ 5 mg only in the morning reported a total of 341 LCTZ somnolence/sedation, fatigue and asthenia

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TEAEs, which accounted for 28.4% of the total number of LCTZ ≤ 5 mg TEAEs (i.e., 1202) reported in these studies.

Table 10: Levocetirizine Only-Morning Dosing Studies (n=32; per Reviewer)

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 (all 5 mg)	1	0	0	0
A221	24 (all 10 mg)	14	0	6	0
A230	18 (all 5 mg)	8	0	0	0
A232	24 (all 5 mg)	22	4	3	0
A233	4 (all 5 mg)	3	0	0	0
A238	21 (all 5 mg)	28	5	6	0
A245	38 (all 5 mg)	2	0	0	0
A246	49 (all 5 mg)	236	93	30	9
A252	19 (all 5 mg)	3	0	1	0
A254	15 (all 5 mg)	1	0	0	0
A256	70 (all 5 mg)	1	0	0	0
A00260	18 (all 5 mg)	15	4	0	4
A00263	36 (all 30 mg)	75	20	11	0
A00280	18 (all 5 mg)	17	13	2	0
A00297	24 (all 5 mg)	13	0	2	0
A00318	24 (all 5 mg)	51	17	0	0
A00331	141 (all 5 mg)	87	6	4	0
A00340	12 (all 5 mg)	0	0	0	0
A00351	30 (all 5 mg)	3	0	1	0
A00373	18 (all 5 mg)	1	0	0	0
A00379	240 (all 5 mg)	44	0	5	0
A00391	100 (all 5 mg)	108	0	16	0
A00392	62 (all 5 mg)	24	4	0	0
A00394	438 (all 5 mg)	284	36 (including one premature discontinuation)	19	2
A00401	342 (all 5 mg)	93	13 (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 (all 5 mg)	16	2	3	0
A00415	152 (all 5 mg)	35	5	3	0
A00419	52 (each dosed with 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 (all 5 mg)	2	0	0	0
Totals	2496	1319	244	128	23

Sources: 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

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“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 only 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 incomplete data regarding the number of LCTZ somnolence, fatigue or asthenia TEAEs were available in the limited clinical summaries provided by the sponsor.

Per Table 11, the 3821 subjects dosed with **LCTZ only in the evening/bedtime** reported a total of **386 LCTZ somnolence, fatigue and asthenia TEAEs**, which accounted for **8.5%** of the total number of LCTZ TEAEs (i.e., 4549) reported in these 17 studies. When the 416 subjects only administered LCTZ > 5 mg (i.e., 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 > 5 mg (i.e., 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 **7.8%** of the total number of LCTZ ≤ 5 mg TEAEs (i.e., 4125) reported in these studies.

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

Study	# LCTZ Subjects	# LCTZ TEAEs	# LCTZ Somnolence/Sedation 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 was located in study report; so all AE information was presumed to be TEAEs.]	201 (56 on 2.5 mg, 51 on 5 mg, 94 on 10 mg)	17 (3 on 2.5 mg, 2 on 5 mg, 12 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)	14 (7 on 2.5 mg, 4 on 5 mg, 3 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 (all 5 mg)	522	28	8	6
A00264	278 (all 5 mg)	995	21 (including 5 premature discontinuations of treatment due to somnolence)	32 (including 3 premature discontinuation of treatment due to tiredness)	5
A00265	391 (133 on 2.5	507 (183 on	26 (7 on 2.5 mg, 7 on 5	17 (3 on 2.5	10 (4 on 2.5

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Study	# LCTZ Subjects	# LCTZ TEAEs	# LCTZ Somnolence/Sedation TEAEs	# LCTZ Fatigue TEAEs	# LCTZ Asthenia TEAEs
	mg, 128 on 5 mg, 130 on 10 mg)	2.5 mg, 165 on 5 mg, 159 on 10 mg)	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)	mg, 11 on 5 mg, 3 on 10 mg) including 1 premature discontinuation due to fatigue on 5 mg	mg, 1 on 5 mg, 5 on 10 mg)
A00266 bedtime	150 (all 5 mg)	384	9	7	1
A00268	119 (all 5 mg)	163	7	4	0
A00269	81 (all 5 mg)	89	0	10	1
A00270	194 (70 on 2.5 mg, 65 on 5 mg, 59 on 10 mg)	263 (71 on 2.5 mg, 92 on 5 mg, 100 on 10 mg)	24 (5 on 2.5 mg, 8 on 5 mg, 11 on 10 mg , including 2 premature discontinuations due to somnolence, both on 10 mg)	5 (4 on 5 mg, 1 on 10 mg)	5 (5 on 10 mg)
A00299 bedtime	30 (all 5 mg)	12	0	0	0
A00303	89 (all 5 mg)	45	1	1	2
A00304	154 (all 5 mg)	150	6	3	0
A00306	303 (all 5 mg; 150 LCTZ/LCTZ; 153 PBO/LCTZ)	424 (217 LCTZ/LCTZ; 207 PBO/LCTZ); including 1 sedation TEAE in LCTZ/LCTZ resulting in premature discontinuation)	7 (5 LCTZ/LCTZ; 2 PBO/LCTZ; including 1 premature discontinuation in LCTZ/LCTZ due to somnolence)	15 (12 LCTZ/LCTZ; 3 PBO/LCTZ)	6 (3 LCTZ/LCTZ; 3 PBO/LCTZ including 1 premature discontinuation in LCTZ/LCTZ due to asthenia)
A00333	226 (all 5 mg)	165	18 (including 4 premature discontinuations due to somnolence)	6	6 (including one premature discontinuation due to asthenia)
A00410 bedtime	231 (all 5 mg)	12	2	0	0
A00430	301 (all 5 mg)	120	16	9	0
A00431	287 (all 5 mg)	82	2	5	0
Totals	3821	4549	198	137	51

Sources: 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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Reviewer's comments:

1.  (b) (4)
2. *In the clinical studies submitted by the sponsor, a significantly smaller percentage of somnolence/sedation, fatigue and asthenia LCTZ TEAEs (i.e., **8.5%** or 386 of the total 4549 LCTZ TEAEs) were reported when levocetirizine was **administered only in the evening/bedtime** (to 3821 subjects in 17 studies) compared to the much larger percentage of somnolence/sedation, fatigue and asthenia LCTZ TEAEs (i.e., **29.9%** or 395 of the total 1319 LCTZ TEAEs) that were reported when levocetirizine was **administered only in the morning** (to 2496 subjects in 32 studies).*
3. *In the clinical studies submitted by the sponsor, a significantly smaller percentage of somnolence/sedation LCTZ TEAEs (i.e., **4.4%** or 198 of the total 4549 LCTZ TEAEs) were reported when levocetirizine was **administered only in the evening/bedtime** (to 3821 subjects in 17 studies) compared to the much larger percentage of somnolence/sedation, fatigue and asthenia LCTZ TEAEs (i.e., **18.5%** or 244 of the total 1319 LCTZ TEAEs) that were reported when levocetirizine was administered **only in the morning** (to 2496 subjects in 32 studies).*

7.5.3 Drug-Demographic Interactions

The overall percentage of subjects with any TEAE was greatest among the younger age groups; however, somnolence was a common TEAE only in the subjects ≥ 12 years of age. In subjects ≥ 12 years of age, female subjects had a higher overall incidence of TEAEs compared to male subjects; however, gender was not a meaningful interaction in children < 12 years of age. No meaningful differences between treatment groups based on race were noted; however, the overall number of non-white subjects was small.

7.5.4 Drug-Disease Interactions

No new analyses or clinical studies evaluating drug-disease interactions were submitted in NDA 209089 or NDA 209090. Previously submitted data in the levocetirizine NDAs have demonstrated that levocetirizine exposure or area under the curve (AUC) is increased by 1.8-, 3.2- and 4.3-fold in subjects with mild, moderate and severe renal impairment (Study A230) and subjects with end stage renal disease had an increase of 5.7-fold (Study A234). Levocetirizine has not been studied in subjects with hepatic impairment because it is mainly excreted unchanged by the kidney.

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7.5.5 Drug-Drug Interactions

No studies of drug-drug interactions have been conducted in the UCB clinical development program for levocetirizine because the extent of metabolism of levocetirizine in humans is less than 14% of the dose; therefore, negligible interactions are expected with concomitant CYP450 inhibitors or inducers on levocetirizine exposure. 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.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

This reviewer is unaware of any safety signal for human carcinogenicity that has been linked to levocetirizine. Levocetirizine was not mutagenic in the Ames test, and not clastogenic in the in vitro human lymphocyte assay and mouse lymphoma assay, and in vivo micronucleus test in mice.

7.6.2 Human Reproduction and Pregnancy Data

A total of 11 subjects (eight in the levocetirizine group and three in the placebo group) became pregnant during the levocetirizine clinical studies. In the levocetirizine group, five subjects were discontinued when it was learned that they were pregnant, two subjects had already completed treatment at the time that the pregnancy was discovered, and one subject the action taken was recorded as "not applicable" (although the Clinical Study Report indicates that the subject discontinued treatment when the pregnancy was discovered). Four women delivered healthy babies, two had unknown outcomes, one pregnancy was voluntarily terminated, and one delivered a child with hypospadias (attributed to family history). There were no reports from the clinical database for the use of levocetirizine during lactation. It should be noted that an observational cohort study (including 78 pregnancies exposed to cetirizine during the first trimester, 56 pregnancies exposed during second and/or third trimester and 134 pregnancies exposed to non-teratogenic drugs) and meta-analysis (10 studies) pertaining to the fetal safety of cetirizine has been published with the conclusion that cetirizine is not associated with a clinically important increase in risk of adverse fetal outcomes.¹⁹²

¹⁹² Etwel F et al. The fetal safety of cetirizine: an observational cohort study and meta-analysis. *J Obstet Gynaecol.* 2014 Jul; 34 (5): 392-9.

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In the NDA 209089 ISS and the FAERS database re: levocetirizine, this reviewer located a total of five postmarketing cases involving "fetal malformation":

- 1) **Manufacturer's report number UCBSA-8012508 (associated case UCBSA-8012506 for mother):** AE "elective termination" occurred in "May 2005" after a fetal malformation (not specified) was confirmed after an amniocentesis was performed during 4th month of pregnancy; 30 year old female in Greece took LCTZ 5 mg TID and Medrol (methylprednisolone) during "January 2005" (specific dates not provided) for wheals and itching and stopped both medications during the second week of treatment when she realized she was pregnant.
- 2) **FAERS Case 6563017 (version 1); Manufacturer's report number UCBSA-8029691 (associated case UCBSA-8023420 for mother):** AE "elective pregnancy termination" occurred in "2007" after fetal malformation "Tetralogy of Fallot" diagnosed "July 2007" during echography at 22 weeks gestation; fetal karyotype indicated 22Q deletion; 34 year old female G1P0000 in France with no relevant medical history took 4 or 5 tablets of LCTZ in early pregnancy before she realized that she was pregnant (exposure to LCTZ occurred at 1.5 months of pregnancy); Initial reporter's occupation: physician.
- 3) **FAERS Case # 7067016 (version 1); Manufacturer's report number UCBSA-8049388 (associated case UCBSA-8049402 for mother; same case also reported by AstraZeneca FR-ASTRAZENECA-2009SE05569):** AE "elective pregnancy termination" occurred on 4/15/09 after fetal malformation "spina bifida; lumbo-sacral lumbo-myelo-meningocele" diagnosed 3/23/09 during echography at 12 weeks gestation; 25 year old female G1P0000 in France with history of multiple allergies took LCTZ tablets once daily in early pregnancy until 2/14/09, when she was 7.5 weeks pregnant); also took Rhinocort (nasal budesonide dosed every other day) and Mucohime (nasal homeopathy drug dosed every other day) until 2/14/09; Initial reporter's occupation: physician.
- 4) **FAERS Cases 8047676 (version 1; received on 6/22/09) and 7039218 (version 2; received on 8/19/09)** were submitted regarding a fetus exposed in utero during the first 8 weeks of the first trimester to Xyzal resulting in a miscarriage on 3/1/09 at 19 weeks gestation (weight 0.25 kg) with the fetus having numerous abnormalities (i.e., small mouth, low set ears, receding chin and talipes). During this pregnancy, an amniocentesis for increased Down's risk was performed (presumably at 16 weeks gestation) and the chromosomes were normal. The mother was 32 years old, had two previous normal births, her LMP was 11/8/08, concomitant medication included steroid inhalations for asthma and she "took 10 units of alcohol per week but did not drink alcohol".
- 5) **FAERS Case 7768389 (version 1); Manufacturer's report number UCBSA-023801:** AE "death" due to "medical termination of pregnancy" occurred on (b) (6) in France at 36 weeks and 3 days gestation after major congenital hydrocephalus of 4 ventricles with necrotic mass in parietal foramen ("central nervous system necrosis") was diagnosed by ultrasonography on 8/18/09; mother had taken LCTZ at an unknown dose, unknown frequency and for an unknown indication, in addition to taking Celestamine (betamethasone;

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chlorphenamin), Spasfon (phloroglucinol, trimethylphloroglucinol) and Doliprane (paracetamol) during the pregnancy; Initial reporter's occupation: physician

Reviewer's comment: *It is the opinion of this reviewer that attribution of these fetal malformations to LCTZ is not possible because of the limited number of reports and the relatively high expected rate of fetal malformations (i.e., 2.35% (n=243) of 10,414 fetuses evaluated by second trimester ultrasound and as newborn had congenital abnormalities).*¹⁹³

7.6.3 Pediatrics and Assessment of Effects on Growth

The eight Phase 2-3-4 clinical studies previously conducted by UCB in children aged 6 months to 12 years old (n=8) have provided reassuring safety information regarding the use of LCTZ in this population. For example, in the Phase 2-3-4 short-term studies in children, of 447 subjects exposed to levocetirizine at a dose of 1.25 mg, 2.5 mg, or 5 mg, 210 subjects (47.0%) reported at least one TEAE, and of 323 subjects exposed to placebo, 145 subjects (44.9%) experienced at least one TEAE. The incidence of TEAEs in all treatment groups was greater in the pool of studies with children compared with adults/adolescents aged ≥ 12 years. This reviewer has not located any safety signal regarding a negative effect of LCTZ on pediatric growth.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In the clinical database, one subject experienced an accidental overdose and two subjects experienced an overdose in the 5 mg levocetirizine group. Each of these events occurred in adult subjects (ages 18 to 30 years). Only one of these subjects permanently discontinued IMP due to overdose. None of these events was considered serious and all subjects recovered. Per the sponsor (Module 2.7.4 pg. 50), most misuse cases were either nonfatal, off-label use, or intentional overdoses, levocetirizine did not appear to have any liability as a drug of abuse, the assessment of suicidality showed no verifiable relationship between levocetirizine and suicidal ideation and none of the cases of suicidality resulted in death.

7.7 Additional Submissions / Safety Issues

An important safety issue is the effect of levocetirizine on the consumer's ability to drive or operate machinery and whether there is impairment of consumer's mental ability. Two studies have been conducted to examine the effect of levocetirizine on cognitive function (Study A00260) and driving performance (Study A246). Study A00260 evaluated the effect of 5 mg levocetirizine on overall central nervous system activity

¹⁹³ Rydberg C, Tunon K. Detection of fetal abnormalities by second trimester ultrasound screening in a non-selected population. *Acta Obstet Gynecol Scand*. 2016 Oct 7. doi: 10.1111/aogs.13037. [Epub ahead of print]

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measured mainly by the critical flicker fusion test in 18 healthy male subjects.

Levocetirizine did not produce any negative effect on cognitive and psychometric functions compared with placebo. Study A246 investigated the effects of levocetirizine 5 mg, on driving ability during normal traffic. No difference was observed between levocetirizine and placebo in the primary efficacy parameter (standard deviation of lateral position).

Reviewer's comment: *It is the opinion of this reviewer that the cognitive function study A00260 and the driving information study A246 does not fully address the concern of potential somnolence if levocetirizine is taken in the daytime. This reviewer notes that 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).*

In the medical literature, a prospective, ascending multiple-dose first in human type IQ-CSRC¹⁹⁴ study (designed to replace the currently applied thorough QT study) correctly categorized levocetirizine as a QTc-negative drug.¹⁹⁵ In the future, such studies may be used, in addition to, or instead of, the currently recommended thorough QT study.

8 Postmarket Experience

It should first be noted that postmarket experience has limitations:

Adverse drug reaction (ADR) reports are generated by case recognition and result in anecdotal reports of probably less than 10% of all events. The system relies on either the patient bringing the side-effect to the attention of the doctor or the doctor recognising the event and then, in either case, taking the time to make the report. All such reports have difficulties relating to the classification of exposure to the drug and the classification of endpoints, and, importantly, recall or reporting bias strongly influences individual drugs and drugs within similar classes. These factors would result in a baseline or background level of reports that are not actually due to the drug.¹⁹⁶

Per the sponsor's analysis of the worldwide sales data available from IMS Health for levocetirizine from January 1, 2006 through June 30, 2015 for 5 mg tablets and oral solution, it is estimated that (b) (4) tablets and (b) (4) of oral solution and oral drops were distributed globally. Using a defined daily dose for

¹⁹⁴ This IQ-CSRC study was a collaborative project between the IQ-consortium (Consortium for Innovation and Quality in Pharmaceutical Development, CSRC (Cardia Safety Research Consortium) and the FDA.

¹⁹⁵ Cavero I et al. The prospective IQ-CSRC trial: a prototype early clinical proarrhythmia assessment investigation for replacing the ICH E14 thorough QTc (TQT) study. *J Pharmacol Toxicol Methods*. 2016 Jul-Aug; 80: 1-8.

¹⁹⁶ Cohen AT. Dangers of non-sedating antihistamines. *Lancet*. 1997 Jul 5; 350 (9070): 69.

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levocetirizine of 5 mg these distributed amounts equate to 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.

In UCB's internal post marketing safety database, a total of 955 serious events for LCTZ 5 mg oral tablets were reported in 459 cases, with the ten most common serious events MedDRA preferred terms being suicide attempt (n=22), seizure (n=22), dyspnea (n=18), somnolence (n=18), loss of consciousness (n=16), angioedema (n=14), malaise (n=13), intentional overdose (n=12), urticaria (n=12), anaphylactic shock (n=11). In UCB's internal post marketing safety database, a total of 710 serious events for LCTZ oral drops and LCTZ formulation unknown were reported in 359 cases, with ten most common serious events MedDRA preferred terms being exposure during pregnancy (n=28), abortion spontaneous (n=24), angioedema (n=23), urticaria (n=20), somnolence (n=16), seizure (n=14), overdose (n=13), abortion induced (n=11), dyspnea (n=9) and hepatitis n=9. In UCB's internal post marketing safety database, a total of 56 serious events for LCTZ oral solution were reported in 25 cases, with only six serious events MedDRA preferred terms occurring more often than once, i.e., overdose (n=4), anaphylactic reaction (n=3), rash (n=3), dizziness (n=2), seizure (n=2) and somnolence (n=2).

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 several events associated with the use of 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 USPI 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.

The Drug Abuse Warning Network (DAWN) 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.¹⁹⁷ 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.¹⁹⁸

¹⁹⁷ Substance Abuse and Mental Health Services Administration (SAMHSA) website accessed on August 30, 2016 at: <http://www.samhsa.gov/data/emergency-department-data-dawn>

¹⁹⁸ Center for Behavioral Health Statistics and Quality. *Drug Abuse Warning Network Methodology*

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Levocetirizine was first approved in the USD in 2007. Per the sponsor, 66 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.

The NPDS 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.

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.

The sponsor also 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. 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

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>

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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.

Reviewer's comment: *The clinical reviewer concurs with the sponsor that no new safety signals precluding approval of the Rx to OTC switch for levocetirizine or warranting further investigation for levocetirizine were located in the AE reporting databases or in postmarketing experience.*

9 Appendices

9.1 Literature Review/References

Reviewer's comment: Specifically regarding information from the medical literature, the sponsor submitted a 108-page "ISS -Tabular summary of medical literature" pertaining to levocetirizine in Original NDA 209089 Section 5.3.5.3. The summaries of the 283 literature references contained in this document were reviewed, 65 of these literature references were determined by this reviewer to be potentially relevant to the safety of levocetirizine and all 65 of these references were obtained, reviewed in detail and included in the reference listing located in Section 9.1 of this review. The 78 literature references provided in Original NDA 209089 Section 5.4 were reviewed, 41 of these literature references were determined by this reviewer to be potentially relevant to the safety of levocetirizine and all 41 of these references were obtained, reviewed in detail and included in the reference listing located in Section 9.1 of this review. A separate PubMed search of "levocetirizine" was conducted by this reviewer and of the 348 listed references, six additional literature references were considered by this reviewer to be potentially relevant to the safety of levocetirizine and all six of these references were obtained, reviewed in detail and included in the reference listing located in Section 9.1 of this review. In addition, a separate EMBASE search of "levocetirizine AND safety" was conducted by this reviewer and of the 340 listed references, five additional literature references were considered by this reviewer to be potentially relevant to the safety of levocetirizine and all five of these references were obtained, reviewed in detail and included in the reference listing located in Section 9.1 of this review.

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- 2) [No authors listed] Levocetirizine: new preparation. Me-too: simply the active enantiomer of cetirizine. *Prescrire Int.* 2003;12 (67):171-2.
- 3) [No authors listed] Levocetirizine offers no benefits according to French reviewers. *Pharmaceutical Journal.* 2003 Oct 11; 271 (7270): 484.
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9.2 Labeling Recommendations

The following is the sponsor's proposed DFL submitted in Original NDA 209089:

(b) (4)

3 Page(s) of Draft Labeling have been withheld in Full as b4 (CC1/15) immediately following this page

Reviewer's comments:

1.

(b) (4)

All of the subjects in the pivotal Phase 3 placebo-controlled, double-blind clinical trials included in the pooled analysis of safety supporting the approval of the Rx LCTZ oral tablet NDA 022064 were dosed once daily *in the evening*. The safety concern is whether daytime dosing will result in somnolence and potential problems in maintaining alertness while driving. 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).¹⁹⁹ 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 recommends that OTC Xyzal be dosed once daily *in the evening*.

(b) (4)

In the clinical studies submitted by the sponsor, significantly fewer somnolence/sedation, fatigue and asthenia TEAEs were reported when levocetirizine was dosed only in the evening/bedtime (i.e., when 3821 subjects 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 and Table 11 of this review).

2. The sponsor proposes to split adults into two categories of "up to age 64" and "65 years and older" with different dosing recommendations for the two groups for both OTC dosage forms; 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

¹⁹⁹ Ferrer M. Pharmacokinetics evaluation of levocetirizine. *Expert Opin Drug Metab Toxicol*. 2011 Aug; 7 (8): 1035-47.

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and children 12 years of age and older”). This reviewer believes that the sponsor has taken this precaution for both OTC dosage forms because: a) the safety data generated in the sponsor’s 62 clinical studies were minimal for subjects aged 65 years of age and older, i.e., only 221 (1.8%) of the 11,991 subjects in the safety population submitted in the sponsor’s Integrated Summary of Safety (ISS) were ≥ 65 years of age, and b) the approved Rx Xyzal labeling in Section 2.1 DOSAGE AND ADMINISTRATION states “Some patients may be adequately controlled by 2.5 mg (1/2 tablet or 1 teaspoon [5 mL] oral solution) once daily in the evening”. Because so little safety data is available for the population of adults 65 years of age and older, this reviewer concurs with the sponsor to have adults ≥ 65 years of age “ask a doctor” before taking either OTC Xyzal dosage forms. Physicians may recommend that adults ≥ 65 years of age dose with 2.5 mg LCTZ once daily in the evening, either by splitting the 5 mg tablet in half or using the oral solution.

- 3. The sponsor proposes that OTC Xyzal Allergy 24HR tablet, 5 mg labeling should instruct consumers to “do not use” this drug product in “children under 6 years of age” and “consumers with kidney disease”. While this reviewer believes it may be the safest course for the sponsor to contraindicate (i.e., prohibit or “do not use”) children under 6 years of age and consumers with kidney disease from using OTC Xyzal, this reviewer also notes that the dosing directions for Rx Xyzal provide clear instructions for dose adjustment in patients aged ≥ 12 years with mild, moderate or severe renal impairment and contraindicates use of LCTZ in end-stage renal disease patients (e.g., CL_{CR} , 10 ml/min), patients undergoing hemodialysis, and in children aged 6 months to 11 years with impaired renal function. The Rx Xyzal labeling provides Xyzal tablet dosing instructions for patients aged ≥ 6 months. While the sponsor could revise their proposed OTC Xyzal tablet labeling to: 1) add that consumers aged ≥ 12 years with mild, moderate or severe kidney disease “ask a doctor” before using OTC Xyzal, 2) revise the “do not use” section to include consumers aged ≥ 12 years with end-stage renal disease and consumers undergoing hemodialysis, 3) revise the “do not use” section to include children under 12 years with impaired renal function, and 4) change the recommendation to “ask a doctor” for children from 6 months to under 6 years of age (because a physician would likely recommend Xyzal oral solution for the 6 months to <6 years age group), none of these revised instructions underwent testing in the sponsor’s labeling comprehension study and there may be insufficient space on the box to add all of this revised labeling. In addition, this reviewer considers the sponsor’s proposed “do not use” directions for children aged less than 6 years are correct for the OTC Xyzal Allergy 24HR tablet, 5 mg (e.g., to avoid young children choking on the tablet and to avoid dividing the 5 mg tablet into quarters to permit administration of 1.25 mg). Thus, without evidence that consumers would adequately understand the above rather complicated possible revisions to the OTC Xyzal tablet labeling, this reviewer accepts the sponsor’s proposed OTC Xyzal tablet labeling for “consumers with kidney disease” and “children under 6 years of age”, i.e., “do not use”. This reviewer notes that the dosing directions in the labeling for OTC Zyrtec Allergy (cetirizine HCl) tablets, 10 mg for both “children under 6 years of age” and “consumers with kidney*

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disease” instruct consumers to “ask a doctor”. The Rx Zyrtec labeling for both formulations does not contain any contraindication pertaining to renal impairment.

The sponsor's proposed OTC dosing regimen for Children's Xyzal Allergy 24HR oral solution, 2.5 mg/5 mL is:

(b) (4)

Reviewer's comments:

1. See above Reviewer's comments #1 for discussion of sponsor proposed dosing regimens for both OTC Xyzal formulations (b) (4)
2. See above Reviewer's comments #2 for discussion of sponsor proposed dosing directions for both OTC Xyzal formulations (i.e., different dosing directions for “adults and children 12-64 years of age” and “adults 65 years of age and older”) versus the same dosing directions for “adults and children 12 years of age and older” (in the approved labeling for both Rx Xyzal formulations).
3. The sponsor proposes that OTC Children's Xyzal Allergy 24HR oral solution, 2.5 mg/5 mL labeling should instruct consumers to “do not use” this drug product in “children under 2 years of age”. However, the dosing directions for Rx Xyzal for children 6 months to 5 years of age recommend 1.25 mg (2.5 mL) oral solution once daily dosing in the evening. Because children 6 months to under 2 years of age have Rx oral solution dosing instructions, it may be less confusing to the consumer to revise the “do not use” section in the OTC oral solution labeling to “children under 6 months of age” and revise the “ask a doctor” section in the OTC oral solution labeling to “children aged 6 months to 2 years”, because a physician would likely recommend dosing with 1.25 mg (2.5 mL) oral solution once daily in the evening for the 6 months to under 2 years age group (as recommended in the Rx Xyzal labeling). However, the sponsor may be taking this more conservative approach to ensure that very young children, i.e., children under 2 years of age, are not dosed with OTC Xyzal oral solution until after a doctor has been contacted. This reviewer accepts the sponsor proposal.

9.3 Advisory Committee Meeting

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An Advisory Committee meeting for levocetirizine tablet and/or levocetirizine oral solution is not planned. This reviewer does not recommend holding an Advisory Committee meeting for either of these two drug products.

9.4 Glossary

AAPCC	American Association of Poison Control Centers
ADME	absorption, distribution, metabolism, elimination
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AGEP	acute generalized exanthematous pustulosis
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AR	allergic rhinitis
AUC	area under the concentration time curve; exposure
BE	bioequivalence
BID	twice a day
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	cutaneous inflammation (type of pharmacodynamic study)
CIU	chronic idiopathic urticaria
CL _{CR}	creatinine clearance
C _{max}	maximum (or peak) observed serum concentration that a drug achieves in a specified compartment or test area of the body after the drug has been administered and before the administration of a second dose
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CSR	clinical study report
CTZ	cetirizine
CYP	cytochrome P450 enzymes
DAWN	Drug Abuse Warning Network
DES	desloratadine
DEX	dextrocetirizine (ucb28557)
DFL	Drug Facts Label
DIP	diphenhydramine
DNDP	Division of Nonprescription Drug Products
DP	dose proportionality (type of pharmacokinetic study)
DPARP	Division of Pulmonary, Allergy, and Rheumatology Products
DPV	Division of Pharmacovigilance
EBA	ebastine
ECG	electrocardiogram
EEC	environmental exposure chamber
EEU	environmental exposure unit

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ED	emergency department
ER	extended release
FAERS	FDA adverse event reporting system
FDA	Food and Drug Administration
FDE	fixed drug eruption
FEX	fexofenadine
HCl	hydrochloride
H ₁	type of receptors involved in allergic reactions, e.g., H ₁ antihistamines are drugs that counteract the effects of histamine and block the H ₁ type of receptors involved in allergic reactions
hr	hour
HYD	hydroxyzine
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDS	interdisciplinary scientist
IgE	immunoglobulin E
IM	intramuscular
IND	investigational new drug
INH	inhalation
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
IT	infrared thermography (type of pharmacodynamic study)
iTNSS	instantaneous total nasal symptom score
ITT	intent to treat
kg	kilogram
K _i	inhibitory constant; dissociation constant of the enzyme-inhibitor complex; reciprocal of the binding affinity of the inhibitor to the enzyme
L	liter
LFT	liver function test
LLT	lower level term
LCTZ	levocetirizine (ucb 28556)
LOR	loratadine
m ²	square meter; meter squared; area of a square whose sides measure exactly one meter
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
mITT	modified intent to treat (population)
MIZ	mizolastine
mL	milliliter
MONT	montelukast
MOX	moxifloxacin
MSC	major symptom complex (runny nose, itchy nose, sniffles, nose blows, sneezes and watery eyes)

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NDA	new drug application
ng	nanogram
NPDS	National Poison Data System
NPT	nasal provocation/temperature (type of pharmacodynamic study)
ODE IV	Office of Drug Evaluation IV
OND	Office of New Drugs
OSE	Office of Surveillance and Epidemiology
OTC	over-the-counter
PAR	perennial allergic rhinitis
PBO	placebo
PD	pharmacodynamics
PEM	prescription-event monitoring
PER	persistent allergic rhinitis
PET	positron emission tomography
PK	pharmacokinetics
preIND	pre-investigational drug
PSE	pseudoephedrine
PT	preferred term
QD	once a day
QID	four times a day
QOL	quality of life
QTc	corrected QT interval
rTNSS	reflective total nasal symptom score
R-enantiomer	to distinguish between enantiomers (i.e., chiral molecules that are mirror images of one another and are non-superimposable on one another), the R and S classification system is used. If the curve drawn from the number 1 to 2 to 3 primary substituents (with the number 4 primary substituent in the back) of the stereocenter (carbon with four non-identical substituents around it) is clockwise, then it is the R configuration and if it is counterclockwise, then it is the S configuration.
Rx	prescription
SAE	serious adverse event
SAR	seasonal allergic rhinitis
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SDN	Supporting Document Number
SOC	system organ class
SS	steady state
SSS	SAR symptom scores (type of pharmacodynamic study)
T4SS	total 4 symptom score (sneezing, rhinorrhea, nasal pruritus, ocular pruritus);
T5SS	total 5 symptom score (sneezing, rhinorrhea, nasal congestion, nasal and ocular pruritus)
TEAE	treatment emergent adverse event

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TdP Torsades de Pointes

TID three times a day

T_{max} time at which the C_{max} is observed

TNSS total nasal symptoms score **[NOTE]**: TNSS is usually calculated as the sum of the patients’ scoring of the 4 individual nasal symptoms (rhinorrhea, nasal congestion, sneezing, and nasal itching) on a 0 to 3 categorical severity scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe), which results in the TNSS ranging from 0 to 12.]

TSI tracked safety issue

TSS total symptoms score

UGT1A a uridine diphosphate glucuronyltransferase (UDPGT), an enzyme of the glucuronidation pathway that transforms small lipophilic molecules, such as steroids, bilirubin, hormones, and drugs into water-soluble, excretable metabolites

UK United Kingdom

US United States

VCC Vienna Challenge Chamber

WAF wheal and flare (type of pharmacodynamic study)

WHO World Health Organization

9.5 Allergic Rhinitis Pharmacologic Treatments

Table 12: Summary of Pharmacologic Treatment Armamentarium Relevant to Allergic Rhinitis

Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Antihistamine OTC Monograph Active Ingredients²⁰⁰						
Brompheniramine maleate Search of DailyMed conducted on 8/8/16 revealed labeling for 148 different drug products containing	Relief of the symptoms of hay fever and upper respiratory allergies (allergic rhinitis), commonly stated as “for the temporary	Not applicable (OTC monograph active ingredients are not approved)	<u>Adults and children 12 years of age and older</u> : oral dose is 4 mg every 4 to 6 hours, not to exceed 24 mg in 24 hours or as directed by a doctor. <u>Children 6 to under 12 years</u>	No efficacy information provided in 21 CFR 341 or in labeling.	May cause excitability especially in children. Do not take this product, unless directed by a doctor, if you have a breathing problem such as emphysema or chronic	May cause drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages

²⁰⁰ These 13 antihistamine OTC monograph active ingredients used for relief of the symptoms of hay fever and upper respiratory allergies (allergic rhinitis) are listed in 21 CFR 341.12.

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
brompheniramine maleate.	relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever or other upper respiratory allergies”.		<u>of age</u> : oral dose is 2 mg every 4-6 hours, not to exceed 12 mg in 24 hours , or as directed by a doctor.		bronchitis, or if you have glaucoma or difficulty in urination due to enlargement of the prostate gland.	while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery.
Chlorcyclizine HCl Search of DailyMed conducted on 8/8/16 revealed labeling for 14 different drug products containing chlorcyclizine HCl.	Same as above	Same as above	<u>Adults and children 12 years of age and older</u> : oral dose is 25 mg every 6 to 8 hours, not to exceed 75 mg in 24 hours or as directed by a doctor.	Same as above	Same as above	Same as above
Chlorpheniramine maleate Search of DailyMed conducted on 8/8/16 revealed labeling for 562 different drug products containing chlorpheniramine maleate.	Same as above	Same as above	<u>Adults and children 12 years of age and older</u> : oral dose is 4 mg every 4 to 6 hours, not to exceed 24 mg in 24 hours or as directed by a doctor. <u>Children 6 to under 12 years of age</u> : oral dosage is 2 mg every 4 to 6	Same as above	Same as above	Same as above

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
			hours not to exceed 12 mg in 24 hours, or as directed by a doctor.			
Dexbrompheniramine maleate Search of DailyMed conducted on 8/8/16 revealed labeling for 26 different drug products containing dexbrompheniramine maleate.	Same as above	Same as above	<u>Adults and children 12 years of age and older</u> : oral dose is 2 mg every 4 to 6 hours, not to exceed 12 mg in 24 hours or as directed by a doctor. <u>Children 6 to under 12 years of age</u> : oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours, or as directed by a doctor.	Same as above	Same as above	Same as above
Dexchlorpheniramine maleate Search of DailyMed conducted on 8/8/16 revealed labeling for 12 different drug products containing dexchlorpheniramine maleate.	Same as above	Same as above	Same as above	Same as above	Same as above	Same as above
Diphenhydramine citrate Search of DailyMed	Same as above	Same as above	<u>Adults and children 12 years of age and older</u> : oral dose is 38 to 76 mg	Same as above	Same as above	May cause <u>marked</u> drowsiness; remainder is same as first

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
conducted on 8/8/16 revealed labeling for 63 different drug products containing diphenhydramine citrate used as nighttime sleep aid and pain reliever (none are currently used in US for symptoms of allergic rhinitis). ²⁰¹			every 4 to 6 hours, not to exceed 456 mg in 24 hours or as directed by a doctor. <u>Children 6 to under 12 years of age:</u> oral dosage is 19 to 38 mg every 4 to 6 hours not to exceed 228 mg in 24 hours, or as directed by a doctor.			listing, <u>plus:</u> Do not use this product with any other product containing diphenhydramine, even one used on skin.
Diphenhydramine HCl Search of DailyMed conducted on 8/8/16 revealed labeling for 741 different drug products containing diphenhydramine HCl. Some are used for symptoms of allergic rhinitis; others are used for relief	Same as above	Same as above	<u>Adults and children 12 years of age and older:</u> oral dose is 25 to 50 mg every 4 to 6 hours, not to exceed 300 mg in 24 hours or as directed by a doctor. <u>Children 6 to under 12 years of age:</u> oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours, or as directed by a doctor.	Same as above	Same as above	May cause <u>marked</u> drowsiness; remainder is same as first listing, <u>plus:</u> Do not use this product with any other product containing diphenhydramine, even one used on skin

²⁰¹ Per DailyMed and Google searches conducted by this reviewer on 8/8/16, no labeling for any drug product containing the OTC monograph antihistamine active ingredient diphenhydramine citrate used for symptoms of allergic rhinitis was located. All drug products currently available in the US containing diphenhydramine citrate appear to be combined with ibuprofen, naproxen or acetaminophen for use as a nighttime sleep aid and pain reliever.

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
of minor aches and pains with accompanying sleeplessness.						
Doxylamine succinate Search of DailyMed conducted on 8/8/16 revealed labeling for 795 different drug products containing doxylamine succinate. However, when doxylamine succinate is the only active ingredient, use is only as a “sleep aid”.	Same as above	Same as above	<u>Adults and children 12 years of age and older</u> : oral dose is 7.5 to 12.5 mg every 4 to 6 hours, not to exceed 75 mg in 24 hours or as directed by a doctor. <u>Children 6 to under 12 years of age</u> : oral dosage is 3.75 to 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours, or as directed by a doctor	Same as above	Same as above	May cause <u>marked</u> drowsiness; remainder is same as first listing.
Phenindamine tartrate Search of DailyMed conducted on 8/8/16 revealed no labeling for drug products containing phenindamine tartrate. ²⁰²	Same as above	Same as above	<u>Adults and children 12 years of age and older</u> : oral dose is 25 mg every 4 to 6 hours, not to exceed 150 mg in 24 hours or as directed by a doctor. <u>Children 6 to under 12 years of age</u> : oral	Same as above	Same as above	Same as first listing <u>plus</u> : May cause nervousness and insomnia in some individuals.

²⁰² Per DailyMed search conducted by this reviewer on 8/8/16, no labeling for any drug product containing phenindamine tartrate was located. Per Google search conducted by this reviewer on 8/8/16, it appears that drug products containing phenindamine tartrate are no longer available in the USA, e.g., Nolahist®

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
			dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours, or as directed by a doctor			
Pheniramine maleate Search of DailyMed conducted on 8/8/16 revealed labeling for at least 42 different drug products containing pheniramine maleate. Some of these drug products are used to treat symptoms of AR and others are used to decrease eye redness and itching.	Same as above	Same as above	<u>Adults and children 12 years of age and older:</u> oral dose is 12.5 to 25 mg every 4 to 6 hours, not to exceed 150 mg in 24 hours or as directed by a doctor. <u>Children 6 to under 12 years of age:</u> oral dosage is 6.25 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours, or as directed by a doctor	Same as above	Same as above	Same as first listing
Pyrilamine maleate Search of DailyMed conducted on 8/8/16 revealed labeling for 78 different drug products	Same as above	Same as above	<u>Adults and children 12 years of age and older:</u> oral dose is 25 to 50 mg every 6 to 8 hours, not to exceed 200 mg in 24 hours or as directed by a doctor.	Same as above	Same as above	Same as first listing

has not been available for US market since 2005 and marketing of both Amilon® and Nolamine® has been discontinued.

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
containing pyrilamine maleate, some of which are used for temporary relief of symptoms associated with menstrual periods.			<u>Children 6 to under 12 years of age:</u> oral dosage is 12.5 to 25 mg every 6 to 8 hours not to exceed 100 mg in 24 hours, or as directed by a doctor			
Thonzylamine HCl Search of DailyMed conducted on 8/8/16 revealed labeling for 3 different drug products containing thonzylamine HCl.	Same as above	Same as above	<u>Adults and children 12 years of age and older:</u> oral dose is 50 to 100 mg every 4 to 6 hours, not to exceed 600 mg in 24 hours or as directed by a doctor. <u>Children 6 to under 12 years of age:</u> oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours, or as directed by a doctor.	Same as above	Same as above	Same as first listing
Tripolidine HCl Search of DailyMed conducted on 8/8/16 revealed labeling for 17 different drug products containing	Same as above	Same as above	<u>Adults and children 12 years of age and older:</u> oral dose is 2.5 mg every 4 to 6 hours, not to exceed 10 mg in 24 hours or as directed by a doctor. <u>Children 6 to under 12 years</u>	Same as above	Same as above	Same as first listing

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
triprolidine HCl.			of age: oral dosage is 1.25 mg every 4 to 6 hours not to exceed 5 mg in 24 hours, or as directed by a doctor.			
Antihistamine Rx and/or OTC FDA Currently Approved and Marketed Drug Products (with or without decongestants)						
Acrivastine 8 mg/Pseudoephedrine 60 mg capsule (Semprex-D®) NDA 019806	SAR	Rx 1994	<u>Adults and adolescents 12 years of age and older</u> : one capsule every 4 to 6 hours, four times a day (QID).	Five randomized, placebo- and/or active-controlled trials compared SEMPREX-D with its acrivastine and pseudoephedrine components for the symptomatic relief of seasonal allergic rhinitis. A total of 669 patients received Semprex-D or the same doses of the components four times a day for 14 days. The combination reduced the intensity of sneezing, rhinorrhea, pruritus, and lacrimation more than pseudoephedrine and reduced the intensity of nasal congestion more than acrivastine, demonstrating a	In controlled clinical trials, the following most common adverse events were reported for the 1650 patients who took Semprex-D and were higher than the placebo group (n=1767): Headache=19% Somnolence=12% Dry mouth=7% Insomnia=4% Nervousness=3% Dizziness=3% Pharyngitis=3% Cough Increase=2% Dysmenorrhea=2% Dyspepsia=2%	Post-marketing clinical experience reports with acrivastine and acrivastine plus pseudoephedrine have included rare serious hypersensitivity reactions manifested by anaphylaxis, angioedema, bronchospasm, and erythema multiforme. Pseudoephedrine may cause ephedrine-like reactions such as tachycardia, palpitations, headache, dizziness, or nausea

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				contribution of each of the components.		
Azelastine HCl metered nasal spray EQ 0.125 mg base/spray (Astelin®) NDA 020114	SAR; vasomotor rhinitis	Rx 1996	SAR: Adults and adolescents 12 years of age and older: 1 or 2 sprays per nostril twice daily. Children 5 to 11 years of age: 1 spray per nostril twice daily. Vasomotor rhinitis: Adults and adolescents 12 years of age and older: 2 sprays per nostril.	SAR: efficacy evaluated in 3 placebo-controlled clinical trials in 322 patients aged 12 years and above with SAR dosed with 2 sprays per nostril twice a day for up to 4 weeks. Total Symptom Complex (TSC) and Major Symptom Complex (MSC; nose blows, sneezes, runny nose/sniffles, itchy nose and watery eyes on 0-5 scale) were assessed with reflective MSC score difference of -1.35 to -2.03 with p-value <0.01 in all 3 studies.	Can cause sleepiness. Do not drive, operate machinery, or do other dangerous activities until you know how Astelin® affects you. Avoid concurrent use of Astelin® with alcohol or other CNS depressants because additional reductions in alertness and additional impairment of CNS performance may occur.	Treatment may lead to AEs, which include bitter taste, headache, somnolence, dysesthesia, rhinitis, nasal burning, pharyngitis, epistaxis, sinusitis, paroxysmal sneezing, nausea, dry mouth, fatigue, dizziness, and weight increase.
Azelastine HCl metered nasal spray 0.1%, 0.15% (Astepro®) NDA 022203	SAR; PAR	Rx 2008	SAR: Adults and adolescents 12 years of age and older: 1 or 2 sprays of 0.1% or 0.15% per nostril twice daily. Children 6 to 11 years: 1 spray of 0.01% or 0.15% per nostril twice daily.	SAR efficacy of Astepro® 0.1% 2 sprays per nostril twice daily assessed in 2-week placebo-controlled trial in 834 subjects aged 12 years and older using reflective total nasal symptoms score (rTNSS)	Somnolence: Avoid engaging in hazardous occupations requiring complete mental alertness such as driving or operating machinery when taking Astepro®. Avoid concurrent use	Most common AEs (≥2% incidence) are: pyrexia, dysgeusia, nasal discomfort, epistaxis, headache, sneezing, fatigue, somnolence,

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
			<p><u>Children 2 to 5 years</u>: 1 spray of 0.01% per nostril twice daily PAR: Adults and adolescents 12 years of age and older: 2 sprays of 0.15% per nostril twice daily. <u>Children 6-11 years</u>: 1 spray of 0.01% or 0.15% per nostril twice daily. <u>Children 6 months to 5 years</u>: 1 spray of 0.01% per nostril twice daily.</p>	<p>assessed rhinorrhea, nasal congestion, sneezing, and nasal itching each on 0 to 2 scale over previous 12 hours. Difference from placebo was -2.2 (p-value <0.001). PAR efficacy of Astepro® 0.15% 2 sprays per nostril twice daily assessed in 4-week placebo controlled trial in 578 subjects aged 12 years and older. Difference from placebo for rTNSS was -0.9 (p-value 0.03).</p>	<p>of alcohol or other CNS depressants with Asterpro® because further decreased alertness and impairment of CNS performance may occur.</p>	<p>upper respiratory infection, cough, rhinalgia, vomiting, otitis media, contact dermatitis, and oropharyngeal pain.</p>
<p>Carbinoxamine maleate a) Multiple Rx ANDAs oral tablet, 4 mg and 6 mg b) Multiple Rx ANDA oral solution 4 mg/5 mL</p>	SAR, PAR	<p>Rx 1953 (NDA 008915 Clistin® oral tablet was withdrawn 1994; BDA 008955 Clistin® oral elixir was withdrawn)</p>	<p>Tablets Usual Adult Dosage: 1 or 2 tablets (4 to 8 mg) 3 to 4 times daily. Usual Child’s Dosage: 6 to 11 years – 1/2 to 1 tablet (2 to 4 mg) 3 to 4 times daily. Oral Solution Usual Adult Dosage: 1 or 2 teaspoonfuls (4 to 8 mg) 3 to 4 times daily. Usual Child’s</p>	<p>No efficacy information provided in label.</p>	<p>Antihistamines should be used with considerable caution in patients with: narrow angle glaucoma, stenosing peptic ulcer, symptomatic prostatic hypertrophy, bladder neck obstruction, pyloroduodenal obstruction. Carbinoxamine maleate may cause</p>	<p>Contraindicated in children younger than 2 years of age, nursing women and patients taking monoamine oxidase inhibitors (MAOIs). MAOIs prolong and intensify the anticholinergic (drying) effects of antihistamines</p>

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
			<p>Dosage: (approximately 0.2 to 0.4 mg/kg/day, divided into 3 to 4 doses):</p> <p>6 to 11 years – 1/2 to 1 teaspoonful (2 to 4 mg) 3 to 4 times daily.</p> <p>Dosing for children 2 to 5 years of age should be based on weight whenever possible. The usual dosage for children 2 to 5 years of age is approximately 0.2 to 0.4 mg/kg/day, divided into 3 to 4 daily doses. In general, this corresponds to a dose of 1/4 to 1/2 teaspoonful (1 to 2 mg) 3 to 4 times daily.</p>		<p>drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery.</p>	
<p>Carbinoxamine maleate Karbinal™ ER oral extended release suspension NDA 022556 approved 2013</p>	SAR, PAR	Rx 2013	<p>Adults and Adolescents 12 years of age and older: 7.5 mL to 20 mL (6 to 16 mg) every 12 hours</p> <p>Children 2-11 years of age (approximately 0.2 to 0.4 mg/kg/day) :</p>	The efficacy and safety of Karbinal ER is based on demonstration of bioequivalence to the immediate release reference product. Karbinal ER after single-dose administration of 16 mg was	Avoid engaging in hazardous tasks requiring complete mental alertness such as driving or operating machinery. Use with caution in patients with increased intraocular	Contraindicated in children younger than 2 years of age, nursing women and patients taking monoamine oxidase inhibitors (MAOIs). MAOIs prolong

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
			<p>2 to 3 years – 3.75 mL to 5 mL (3 to 4 mg) every 12 hours</p> <p>4 to 5 years – 3.75 mL to 10 mL (3 to 8 mg) every 12 hours</p> <p>6 to 11 years – 7.5 mL to 15 mL (6 to 12 mg) every 12 hours</p>	bioequivalent to the reference carbinoxamine immediate-release oral solution after the administration of two doses of 8 mg six hours apart under fasting conditions.	pressure, narrow angle glaucoma, hyperthyroidism, cardiovascular disease, hypertension, stenosing peptic ulcer, symptomatic prostatic hypertrophy, bladder neck obstruction, pyloroduodenal obstruction. Most common adverse reactions are: sedation, sleepiness, dizziness, disturbed coordination, epigastric distress, and thickening of bronchial secretions.	and intensify the anticholinergic (drying) effects Contains sodium metabisulfite, a sulfite that may cause anaphylaxis including life-threatening or less severe asthmatic episodes in susceptible individuals.
<p>Cetirizine HCl (Zyrtec Allergy®)^{203,204}</p> <p>a) NDA 019835 oral tablet 5 mg & 10 mg</p> <p>b) NDA</p>	Temporarily relieves these symptoms due to hay fever or other upper respiratory	<p>a) Rx 1995 OTC 2007</p> <p>b) OTC 2007</p> <p>c) OTC 2010</p>	a) <u>Adults and children 6 years and older</u> : one or two 5 mg tablets once daily (depending upon severity of symptoms) OR	Original NDA 019835 approval for allergic rhinitis was based upon nine multicenter, randomized, double blind and	Do not use if you have ever had an allergic reaction to this product or any of its ingredients or to an antihistamine	When using this product, drowsiness can occur; avoid alcoholic drinks. Alcohol,

²⁰³ Neither the Orange Book nor Drugs@FDA list NDA 020346 Zyrtec® (cetirizine HCl) oral syrup 5 mg/5 mL as “Discontinued”; however, in NDA 020346 SDN 204 dated 10/2/13, McNeil Consumer Healthcare stated that this product for Rx use has not been distributed since McNeil Consumer Healthcare acquired the NDA from Pfizer in January 2008 and withdrawal of this NDA was also requested. Because this drug product is not currently being marketed, NDA 020346 does not appear in this table.

²⁰⁴ Per the Orange Book and Drugs@FDA, marketing of NDA 021621 Children’s Zyrtec Allergy and Children’s Hives Relief oral chewable tablet, 5 mg and 10 mg has been discontinued; thus, NDA 021621 does not appear in this table. 80 Federal Register 5560 ([Docket No. FDA-2015-N-0175]) dated February 2, 2015 announced that FDA has determined that NDA 021621 product was not withdrawn from sale for reasons of safety or effectiveness.

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
022155 Children’s oral syrup 5 mg/5 mL c) NDA 022578 orally disintegrating tablet, 10 mg	allergies: runny nose, sneezing, itchy watery eyes, itching of the nose or throat		one 10 mg tablet once daily. <u>Adults 65 years and older</u> : one 5 mg tablet daily. b) <u>Adults and children 6 years and older</u> : 5 mL or 10 mL once daily depending upon severity of symptoms. <u>Adults 65 years and over</u> : 5 mL daily. <u>Children 2 to under 6 years of age</u> : 2.5 mL once daily (if needed, dose can be increased to a maximum of 5 mL once daily or 2.5 mL every 12 hours). c) <u>Adults and children 6 years and over</u> : one 10 mg tablet once daily.	placebo controlled clinical trials with doses ranging from 5 mg to 20 mg cetirizine compared to placebo. Of the nine studies, three demonstrated statistically significant reductions in symptoms of SAR (1 to 4 week studies) and 2 in PAR (8-week studies). In general, the 10-mg dose was more effective than the 5-mg dose and the 20-mg dose did not provide any additional benefit. The primary efficacy variable in the majority of these studies was the weekly total symptom score (TSS), a composite endpoint of: sneezing, runny nose, eye itching, eye watering, eye redness, nose itching, and mouth itching. ²⁰⁵	containing hydroxyzine. Ask a doctor before use if you have liver or kidney disease. Ask a doctor or pharmacist before using if you are taking tranquilizers or sedatives. If breast-feeding, not recommended.	sedatives and tranquilizers may increase drowsiness. Be careful when driving a motor vehicle or operating machinery. If pregnant, ask a health professional before use.

²⁰⁵ NDAs 019835, 021150, 021621 and 022155 Clinical Review by Susan Limb, MD finalized in DARRTS on 9/10/07; pg. 9 of 17.

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				No new clinical studies were submitted with the OTC switch application. ²⁰⁶		
Cetirizine HCl NDA 022429 oral (liquid filled) capsule 5 mg and 10 mg	Same as above	OTC 2009	<u>Adults and children 6 years and older</u> : take one or two 5 mg capsules once daily (depending on symptoms) or one 10 mg capsule once daily.	No efficacy trials were conducted for this application. Approval was based upon PK evaluations. ²⁰⁷	Same as above	Same as above
Cetirizine HCl/Pseudoephedrine (Zyrtec-D®) NDA 021150 ER tablet 5 mg; 120 mg	Same as above <u>plus</u> : reduces swelling of nasal passages; temporarily relieves sinus congestion and pressure; temporarily restores freer breathing through the nose	Rx 2001 OTC 2007	<u>Adults and children 12 years of age and older</u> : take one tablet every 12 hours.	Sponsor submitted two pivotal in vivo pharmacokinetic studies (143-006 and 143-007) addressing the comparative bioavailability between the proposed combination product and the co-administration of the individual active ingredients separately, and issues of possible interaction of the bilayer tablet with food. No efficacy and safety studies were done with the new formulation. ²⁰⁸	Same as above <u>plus</u> : Do not use if you are taking a Rx monoamine oxidase inhibitor (MAOI) [certain drugs for depression, psychiatric, or emotional conditions, or Parkinson’s disease] or for two weeks after stopping the MAOI drug. Ask a doctor before use if you have heart disease, thyroid disease, diabetes, glaucoma, high blood pressure, or trouble urinating due to an enlarged prostate.	Same as above

²⁰⁶ NDAs 019835, 021621 and 022155 Clinical Review by Lolita A. Lopez, MD finalized in DARRTS on 10/2/07; pg. 14 of 83.

²⁰⁷ NDA 022429 Clinical Review by Lolita A. Lopez, MD finalized in DARRTS on 4/8/09; pg. 5 of 61.

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				No new efficacy studies were submitted with switch application. ²⁰⁹		
Clemastine Fumarate a) Rx ANDAs 073283 & 073459 oral tablet 2.68 mg b) Rx ANDAs 073399 & 074863 oral syrup EQ 0.5 mg Base/5 mL c) OTC NDA 020925 Tavist Allergy oral tablet 1.34 mg	Temporarily relieves these symptoms of the common cold, hay fever or other upper respiratory allergies: runny nose, itchy watery eyes, sneezing, itching of the nose or throat	a) Rx NDA 017661 was approved for 1.34 mg and 2.68 mg oral tablets in 1977 and withdrawn in 2005 b) Rx NDA 018675 was approved in 1985 and withdrawn in 2006 c) OTC 1992	a) <u>Adults and children 12 years and older:</u> one tablet every 12 hours. b) <u>Adults and children 12 years and older:</u> 2 teaspoons twice daily with increase as required up to 12 teaspoons daily. <u>Children aged 6-12 years:</u> 1 teaspoon twice daily with increase as required up to 6 teaspoons daily. c) <u>Adults and children 12 years and older:</u> one tablet every 12 hours.	No efficacy data was provided in available Rx labeling. Per Turner et al, clemastine fumarate demonstrated statistical significance for rhinorrhea on days 3 & 4 and for sneezing on days 2-4 (both compared to placebo) with sedation occurring in 14% of clemastine fumarate-treated subjects versus 1.5% of placebo-treated subjects. ²¹⁰	Contraindicated in patients hypersensitive to the drug. Ask a doctor before use if you have glaucoma, a breathing problem such as emphysema or chronic bronchitis or trouble urinating due to an enlarged prostate gland. Ask a doctor or pharmacist before use if you are taking sedatives or tranquilizers.	If pregnant or breast-feeding, ask a health professional before use. When using this product, you may get drowsy, avoid alcoholic drinks, alcohol, sedatives, and tranquilizers may increase drowsiness. Be careful when driving a motor vehicle or operating machinery. Excitability may occur, especially in children.
Cyproheptadine HCl a) Multiple Rx ANDAs oral tablet 4 mg	PAR, SAR	a) Rx NDA 012649 Periactin was approved	<u>Adults:</u> 4 to 20 mg/day, with the majority of adults requiring 12 to 16 mg a	No efficacy information provided in NDA 012649 approved labeling dated	Contraindicated in newborn or premature infants, in elderly	Overdosage of antihistamines, particularly

²⁰⁸ NDA 021150 Medical Team Leader Memorandum by Badrul A. Chowdhury, MD finalized in DARRTS on 1/5/01; pg. 2 of 6.

²⁰⁹ NDA 021150 Summary Basis for Regulatory Action by Andrea Leonard-Segal, MD finalized in DARRTS on 11/7/07; pg. 2 of 7.

²¹⁰ Turner RB et al. Effectiveness of clemastine fumarate for treatment of rhinorrhea and sneezing associated with the common cold. *Clinical Infection Diseases*. 1997; 25: 824-30.

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
b) Multiple Rx ANDAs oral syrup 2 mg/5 mL		1961 and withdrawn 2006. b) Rx NDA 013220 Periactin was approved 1962 and withdrawn 2006.	day. It is suggested that dosage be initiated with 4 mg TID and adjusted according to the size and response of the patient. <u>Children aged 7 to 14 years:</u> usual dose is 4 mg BID or TID, adjusted as necessary to the size and response of the patient. Total daily dose not to exceed 16 mg. <u>Children aged 2 to 6 years:</u> Dose is based on body weight (0.25 mg/kg/day) or body area (8 mg per square meter of body surface). Usual dose is 2 mg BID or TID, adjusted as necessary to the size and response of the patient. The dose is not to exceed 12 mg/day.	1/99 or at Drugs@FDA website.	debilitated patients and in patients with hypersensitivity to cyproheptadine or other drugs of similar structure, in patients taking MOAI therapy and in patients with angle-closure glaucoma, stenosing peptic ulcer, symptomatic prostatic hypertrophy, bladder neck obstruction or pyloroduodenal obstruction. Patients should be warned about engaging in activities requiring mental alertness and motor coordination, such as driving a car or operating machinery.	in infants and young children, may produce hallucinations, central nervous system (CNS) depression, convulsions, and death. Antihistamines may diminish mental alertness; conversely, particularly, in the young child, they may occasionally produce excitation. Antihistamines may have additive effects with alcohol and other CNS depressants, e.g., hypnotics, sedatives, tranquilizers, antianxiety agents. Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
<p>Desloratadine (Clarinetix®)</p> <p>a) NDA 021165 oral tablet, 5 mg</p> <p>b) NDA 021312 oral disintegrating tablet 2.5 mg and 5 mg</p> <p>c) NDA 021300 oral solution 0.5 mg/mL</p>	<p>1) Relief of nasal and non-nasal symptoms of SAR in patients 2 years of age and older.</p> <p>2) Relief of nasal and non-nasal symptoms associated with PAR in patients 6 months of age and older.</p>	<p>a) Rx 2001</p> <p>b) Rx 2002</p> <p>c) Rx 2004</p>	<p>a) and b) <u>Adults and adolescents 12 years of age and over</u>: one 5 mg tablet once daily.</p> <p>b) <u>Children 6 to 11 years</u>: one 2.5 mg tablet once daily.</p> <p>c) <u>Adults and children 12 years of age and over</u>: 2 teaspoons (5 mg in 10 mL) once daily.</p> <p><u>Children 6 to 11 years</u>: 1 teaspoon (2.5 mg in 5 mL) once daily.</p> <p><u>Children 12 months to 5 years of age</u>: ½ teaspoon (1.25 mg in 2.5 mL) once daily.</p> <p><u>Children 6 to 11 months of age</u>: 2 mL (1 mg) once daily.</p>	<p>In two 4-week studies of 924 patients (aged 15 to 75 years) with SAR and concomitant asthma, Clarinetix Tablets 5 mg once daily improved rhinitis symptoms, with no decrease in pulmonary function. In a 2-week clinical trial in patients with SAR, Clarinetix 5 mg tablet once daily (n=171 subjects) reduced TSS from 14.2 to 9.9 (-4.3) compared to a change for the placebo (n=173) from 13.7 to 11.2 (-2.5) and placebo comparison was significant (p<0.01). TSS possible scores were 0 (no symptoms) to 24.</p>	<p>The most common adverse events (AEs) (reported in ≥2% of adult and adolescent patients with allergic rhinitis and greater than placebo) were pharyngitis, dry mouth, myalgia, fatigue, somnolence and dysmenorrhea. Dosage adjustment is recommended for renal and hepatic impairment.</p>	<p>Hypersensitivity reactions including rash, pruritus, urticaria, edema, dyspnea, and anaphylaxis have been reported. In such cases, stop Clarinetix at once and consider alternative treatments.</p>
<p>Desloratadine; Pseudoephedrine sulfate (Clarinetix D)</p> <p>a) NDA 021313 oral ER tablet 2.5 mg; 120 mg</p> <p>b) NDA 021605 oral ER tablet 5</p>	<p>Relief of nasal and non-nasal symptoms of SAR including nasal congestion</p>	<p>a) Rx 2006</p> <p>b) Rx 2005</p>	<p>a) <u>Adults and adolescents 12 years of age and over</u>: 1 tablet twice daily.</p> <p>b) <u>Adults and adolescents 12 years of age and over</u>: 1 tablet once daily.</p>	<p>In a 2-week SAR clinical trial (n=593) evaluating four nasal symptoms and 4 non-nasal symptoms, each on a 4 point scale (TSS possible scores of 0 to 32), the 199 subjects on</p>	<p>Contraindicated in patients with hypersensitivity to any of its ingredient, or to loratadine, narrow-angle glaucoma, urinary retention, receiving MAOI therapy or</p>	<p>Patients should be advised against the concurrent use of Clarinetix-D Extended Release Tablets with other antihistamine</p>

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
mg; 240 mg				Clarinet-D significantly (p<0.001) decreased their TSS 1.5 points more from baseline than either component given individually.	within 14 days of stopping such treatment, severe hypertension or severe coronary artery disease. Generally avoid use in patients with renal or hepatic impairment.	s and/or decongestant s. Patients should be instructed not to break, crush, or chew the tablet. The tablet should be swallowed whole, and can be taken without regard to meals.
Fexofenadine HCl (Allegra) ²¹¹ a)NDA 020872 oral tablet, 30 mg, 60 mg, 180 mg (180 mg available as plain tablet and gel coated tablet, i.e., “gelcap”) b)NDA 021909 orally disintegrating tablet (ODT) 30 mg c)NDA 021963 oral suspension 30 mg/5 mL ²¹² d)NDA 201373 oral	a), b) and d) OTC: Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: runny nose, sneezing, itchy watery eyes, itching of the nose or throat c) Rx: SAR	a) Rx 2000 OTC 2011 b) Rx 2007 OTC 2011 c) Rx 2006 d) Rx 2006 OTC 2011	a) <u>Adults and children 12 years of age and over</u> : one 60 mg tablet every 12 hours OR one 180 mg tablet or gel coated tablet (“gelcap”) once daily. <u>Children 6 to 11 years</u> : one 30 mg tablet twice daily. b) <u>Adults and children 12 years of age and over</u> : two tablets every 12 hours on an empty stomach <u>Children 6 to under 12 years</u>	In three 2-week, multicenter, randomized, double-blind, placebo-controlled trials in subjects 12 to 68 years of age with SAR (n=1634), fexofenadine HCl 60 mg twice daily significantly reduced TSS (the sum of the individual scores for sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes) compared to placebo. ²¹³	Stop use and ask a doctor if an allergic reaction to this product occurs. Seek medical help right away. Ask a doctor before use if you have kidney disease. If pregnant or breast feeding, ask a health professional before use.	Do not take with fruit juices. Do not take at the same time as aluminum or magnesium antacids.

²¹¹ The Rx NDA 020625 Allegra (fexofenadine HCl) oral (hard gelatin) capsule, 60 mg was approved in 1996; however, marketing was discontinued in 2002. Thus, NDA 020625 does not appear in this table.

²¹² It is unclear whether this Rx product is being distributed because the recent Annual Reports for NDA 021963 have not provided any distribution data because “Sanofi Aventis US LLC considers the distribution data to be a trade secret and protected from disclosure under the provisions of CFR 314.430(g)(2)”.

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
suspension 30 mg/5 mL			of age: one tablet every 12 hours on an empty stomach. d) <u>Children 2 to 11 years</u> : 30 mg twice daily. <u>Children 6 months to less than 2 years</u> : 15 mg twice daily. e) <u>Adults and children 12 years of age and over</u> : 2 teaspoons (10 mL) every 12 hours. <u>Children 2 to under 12 years</u> : 1 teaspoon (5 mL) every 12 hours.			
Fexofenadine HCl; Pseudoephedrine HCL (Allegra-D®) a)NDA 020786 ER oral tablet 60 mg; 120 mg; b)NDA 021704 ER oral tablet 180 mg; 240 mg	Same as above plus: reduces swelling of nasal passages, temporarily relieves sinus congestion and pressure, temporarily restores freer breathing through the nose	a) Rx 1997 OTC 2011 b) Rx 2004 OTC 2011	a) <u>Adults and children 12 years of age and older</u> : take one tablet with a glass of water every 12 hours on an empty stomach. b) <u>Adults and children 12 years of age and older</u> : take one tablet once daily on an empty stomach with water.	Clinical efficacy and safety studies were not conducted with this combination product. The effectiveness of the product for the treatment of seasonal allergic rhinitis is based on an extrapolation of the demonstrated efficacy of Allegra and the nasal decongestant properties of pseudoephedrine	Same as above plus: if you are now taking a Rx MAOI (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson’s disease), or for 2 weeks after stopping the MAOI drug or if you have difficulty swallowing. Ask a doctor before use if you have heart disease, thyroid disease,	Same as above plus: the tablet coating may be seen in the stool (this is normal). Continue to take as directed. Stop and ask a doctor is you get nervous, dizzy or sleepless.

²¹³ NDA 021963 Rx Labeling for Allegra tablet, ODT and oral suspension revised 6/25/08.

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				HCl. ²¹⁴	glaucoma, high blood pressure, diabetes or trouble urinating due to an enlarged prostate gland.	
Levocetirizine dihydrochloride (Xyzal®) a) NDA 022064 oral scored tablet 5 mg b) NDA 022157 oral solution 2.5 mg/5 mL	1) relief of symptoms associated with SAR in adults and children 2 years of age and older; 2) relief of symptoms associated with PAR in adults and children 6 months of age and older; 3) treatment of the uncomplicated skin manifestation of chronic idiopathic urticaria in adult and children 6 months of age and older	a) Rx 2007 [NOTE: sponsor is requesting OTC switch for indications 1) and 2) in NDA 209089, i.e., submission under review] b) Rx 2008 [NOTE: sponsor is requesting OTC switch for indications 1) and 2) in NDA 209090, i.e., submission under review]	<u>Adults and children 12 years of age and older</u> : 5 mg once daily in the evening. <u>Children 6 to 11 years of age</u> : 2.5 mg (1/2 tablet) oral tablet or 1 teaspoon [5 mL] oral solution once daily in the evening. <u>Children 6 months to 5 years of age</u> : 1.25 mg (1/2 teaspoon [2.5 mL]) oral solution once daily in the evening.	In three SAR and three PAR clinical trials, Xyzal decreased the TSS of four symptoms (i.e., sneezing, rhinorrhea, nasal pruritus and ocular pruritus, each rated 0-3; possible TSS scores are 0-12) compared to placebo by approximately 1.1 (estimated differences from placebo ranged from -0.73 to -1.61).	Contraindications are: 1) known hypersensitivity to levocetirizine or any of the ingredients of Xyzal or to cetirizine, 2) patients with end-stage renal disease at less than 10-mL/min creatinine clearance or patients undergoing hemodialysis and 3) children 6 months to 11 years of age with impaired renal function. The most common AEs were somnolence, nasopharyngitis, fatigue, dry mouth, and pharyngitis in subjects 12 years of age and older, and pyrexia, somnolence,	Adjust dose in patients 12 years of age and older with decreased renal function. Avoid concurrent use of alcohol or other CNS depressants. Avoid engaging in hazardous occupations requiring complete mental alertness such as driving or operating machinery. Should be used with caution in patients with predisposing factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia)

²¹⁴ Rx labeling for Allegra-D 24 Hour Extended-Release Tablets dated December 2009.

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
					cough, and epistaxis in children 6 to 12 years of age. In subjects 1 to 5 years of age, the most common AEs were pyrexia, diarrhea, vomiting, and otitis media. In subjects 6 to 11 months of age, the most common AEs were diarrhea and constipation.	as Xyzal may increase the risk of urinary retention.
<p>Loratadine (Claritin®)</p> <p>a) NDA 019658 oral tablet 10 mg</p> <p>b) NDA 020641 oral syrup 1 mg/mL</p> <p>c) NDA 021952 oral capsule 10 mg</p> <p>d) NDA 020704 oral RediTabs 10 mg</p> <p>e) NDA 021993 oral RediTabs, 5 mg</p> <p>f) NDA 021891 Children’s chewable oral</p>	Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: runny nose, sneezing, itchy watery eyes, itching of the nose or throat	<p>a) Rx 1993 OTC 2002</p> <p>b) Rx 1996 OTC 2002</p> <p>c) OTC 2008</p> <p>d) Rx 1996 OTC 2002</p> <p>e) OTC 2006</p> <p>f) OTC 2006</p>	<p>a) <u>Adults and children 6 years and over</u>: 1 tablet (10 mg) daily.</p> <p>b) <u>Adults and children 6 years and over</u>: 2 tsp (10 mL, 10 mg) daily.</p> <p><u>Children 2 to under 6 years</u>: 1 tsp (5 mL, 5 mg) daily.</p> <p>c) <u>Adults and children 6 years and over</u>: 1 capsule (10 mg) daily.</p> <p>d) <u>Adults and children 6 years and over</u>: 1 tablet (10 mg) daily.</p> <p>e) <u>Adults and</u></p>	<p>Since 1984, approximately 100,000 subjects have been treated with loratadine in controlled or uncontrolled clinical studies. For SAR, four pivotal randomized, double blind, placebo controlled, multicenter parallel group studies were submitted in NDA 019658 with the difference between loratadine 10 mg and placebo in change from</p>	<p>Do not use if you have ever had an allergic reactions to this product or any of its ingredients. Ask a doctor before use if you have liver or kidney disease.</p>	<p>AEs in clinical trials of loratadine tablets, RediTabs, and syrup were similar in character and frequency to that of the placebo. Somnolence and fatigue were reported more frequently in subjects treated with clemastine than with loratadine or placebo.²¹⁶</p>

²¹⁶ *Ibid.*, pg. 31 of 72.

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Original NDAs 209089 Xyzal® Allergy 24HR (levocetirizine dihydrochloride) Tablet, 5 mg and 209090 Children’s Xyzal® Allergy 24HR (levocetirizine dihydrochloride) Oral Solution, 2.5 mg/5 mL

Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
	relieves sinus congestion and pressure; temporarily restores freer breathing through the nose			Difference between loratadine 5 mg/PSE 120 mg and loratadine 5 mg in change from baseline in percent improvement in TSS at Day 4 ranged from 2% to 20% and was statistically significant in 3 of the 4 studies. ²¹⁹		nervousness, and dizziness. ²²
Olopatadine HCl metered nasal spray 0.665 mg/ spray (Patanase®) NDA 021861	SAR	Rx 2008	<u>Adults and adolescents 12 years of age and older</u> : 2 sprays in each nostril twice daily. <u>Children 6 to 11 years of age and older</u> : 1 spray in each nostril twice daily.	For SAR, three randomized, double blind, placebo controlled, parallel group, 2-week duration studies were conducted in the US in a total of 1598 patients aged 12 years and older (587 treated with Patanase 0.6%, 418 with Patanase 0.4% and 593 with vehicle nasal spray). Four nasal symptoms (nasal congestion, rhinorrhea, itchy nose and sneezing) were recorded by patient on 0-3 scale as reflective	In the 3 efficacy and safety trials of 2 weeks duration conducted in patients 12 years and older, the following adverse events occurred at least 1% more frequently in patients treated with Patanase 0.6% compared to vehicle: Bitter taste 12.8% vs 0.8% and Epistaxis 3.2% vs. 1.7%. In the 3 efficacy and safety trials of 2 weeks duration conducted in subjects aged 6 to 11 years of age, the following	In a 12-month, placebo (vehicle nasal spray)-controlled, safety trial, 890 patients 12 years of age and older with PAR were randomized to treatment with Patanase or vehicle (2 sprays per nostril twice daily). Most frequently reported adverse reaction was epistaxis (25% of Patanase group and 28% of

²²⁰ *Ibid.*, pg. 31 of 72.

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				or instantaneous scores. In all 3 trials, patients treated with Patanase had statistically significantly greater decreases in reflective total nasal symptoms score (rTNSS) compared to vehicle nasal spray. Change from baseline was approximately -3.3 for Patanase 0.6% vs -2.3 for vehicle.	adverse events occurred at least 1% more frequently in patients treated with Patanase 0.6% compared to vehicle: Epistaxis 5.7% vs. 3.7%; Upper respiratory tract infection 2.6% vs. 0; Rash 1.3% vs. 0; Bitter taste 1% vs. 0.	vehicle group). Epistaxis resulted in discontinuation of 0.9% of Patanase group and 0.2% of vehicle group. Nasal ulcerations occurred in 10% of Patanase group and 9% of vehicle group. Nasal ulcerations resulted in discontinuation of 0.4% in Patanase group and 0.2% in vehicle group. No nasal septal perforations occurred. Somnolence was reported in 2 patients (1 per group)
Promethazine HCl (multiple generics are being marketed for 12.5 mg, 25 mg, 50 mg oral tablet and rectal suppositories)	PAR; SAR; Vasomotor rhinitis	Rx 1951 (NDA 007935 Phenergan; withdrawn Federal Register effective 2009)	Allergy: The average oral dose is 25 mg taken before retiring; however, 12.5 mg may be taken before meals and on retiring, if necessary. Single 25-mg	No efficacy information provided in NDA 007935 Rx label revised 7/05 or in generic labels.	Potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with promethazine	Contraindicated in use in pediatric patients less than two years of age. Antihistamines are contraindicated for use in the treatment of

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
			doses at bedtime or 6.25 to 12.5 mg taken three times daily will usually suffice. After initiation of treatment in children or adults, dosage should be adjusted to the smallest amount adequate to relieve symptoms.		HCl alone or in combination with antipsychotic drugs. Should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, bladder-neck obstruction, cardiovascular disease or impairment of liver function. Drowsiness is the most prominent CNS effect of this drug.	lower respiratory tract symptoms including asthma. Use may lead to potentially fatal respiratory depression, lower seizure threshold, or impair the mental and/or physical abilities required for performance of potentially hazardous tasks, such as driving a vehicle or operating machinery.
Nasal Steroid Rx and/or OTC FDA Approved Drug Products (with or without antihistamines)						
Azelastine HCl/fluticasone propionate metered nasal spray EQ 0.125 mg base(137 mcg azelastine HCl)/spray; 0.05 mg (50 mcg)/spray (Dymista®) NDA 202236	SAR	Rx 2012	<u>Adults and children 6 years of age and older</u> : 1 spray in each nostril twice daily.	Efficacy was assessed in four placebo-controlled two-week duration clinical trials (4001, 4002, 4004 and 4006) conducted in a total of 4022 subjects aged 12 years and older using rTNSS as primary efficacy endpoint in all four studies. Treatment difference from	Same as above plus Epistaxis, nasal ulcerations, nasal septal perforation, impaired wound healing, and <i>Candida albicans</i> infection. Monitor patients periodically for signs of adverse effects on the nasal mucosa. Avoid use in patients with recent nasal	Most common AEs (≥2% incidence) are: dysgeusia, epistaxis and headache. Safety concerns include: hypercorticism and adrenal suppression with very high dosages or at the regular dosage in susceptible

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				placebo ranged from -2.2 to -3.1 (p-values all <0.001). ²²¹	ulcers, nasal surgery, or nasal trauma, glaucoma or posterior subcapsular cataracts. Potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections or ocular herpes simplex. More serious or even fatal course of chickenpox or measles in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections.	individuals. If such changes occur, discontinue Dymista® slowly. Potential reduction in growth velocity in children. Monitor growth routinely in pediatric patients receiving Dymista®. Monitor patients closely with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.
Beclomethasone dipropionate monohydrate metered nasal spray EQ 0.42 mg dipropionate/ spray (Beconase® AQ) NDA 019389	SAR; PAR; Nonallergic (vasomotor) rhinitis	Rx 1987	<u>Adults and children 12 years and older:</u> 1 or 2 nasal inhalations in each nostril twice a day. <u>Children 6 to 12 years:</u> start with 1 nasal inhalation in each nostril twice daily.	Per approved labeling, results from two clinical trials have shown that significant symptomatic relief was obtained within 3 days. However, symptomatic relief may not occur in some	Contraindicated in patients with hypersensitivity to any of the ingredients. If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or	In general, side effects in clinical studies have been primarily associated with irritation of the nasal mucous membranes. Persons who

²²¹ NDA 202236 Summary Review of Regulatory Action by Badrul A. Chowdhury, MD finalized in DARRTS on 5/1/12; pg. 6-8 of 16.

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
			Patients not adequately responding may use 2 inhalations in each nostril. Once adequate control is achieved, decrease dosage to 1 spray in each nostril twice a day. Use should not be continued beyond 3 weeks in the absence of significant symptomatic improvement and should not be used in the presence of untreated localized infection involving the nasal mucosa.	patients for as long as 2 weeks.	predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, cataracts, and cushingoid features. If such changes occur, BECONASE AQ Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy.	are using drugs that suppress the immune system are more susceptible to Infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids.
Beclomethasone dipropionate metered nasal aerosol 0.04 mg/actuation; 0.8 mg/actuation (Qnasl®) NDA 202813	SAR; PAR	Rx 2012	<u>Adults and children aged 12 years and older:</u> two actuations of 0.8 mg/actuation in each nostril once daily. <u>Children aged 4-11 years:</u> one actuation of 0.4 mg/actuation in each nostril once daily.	Efficacy assessed in 3 randomized, double-blind, parallel-group, multicenter, placebo-controlled clinical trials of 2 to 6 weeks duration in adult and adolescent patients 12 years and older with symptoms of SAR or PAR using rTNSS. Difference from placebo ranged	Contraindicated in patients with a history of hypersensitivity to beclomethasone dipropionate or another Qnasl® ingredient. Most common AEs (≥ 1% and greater than placebo) in patients 12 years of age and older include nasal discomfort,	Nasal discomfort, epistaxis, nasal ulceration, <i>Candida albicans</i> infection, nasal septal perforation, impaired wound healing. Development of glaucoma or posterior subcapsular cataracts.

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				from -0.84 to -0.91, which were statistically significant.	epistaxis, and headache. The most common AEs (≥ 2% and greater than placebo) in children 4 to 11 years of age include headache, pyrexia, upper respiratory tract infection, and nasopharyngitis.	Hypersensitivity, rash, and urticaria. Potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. More serious or even fatal course of chickenpox or measles in susceptible patients. Hypercorticism and adrenal suppression with very high dosages or at the regular dosage in susceptible individuals. Potential reduction in growth velocity in pediatric patients.
Budesonide metered nasal spray 0.032 mg (32 mcg)/spray (Rhinocort®) NDA 020746	Temporarily relieves these symptoms of hay fever or other upper respiratory	Rx 1999 OTC 2015	<u>Adults and children 12 years of age and older</u> : once daily, spray 2 times into each nostril while sniffing gently.	Efficacy for SAR and PAR was assessed in placebo-controlled clinical trials of 3-6 weeks duration in 141 children	Do not use if you have ever had an allergic reaction to any of the ingredients. Ask a doctor before use if you have	When using this product, the growth rate of some children may be slower. Some symptoms

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
	allergies: nasal congestion, runny nose, sneezing and itchy nose.		Once your allergy symptoms improve, reduce to 1 spray in each nostril per day. <u>Children 6 to under 12 years of age:</u> once daily, spray 1 time into each nostril while sniffing gently. If allergy symptoms do not improve, increase to 2 sprays in each nostril per day. Once allergy symptoms improve, reduce to 1 spray in each nostril per day.	aged 6-12 years and 1385 patients aged 12 years and above. Overall, the results of these clinical trials showed that Rhinocort® administered once daily provides statistically significant reduction in the severity of nasal symptoms of seasonal and perennial allergic rhinitis including runny nose, sneezing, and nasal congestion.	had recent nose ulcers or nose surgery, have had a nose injury that has not healed, are using a steroid medicine for asthma, allergies or skin rash, have an eye infection or have or had glaucoma or cataracts. Stop use and ask a doctor if you have, or come into contact with someone who has chickenpox, measles or tuberculosis, you have or develop symptoms of an infection such as persistent fever, you have any change in vision, you have severe or frequent nosebleeds.	may get better on the first day of treatment. It may take up to two weeks of daily use to feel the most symptom relief. Do not share this bottle with anyone else as this may spread germs. If pregnant or breast-feeding: ask a health professional before use.
Ciclesonide metered nasal aerosol 0.036 mg/inhalation (INH) (Zetonna®) NDA 202129	SAR; PAR	Rx 2012	<u>Adults and adolescents 12 years and older:</u> one actuation per nostril daily.	Efficacy was evaluated in 4 clinical trials conducted in 3001 patients with SAR or PAR and assessed with rTNSS. Difference from placebo was <0.001 and	Contraindicated in patients with a known hypersensitivity to ciclesonide or any of the ingredients of Zetonna®. Most common AEs (≥2% incidence) include nasal	Local nasal effects include epistaxis, ulceration, nasal septal perforations, <i>Candida albicans</i> infection, impaired

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				ranged from -0.7 to -0.9. Onset of effect was seen after 36 hours following the first dose. Maximum benefit is usually achieved within 1 to 2 weeks after initiation of dosing.	discomfort, headache and epistaxis. Possible side effects include eye problems such as glaucoma and cataracts, adrenal insufficiency, and slowed or delayed growth in children. Monitor patients periodically for signs of adverse effects on the nasal mucosa. Discontinue Zetonna® if erosions, ulcerations or perforation occur.	wound healing. Prior to initiating therapy, examine patients for evidence of septal perforation, erosions, ulceration, nasal surgery, and trauma. Avoid spraying Zetonna® directly onto the nasal septum. Avoid use in patients with recent septal perforation, nasal erosion, nasal ulcers, nasal surgery, or nasal trauma.
Ciclesonide metered nasal spray 0.05 mg/INH (Omnaris®) NDA 022004	SAR; PAR	Rx 2006	SAR: Adults and children 6 years of age and older: 2 sprays per nostril once daily. PAR: Adults and adolescents 12 years and older: 2 sprays per nostril once daily.	Efficacy was assessed in 3 placebo-controlled clinical trials of 2-6 weeks duration conducted in 1524 adolescents and adults with allergic rhinitis. The difference from placebo in the rTNSS ranged from -0.53 to -0.9 and each was	Same as above plus: most common AEs (>2% incidence) included headache, epistaxis, nasopharyngitis, ear pain, and pharyngolaryngeal pain.	Same as above.

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				statistically significant.		
Fluticasone propionate metered nasal spray 0.05 mg/spray a)Rx Flonase® NDA 020121 b)OTC Flonase Allergy Relief NDA 205434	a) Rx PAR b)OTC Temporarily relieves these symptoms of hay fever or other upper respiratory allergies: nasal congestion, runny nose, sneezing, itchy nose, itchy, watery eyes	a) Rx 1994 b)OTC 2014	a) Rx <u>Adults</u> : 2 sprays per nostril once daily. <u>Rx Adolescents and children aged 4 years and older</u> : 1 spray per nostril once daily. b)OTC <u>Adults and children 12 years of age and older</u> : Week 1, use 2 sprays in each nostril once daily. Week 2-5 months, use 1 or 2 sprays in each nostril once daily, as needed to treat your symptoms. After 6 months daily use, ask your doctor if you can keep using. <u>OTC Children 4-11 years of age</u> : 1 spray in each nostril once daily.	Efficacy was assessed in 3 placebo-controlled trials conducted in 1191 subjects with PAR. Two of the trials demonstrated that subjects treated with Flonase® (100 mcg twice daily) exhibited statistically significant decreases in TNSS compared with subjects treated with vehicle.	Same as above <u>plus</u> : Most common AEs (>3%) are headache, pharyngitis, epistaxis, nasal burning/nasal irritation, nausea/vomiting, asthma symptoms, and cough.	Same as above.
Fluticasone furoate metered nasal spray 0.0275 mg/INH (Veramyst®) NDA 022051	SAR, PAR	Rx 2007	<u>Adults and adolescents 12 years and older</u> : 2 sprays per nostril once daily. <u>Children 2 to 11 years</u> : 1 spray per nostril once daily.	Efficacy assessed in 4 placebo controlled trials (3 SAR and 1 PAR) of 2-4 weeks duration in patients aged 12 years and older. rTNSS difference from	Same as above <u>plus</u> : Most common AEs (>1% incidence) included headache, epistaxis, pharyngolaryngeal pain, nasal ulceration, back	Same as above

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				placebo ranged from -0.78 to -1.47 (SAR) and was -0.71 (PAR).	pain, pyrexia, and cough.	
Mometasone furoate metered nasal spray EQ 0.05 mg/spray (Nasonex®) NDA 020762	Allergic Rhinitis, SAR, prophylaxis of SAR	Rx 1997	Allergic Rhinitis and SAR: Adults and adolescents 12 years and older: 2 sprays in each nostril once daily. Children 2 to 11 years: 1 spray in each nostril once daily. Prophylaxis of SAR: Adults and adolescents 12 years and older: 2 sprays in each nostril once daily.	Efficacy assessed in 18 controlled trials and 1 uncontrolled trials in approximately 3000 patients with SAR or PAR treated with Nasonex® 50 mcg to 800 mcg/day, with the majority at 200 mcg/day. Patients treated with 200 mcg/day had a statistically significant decrease in TNSS compared to placebo-treated patients with no additional benefit observed at doses greater than 200 mcg/day. Efficacy for prophylaxis of SAR was assessed in 284 patients. Those patients dosed with 200 mcg/day for 2-4 weeks demonstrated a statistically significantly smaller mean increase in TNSS	Same as above <u>plus:</u> most common AEs (≥5%) included headache, viral infection, pharyngitis, epistaxis and cough.	Same as above

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				with onset of pollen season compared to placebo patients.		
Triamcinolone metered nasal spray 0.055 mg/spray (Nasacort® Allergy 24 Hour) NDA 020468	Temporarily relieves these symptoms of hay fever or other upper respiratory allergies: nasal congestion, runny nose, sneezing and itchy nose.	Rx 1996 OTC 2013	<u>Adults and children 12 years of age and older:</u> once daily, spray 2 times into each nostril while sniffing gently. Once your allergy symptoms improve, reduce to 1 spray in each nostril per day. <u>Children 6 to under 12 years of age:</u> once daily, spray 1 time into each nostril while sniffing gently. If allergy symptoms do not improve, increase to 2 sprays in each nostril per day. Once allergy symptoms improve, reduce to 1 spray in each nostril per day. <u>Children 2 to 6 years of age:</u> once daily, spray 1 time in each nostril while sniffing gently.	Efficacy was assessed in 10 placebo-controlled trials of 2 to 4 week duration in adults and children 12 years and older with SAR or PAR. When compared to placebo, two sprays in each nostril once daily provided statistically significant relief of nasal symptoms of SAR or PAR including sneezing, stuffiness, discharge and itching.	Do not use if you have ever had an allergic reaction to any of the ingredients. Ask a doctor before use if you have had recent nose ulcers or nose surgery, have had a nose injury that has not healed, are using a steroid medicine for asthma, allergies or skin rash, have an eye infection or have or had glaucoma or cataracts. Stop use and ask a doctor if you have, or come into contact with someone who has chickenpox, measles or tuberculosis, you have or develop symptoms of an infection such as persistent fever, you have any change in vision, you have severe or frequent	When using this product, the growth rate of some children may be slower. Some symptoms may get better on the first day of treatment. It may take up to two weeks of daily use to feel the most symptom relief. Do not share this bottle with anyone else as this may spread germs. If pregnant or breast-feeding: ask a health professional before use.

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
					nosebleeds.	
Leukotriene Inhibitor						
Montelukast sodium (Singulair®) a)NDA 020829 oral tablet EQ 10 mg base b)NDA 020830 oral chewable tablet EQ 4 mg base and 5 mg base c)NDA 021409 oral granule EQ 4 mg base/ packet	SAR, PAR	a) 1998 b) 1998, 2000 c) 2002	SAR, PAR: <u>Adults and adolescents 15 years of age and older:</u> 10 mg tablet once daily. <u>Children 6 to 14 years:</u> 5 mg chewable tablet once daily. <u>Children 2 to 5 years:</u> 4 mg chewable tablet or one packet of 4-mg oral granules once daily. PAR: <u>Children 6 to 23 months of age:</u> one packet of 4-mg oral granules once daily.	Singulair® has been evaluated in 5 placebo-controlled trials enrolling 5029 patients aged at least 15 years with SAR. Four of the five trials showed a significant reduction in daytime nasal symptoms scores compared with placebo. Studies show that montelukast was more beneficial than placebo and equally as effective as loratadine (Claritin) for the treatment of SAR. There was only a marginal benefit in adding montelukast to loratadine, and neither montelukast nor loratadine were as effective as intranasal steroids. ^{222, 223}	Need to adjust dosage in mild to moderate hepatic disease. Phenylketonuric patients should be informed that the 4-mg and 5-mg chewable tablets contain phenylalanine (a component of aspartame), 0.674 and 0.842 mg per 4-mg and 5-mg chewable tablet, respectively.	The following AEs were reported with Singulair® with a frequency ≥1% and at an incidence greater than placebo: sinusitis, upper respiratory infection, sinus headache, cough, epistaxis and increased ALT. The incidence of somnolence was similar to that of placebo.
Nasal Cromolyn						

²²² Meltzer EO et al. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. *J Allergy Clin Immunol.* 2000; 105: 917–22.

²²³ Pullerits T et al. Comparison of a nasal gluco-corticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol.* 2002; 109: 949–55.

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Product(s) Name	Relevant Indication	Year of Approval	Dosing/ Administration for Allergic Rhinitis	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Cromolyn sodium metered nasal spray 5.2 mg/spray (OTC ANDAs 075702 and 075427)	To prevent and relieve nasal symptoms of hay fever and other nasal allergies: runny/itchy nose, sneezing, allergic stuffy nose.	NDA 020463 Nasalcrom® was approved 1997 and withdrawn 2006 (product was transferred and produced under OTC ANDA 075702).	<u>Adults and children 2 years and older</u> : Spray once into each nostril. Repeat 3-4 times a day (every 4-6 hours). If needed, may be used up to 6 times a day. Use every day while in contact with the cause of your allergies (pollen, molds, pets, and dust). To prevent nasal allergy symptoms, use before contact with the cause of your allergies. For best results, start using up to one week before contact.	No efficacy information is provided in the OTC label.	Do not use if you are allergic to any of the ingredients. Ask doctor before use if you have fever, discolored nasal discharge, sinus pain or wheezing. When using this product, it may take several days of use to notice an effect. Your best effect may not be seen for 1-2 weeks. Brief stinging or sneezing may occur right after use. Do not use if to treat sinus infection, asthma, or cold symptoms, do not share this bottle with anyone else as this may spread germs.	Stop use and ask a doctor if shortness of breath, wheezing, or chest tightness occurs, hives or swelling of the mouth or throat occurs, your symptoms worsen, you have new symptoms, your symptoms do not begin to improve within two weeks, you need to use for more than 12 weeks. If pregnant or breast feeding, ask a health professional before use.

Source: Per 21 CFR 341.12 and searches conducted by this reviewer of DailyMed (U.S. National Library of Medicine Drug Labels), DARRTS, Drugs@FDA, Google and Orange Book.

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/s/

BRENDA S GIERHART
11/14/2016

STEVEN F OSBORNE
11/15/2016

Xyzal (levocetirizine) Rx-to-OTC switch for 5 mg tablets (adult) and oral solution (children).

(b) (4)

Clinical Filing Checklist

NDA/BLA Number: 209-089 Applicant: UCB, Inc. Stamp Date: March 31, 2016

**Drug Name: Xyzal Allergy 24 HR NDA/BLA Type: Rx-to-OTS
switch**

Review Division DPARP

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	Rx to OTC switch; Original NDA was a 505(b)(2).
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	Dose is the same as Rx drug (One tablet (5 mg) once daily).
EFFICACY					

	Content Parameter	Yes	No	NA	Comment
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?	X			Refer to DNCE reviewer's comments.
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ YES ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Reviewing Medical Officer

Date

Clinical Team Leader

Date

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

/s/

XU WANG
05/26/2016

ANTHONY G DURMOWICZ
05/26/2016

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Numbers: 209089

Applicant: UCB, Inc. (Agent: Sanofi US Services Inc., on behalf of Sanofi-Aventis U.S., LCC)

Stamp Date: 3/31/16

Drug Name: Levocetirizine Dihydrochloride Tablets (Xyzal® Allergy 24HR)

NDA/BLA Type: Type 8- Partial Rx-to-OTC Switch

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	<p>Identify the general format that has been used for this application, e.g. electronic CTD.</p> <p>[NOTE #1: Per minutes of 10/1/15 mtg Question 3 re: cross-referencing Modules 2.4, 2.7.1 and 2.7.2 to the previously submitted information for nonclinical safety, biopharmaceutics, clinical pharmacology and PK data, FDA recommended that while it was, in general, acceptable to cross-reference previously submitted information, FDA recommended that the sponsor include summary documents in the new submission. It appears that the sponsor assumed that the requested summary documents for nonclinical safety ONLY consisted of an <u>overview</u> of the nonclinical data, which contained a table cross-referencing the locations of the nonclinical studies, and did not include “nonclinical <u>written</u> and <u>tabulated summaries</u>”.]</p> <p>[NOTE #2: Per minutes of 10/1/15 mtg Question 8, cross-referencing CMC Drug Substance and Drug Product information was acceptable provided that the multiple time-points profiles comparison showed similarity between proposed debossed tablets and original printed tablet.]</p>				<p>1) Format: electronic CTD. 2) Statement of claimed exclusivity was not located in Module 1 (acceptable because no new clinical studies were conducted to support exclusivity claim). 3) “Nonclinical Written and Tabulated Summaries” was not included in Module 2 (acceptable since nonclinical overview was submitted). 4) Drug Substance information was not included in Module 3 (acceptable because this information was cross-referenced). 5) “Module 4. Nonclinical Study Reports” was not submitted (acceptable because no new nonclinical studies were conducted).</p>
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	<p>Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?</p> <p>[NOTE: “Module 5 Clinical Study Reports” does not contain a table of contents for the entire module. However, it is acceptable to scroll down to see the individual reports provided. The Tabular Listing of Clinical Studies and each individual clinical study report is adequately paginated.]</p>	X			
4.	For an electronic submission, is it possible to navigate the	X			

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?				
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			ISS is located in 5.3.5.3. Sponsor also submitted one Summary of Clinical Safety (SCs) in 2.7.4 for both the tablet and solution NDAs.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)? [NOTE: Per minutes of 10/1/15 mtg Question 5, FDA agreed to accept a waiver for inclusion of an ISE in the tablets and oral solution NDAs.]			X	Instead of an ISE, sponsor submitted one Summary of Clinical Efficacy (SCE) for both the tablet and solution NDAs.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			In ISS Section 6.2.5, sponsor submitted a risk and benefit analysis based on their literature search results.
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				Per the cover letter, this 505(b)(2) application references Xyzal® (levocetirizine dihydrochloride) tablets NDA 022064 and Zyrtec® (cetirizine dihydrochloride) NDA 019835 (5 mg and 10 mg tablets) and NDA 021621 (chewable tablets, 5 mg and 10 mg). An additional reference is made to the prescription cetirizine NDA 020346 (oral syrup, 5 mg/mL).
DOSE: Deferred to DCPII, Bhawana (Bavna) Saluja, Staff Fellow and Anshu Marathen, Senior Staff Fellow					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product				

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p>been exposed at the dose (or dose range) believed to be efficacious?</p> <p>[NOTE: sponsor exposure tables overlapped with children age 12 years included in both the “12 years and older” long-term studies of levocetirizine and in the “children aged 6 month to 12 years” long-term studies of levocetirizine. Thus, the total number of <u>unique</u> subjects with at least 6 months and 1 year of treatment at the dose indicated for their age is currently unclear. However, the Rx NDA was approved based upon these numbers of subjects exposed to levocetirizine, so this reviewer considers the answer to this question to be “yes”.]</p>				to levocetirizine 1.25 mg to 30 mg, with 401 for at least 6 months and 232 for at least one year. In all studies, 5634 subjects were exposed to at least levocetirizine 5 mg (dose for adults and children 12 years of age and older), with 170 for at least 6 months and 8 for at least one year. In addition, 239 children aged 6 months to 12 years were exposed to levocetirizine 2.5 mg (dose for children 6-11 years and more than 1.25 mg dose for children 6 months to 11 years), 227 for at least 6 months and 224 for at least one year.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	<p>Has the applicant submitted the coding dictionary² used for mapping investigator verbatim terms to preferred terms?</p> <p>[NOTE: Clinical reviewer does not consider this to be a filing issue.]</p>		X		While the coding dictionary was not submitted, the data definition file for analysis datasets contains the variables AETERM (AE Verbatim Term), AEMODIFY (AE Modified Reported Term), AEDECOD (Dictionary- Derived Term) and AEPTCD (Preferred Term Code).
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	<p>Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? Per ISS pg. 106-7, only one death (No. 394-126-2649) was reported during the levocetirizine clinical development program and he was randomized to the comparator desloratradine 5 mg, so no narratives were submitted for levocetirizine deaths. Per ISS pg. 110, 77 subjects in the levocetirizine group discontinued due to a TEAE.</p> <p>[NOTE: Clinical reviewer does not consider this to be a filing issue.]</p>		X		Sponsor submitted patient narratives for 10 of the 77 subjects discontinued due to a TEAE. Sponsor submitted narratives for a wide range of SAEs and other important events, e.g., hospitalizations, pregnancy, auto accidents, and certain outpatient illnesses considered to be important.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Sponsor provided the dose-response analyses of the UCB postmarketing safety database and for each of the requested 4 external databases in the analysis of internal data summary.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?	X			Label comprehension study.
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver requested.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			See 5.3.5.3 Drug Abuse Liability Assessment.
FOREIGN STUDIES					
30.	<p>Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?</p> <p>[NOTE: Clinical reviewer does not consider this to be a filing issue because approval of Rx NDA was primarily based upon foreign data for both the SAR and PAR indications.]</p>		X		All ten placebo-controlled studies (i.e., A217, A219, A222, A00264, A00265, A00266, A00268, A00303, A00304, A00306) supporting the SAR and PAR indications were conducted in foreign countries (Belgium, France, German, Italy, South Africa, Spain).
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			Datasets submitted for ISS and Label Comprehension Study
32.	Has the applicant submitted datasets in the format agreed to			X	Format of ISS and

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	previously by the Division?				LCS datasets was not discussed at preIND 126506, 126507 mtg held on 10/1/15 discussing format and content for OTC switch.
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	NDA Reviewer's Guide in 1.2 contains locations of CSR and datasets for all clinical studies.
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				Deferred to DPARP
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	No Case Report Forms were submitted because no new clinical studies were conducted.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	The Division did not request the submission of any additional Case Report Forms.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	No financial forms were submitted because no new clinical studies were conducted.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	No new clinical studies were conducted.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant. N/A.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. None.

(Brenda S. Gierhart, MD) 5/25/16

Reviewing Medical Officer

Date

(Jane Filie, MD)

5/25/16

Clinical Team Leader

Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

BRENDA S GIERHART
05/25/2016

JANE FILIE
05/25/2016

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Numbers: 209090

Applicant: UCB, Inc. (Agent: Sanofi US Services Inc., on behalf of Sanofi-Aventis U.S., LCC)

Stamp Date: 3/31/16

Drug Name: Levocetirizine Dihydrochloride Oral Solution (Xyzal® Allergy 24HR)

NDA/BLA Type: Type 8- Partial Rx-to-OTC Switch

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	<p>Identify the general format that has been used for this application, e.g. electronic CTD.</p> <p>[NOTE #1: Per minutes of 10/1/15 mtg Question 3 re: cross-referencing Modules 2.4, 2.7.1 and 2.7.2 to the previously submitted information for nonclinical safety, biopharmaceutics, clinical pharmacology and PK data, FDA recommended that while it was, in general, acceptable to cross-reference previously submitted information, FDA recommended that the sponsor include summary documents in the new submission. It appears that the sponsor assumed that the requested summary documents for nonclinical safety ONLY consisted of an <u>overview</u> of the nonclinical data, which contained a table cross-referencing the locations of the nonclinical studies, and did not include “nonclinical <u>written</u> and <u>tabulated summaries</u>”.]</p> <p>[NOTE #2: Per minutes of 10/1/15 mtg Question 8, cross-referencing CMC Drug Substance and Drug Product information was acceptable provided that the multiple time-points profiles comparison showed similarity between proposed debossed tablets and original printed tablet.]</p>				<p>1) Format: electronic CTD.</p> <p>2) Statement of claimed exclusivity was not located in Module 1 (acceptable because no new clinical studies were conducted to support exclusivity claim).</p> <p>3) “Nonclinical Written and Tabulated Summaries” was not included in Module 2 (acceptable since nonclinical overview was submitted).</p> <p>4) Drug Substance information was not included in Module 3 (acceptable because this information was cross-referenced).</p> <p>5) “Module 4. Nonclinical Study Reports” was not submitted (acceptable because no new nonclinical studies were conducted).</p>
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	<p>Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?</p> <p>[NOTE: “Module 5 Clinical Study Reports” does not contain a table of contents for the entire module. However, it is acceptable because no individual reports were provided in Module 5. The Tabular Listing of Clinical Studies is adequately paginated.]</p>	X			
4.	For an electronic submission, is it possible to navigate the	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?				
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			Some discipline summaries are cross-referenced to NDA 209089.
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			ISS is located in 5.3.5.3 of NDA 209089. Sponsor also submitted one Summary of Clinical Safety (SCs) in 2.7.4 of NDA 209089 for both the tablet and solution NDAs.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)? [NOTE: Per minutes of 10/1/15 mtg Question 5, FDA agreed to accept a waiver for inclusion of an ISE in the tablets and oral solution NDAs.]			X	Instead of an ISE, sponsor submitted one Summary of Clinical Efficacy (SCE) for both the tablet and solution NDAs in NDA 209089.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			In ISS Section 6.2.5 (submitted to NDA 209089), sponsor submitted a risk and benefit analysis based on their literature search results.
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				Per the cover letter, this 505(b)(2) application references Xyzal® (levocetirizine dihydrochloride) tablet NDAs 022064 and 209089 and oral solution NDA 022157. Additionally, reference is made to Zyrtec® (cetirizine dihydrochloride) NDA 019835 (5 mg and 10 mg tablets) and NDA 021621 (chewable tablets, 5 mg and 10

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	Content Parameter	Yes	No	NA	Comment
					analysis of external safety data, ISS Biological plausibility analyses of postmarketing safety data and ISS Tabulated summary of medical literature
21.	<p>For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure¹) been exposed at the dose (or dose range) believed to be efficacious?</p> <p>[NOTE: sponsor exposure tables overlapped with children age 12 years included in both the “12 years and older” long-term studies of levocetirizine and in the “children aged 6 month to 12 years” long-term studies of levocetirizine. Thus, the total number of <u>unique</u> subjects with at least 6 months and 1 year of treatment at the dose indicated for their age is currently unclear. However, the Rx NDA was approved based upon these numbers of subjects exposed to levocetirizine, so this reviewer considers the answer to this question to be “yes”.]</p>	X			In all studies, 6632 subjects were exposed to levocetirizine 1.25 mg to 30 mg, with 401 for at least 6 months and 232 for at least one year. In all studies, 5634 subjects were exposed to at least levocetirizine 5 mg (dose for adults and children 12 years of age and older), with 170 for at least 6 months and 8 for at least one year. In addition, 239 children aged 6 months to 12 years were exposed to levocetirizine 2.5 mg (dose for children 6-11 years and more than 1.25 mg dose for children 6 months to 11 years), 227 for at least 6 months and 224 for at least one year.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	<p>Has the applicant submitted the coding dictionary² used for mapping investigator verbatim terms to preferred terms?</p> <p>[NOTE: Clinical reviewer does not consider this to be a filing issue.]</p>		X		While the coding dictionary was not submitted, the data definition file for analysis datasets contains the variables AETERM (AE Verbatim Term),

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					AEMODIFY (AE Modified Reported Term), AEDECOD (Dictionary- Derived Term) and AEPTCD (Preferred Term Code).
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? Per ISS submitted to NDA 209089 pg. 106-7, only one death (No. 394-126-2649) was reported during the levocetirizine clinical development program and he was randomized to the comparator desloratadine 5 mg, so no narratives were submitted for levocetirizine deaths. Per ISS submitted to NDA 209089 pg. 110, 77 subjects in the levocetirizine group discontinued due to a TEAE. [NOTE: Clinical reviewer does not consider this to be a filing issue.]		X		Sponsor submitted patient narratives for 10 of the 77 subjects discontinued due to a TEAE. Sponsor submitted narratives for a wide range of SAEs and other important events, e.g., hospitalizations, pregnancy, auto accidents, and certain outpatient illnesses considered to be important.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Sponsor provided the dose-response analyses of the UCB postmarketing safety database and for each of the requested 4 external databases in the analysis of internal data summary submitted to NDA 209089.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?	X			Label comprehension study.
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver requested.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			See Drug Abuse Liability Assessment submitted to NDA 209089 in 5.3.5.3.
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? [NOTE: Clinical reviewer does not consider this to be a		X		All ten placebo-controlled studies (i.e., A217, A219, A222, A00264, A00265, A00266, A00268,

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	Content Parameter	Yes	No	NA	Comment
	filing issue because approval of Rx NDA was primarily based upon foreign data for both the SAR and PAR indications.]				A00303, A00304, A00306) supporting the SAR and PAR indications were conducted in foreign countries (Belgium, France, German, Italy, South Africa, Spain).
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			Datasets submitted in NDA 209089 for ISS and in NDAs 209089 and 209090 for Label Comprehension Study
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	Format of ISS and LCS datasets was not discussed at preIND 126506, 126507 mtg held on 10/1/15 discussing format and content for OTC switch.
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	NDA Reviewer's Guide in 1.2 contains locations of CSR and datasets for all clinical studies.
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				Deferred to DPARP
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	No Case Report Forms were submitted because no new clinical studies were conducted.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	The Division did not request the submission of any additional Case Report Forms.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	No financial forms were submitted because no new clinical studies were conducted.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	No new clinical studies were conducted.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes___

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant. N/A.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. None.

Reviewing Medical Officer (Brenda S. Gierhart, MD) 5/25/16
Date

Clinical Team Leader (Jane Filie, MD) 5/25/16
Date

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

/s/

BRENDA S GIERHART
05/25/2016

JANE FILIE
05/25/2016