CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-064

SUMMARY REVIEW

DIVISION DIRECTOR DECISIONAL REVIEW

Date: May 25, 2007

To: NDA 22-064

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy products, CDER, FDA

Product: Xyzal (levocetirizine dihydrochloride) tablets

Applicant: UCB, Inc.

Administrative and Introduction

UCB submitted a 505(b)(2) new drug application (NDA 22-064) on July 24, 2006, (received on July 25, 2006, CDER stamp date) for use of Xyzal (levocetirizine dihydrochloride) tablets 5 mg for once daily use for the relief of symptoms of seasonal and perennial allergic rhinitis, and uncomplicated skin manifestations of chronic idiopathic urticaria in patients 6 years of age and older. The PDUFA due date for this application is May 25, 2007. Levocetirzine is a H1-receptor antagonist. It is the R enantiomer of cetirizine hydrochloride. This application references cetirizine hydrochloride in support of the 505(b)(2) regulatory pathway. Cetirizine is currently approved in various formulations for seasonal allergic rhinitis in patients 2 years of age and older, and for perennial allergic rhinitis and chronic urticaria in patients 6 months of age and older. UCB submitted the necessary CMC data, pre-clinical data, and clinical data that support approval of this application in patients 6 years of age and older.

Regulatory History

The development program for levocetirizine was conducted entirely outside the United States and none of the studies were conducted under an IND. Levocetirzine is marketed in many countries around the world. UCB had a pre-IND meeting with the Agency in June 2005. This was essentially a pre-NDA meeting because the development program for levocetirizine was already conducted and the discussion was mostly around UCB's plan to submit this NDA for prescription marketing of levocetirizine in the United States. On review of the studies conducted by UCB the Division noted that there were no studies that compared more than one dose of cetirizine to more than one dose of levocetirizine in the same study to support UCB's contention that levocetirizine has the same effect as cetirizine at half the dose. Since the pre-IND meeting UCB conducted one environmental exposure unit pharmacodynamic efficacy study comparing two doses of cetirizine and two doses of levocetirizine.

The Division initially took a Refuse to File action on this application because the submission did not contain an Integrated Summary of Efficacy (ISE). The decision was later rescinded and the application was filed following an explanatory correspondence

from UCB and their agreement to submit the ISE in a timely manner. UCB subsequently submitted the ISE.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation
Xyzal is formulated as immediate release, film-coated, oval-shaped scored tablet containing 5 mg levocetirizine dihydrochloride, and the following excipients: microcrystalline cellulose, lactose monohydrate, colloidal anhydrous silica, and magnesium stearate. The commercial presentations are unit use HDPE bottles containing either 30 tablet or 180 tablets, and 10 tablets per blister card in a 3 card package. The drug substance is manufactured at the UCB facility in Belgium ——— and Switzerland ——— The tablets are packaged into bottles and blisters at the UCB facilities in Belgium and in Rochester, NY, USA. All DMFs associated with this application are acceptable. All the manufacturing and testing facilities associated with this drug product have acceptable EER status. The CMC review team has found the submitted material adequate to support approval.

There were several CMC issues identified by the CMC review team early in the review period. Those were communicated to UCB in discipline review letters. UCB resolved these issues and the CMC team recommends an approval action. I concur with this recommendation. There is one CMC issue worth noting. A ——— was noted to be present in the tablets. The pharmacology-toxicology team determined that the impurity was present at a low level, ——— of the drug product and the maximum daily dose was ——— which was determined to be acceptable.

Nonclinical Pharmacology and Toxicology
Nonclinical pharmacology and toxicology assessment of levocetirizine is primarily based on findings for cetirizine tablets (NDA 19-835), with supplemental bridging studies in rats, dogs, and rabbits, comparing the toxicity profile of levocetirizine and cetirizine. Carcinogenicity studies and reproductive toxicity studies were not performed with levocetirizine. UCB relied on findings of cetirizine, which is acceptable. The PharmTox team has determined that the submitted nonclinical pharmacology and toxicology program are adequate and recommends an approval action. I concur with that recommendation.

Clinical Pharmacology
UCB submitted results from a comprehensive clinical pharmacology program with this application. The submitted studies are reviewed in Dr. Roy's review and found to be adequate to support approval. Comments on some pertinent findings from the program are made in the following paragraphs.

Levocetirizine is rapidly and extensively absorbed following oral administration. Peak plasma concentration is achieved 0.9 hours after dosing, half-life after a single dose is 7-8 hours, and after multiple dosing steady state is achieved in approximately 2 days. Food

has no effect on the extent of exposure (AUC). The extent of metabolism of levocetirizine is less than 14%, therefore, effects of genetic polymorphism of drug metabolizing enzymes and concomitant intake of drug metabolizing enzyme inhibitors are expected to be negligible. The major excretion route of levocetirizine and its metabolites are via urine. The total body clearance of levocetirizine is correlated to creatinine clearance and is progressively reduced based on severity of renal impairment. Therefore, dose adjustment is necessary in patients with renal impairment.

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. 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.

Levocetirizine shows linear kinetics. Plasma concentration of levocetirizine increases approximately proportionately with increasing levocetirizine doses of 2.5 mg to 30 mg in adults. In one pediatric study in subjects 6 to 11 years of age a single dose of 5 mg levocetirizine gave approximately 2-fold greater exposure than that reported in adult subjects based on cross study comparison. The pediatric dosing recommendation of 2.5 mg for patients 6 to 12 years of age is based on this pharmacokinetic consideration. There are no efficacy studies in this age group with 2.5 mg levocetirizine.

Clinical and Statistical

Overview of the clinical program:

The clinical program for Xyzal is larger than typically conducted for a single isomer of an approved racemate. All clinical studies were conducted entirely outside the United States. The pivotal clinical studies that assessed efficacy and safety of Xyzal in patients with seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and chronic idiopathic urticaria (CIU) are shown in Table 1. The pivotal clinical studies in adults and adolescents with SAR and PAR include three dose-ranging studies (A217, A219, A265), five single dose level studies (A268, A222, A266, A306, and A264), and two environmental exposure unit (EEU) studies (A379, A412). The pivotal clinical studies in pediatric patients with SAR and PAR include two single dose level studies (A303, A304). The pivotal clinical studies in adults and adolescents with CIU include one dose-ranging study (A270) and one single dose level study (A269). Detailed review of the clinical program can be found in Dr. Boucher's medical review, Dr. Gebert's statistical review, and in Dr. Gilbert-McClain's medical team leader memorandum. The clinical and statistical teams concluded that the submitted studies support efficacy and safety of Xyzal in patients 6 years and older. I concur with that conclusion. The pivotal clinical studies mentioned above, which have direct bearing on the approvability decision of this application and labeling of this product are briefly reviewed in the following sections.

The design and conduct of these studies are briefly described, followed by efficacy and safety findings and conclusions.

Table 1. Pivotal clinical studies

ID	Disease	Study type	Study duration	Patient Age, yr	Treatment groups*	Study Year#	n	Countries
Seasonal and Perennial Allergic Rhinitis (SAR and PAR), adults and adolescents								
217	SAR	Dose-ranging	2 week	18 - 72	LC 2.5, 5, 10 mg Placebo	1997	470	France, Germany
219	PAR	Dose-ranging	4 week	12 - 65	LC 2.5, 5, 10 mg Placebo	1997	421	France
265	PAR	Dose-ranging	4 week	12 +	LC 2.5, 5, 10 mg Placebo	2000	519	France, Germany
268	SAR	Single dose level	2 week	12 - 71	LC 5 mg Placebo	2000	236	South Africa
222	SAR	Single dose level	1 week	12 - 65	LC 5 mg C 10 mg Placebo	1997	797	France
266	PAR	Single dose level	6 week	12 - 71	LC 5 mg Placebo	2000	294	South Africa
306	SAR	Single dose level	16 week	12 - 68	LC 5 mg Placebo	2004	459	Belgium, Italy, France
264	PAR	Single dose level	6 month	18 - 70	LC 5 mg Placebo	2001	551	Western Europe
379	SAR	EEU	1 dose	16 +	LC 5 mg C 10 mg Placebo	2004	570	Canada
412	SAR	EEU	1 dose	16 +	LC 2.5, 5 mg C 5, 10 mg Placebo	2006	551	Canada
303	SAR	Single dose level	6 week	6 -12	LC 5 mg Placebo	2002	177	France, Germany
304	PAR	Single dose level	4 week	6 - 12	LC 5 mg Placebo	2002	306	South Africa
Chronic Idiopathic Urticaria (CIU)								
270	CIU	Dose-ranging	4 week	18 +	LC 2.5, 5, 10 mg Placebo	2002	257	France
269	CIU	Single dose level	4 week	18 +	LC 5 mg Placebo	2001	166	France, Germany

* LC = levocetirizine, C = cetirizine,
# Year study ended

Design and conduct of the SAR and PAR efficacy and safety studies:

Dose-ranging study in adult and adolescent patients with SAR (A217):

Study A217 was double-blind, placebo-controlled, parallel group in design conducted in 30 centers in France and Germany in patients 18 to 72 years of age with at least a 2 year history of SAR and documented sensitivity to grass pollen or weed pollen or both. The study was conducted in 1997. The study had a 7-day (approximate) screening period,

followed by 2-week double blinded treatment period. The treatment groups were Xyzal 2.5 mg, Xyzal 5 mg, and Xyzal 10 mg, and placebo, all administered once daily in the evening. The primary efficacy variable was reflective patient scoring of four symptoms, (Total Nasal Symptom Score, rTSS - rhinorrhea, nasal pruritus, sneezing, and ocular pruritus) once daily in the PM on a four point scale (0=absent, 1=mild, 2=moderate, and 3=severe). Instantaneous scores were not recorded. Other efficacy variable included the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Safety assessment included recording of adverse events, vital signs, clinical laboratory measures, and physical examinations. The primary efficacy endpoint was the difference from placebo in the mean change from baseline of the average of PM rTSS over the 2 weeks of treatment. The study was designed to have 115 patients per treatment arm to give 80% power to detect a 1.00 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05. A total of 470 patients were randomized approximately equally to the four treatment groups and 406 patients (86%) completed the study. Withdrawals for lack of efficacy were more in the placebo group (23) compared to Xyzal 2.5, 5, or 10 mg groups (8, 8, and 7), respectively. Additionally, there were 5 withdrawals for drowsiness, somnolence, or asthenia; 4 in the Xyzal 10 mg group compared to 1 in the placebo group.

Dose-ranging study in adult and adolescent patients with PAR (A219):

Study A219 was double-blind, placebo-controlled, parallel group in design conducted in 35 centers in France in patients 12 to 65 years of age with at least a 2 year history of PAR and documented sensitivity to house dust mites. The study was conducted in 1997. The study had a 7-day (approximate) screening period, followed by 4-week double blinded treatment period. The treatment groups were Xyzal 2.5 mg, Xyzal 5 mg, and Xyzal 10 mg, and placebo, all administered once daily in the evening. The primary efficacy variable was reflective patient scoring of four symptoms, (Total Nasal Symptom Score, rTSS - rhinorrhea, nasal pruritus, sneezing, and ocular pruritus) once daily in the PM on a four point scale (0=absent, 1=mild, 2=moderate, and 3=severe). Instantaneous scores were not recorded. Other efficacy variables included investigator overall assessment of improvement. Safety assessment included recording of adverse events, vital signs, clinical laboratory measures, and physical examinations. The primary efficacy endpoint was the difference from placebo in the mean change from baseline of the average of PM rTSS over the 4 weeks of treatment. The study was designed to have 115 patients per treatment arm to give 80% power to detect a 1.0 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05. A total of 425 patients were randomized approximately equally to the four treatment groups and 390 patients (92%) completed the study. Of the 425 randomized patients 3 patients did not take any study medication and one patient was lost to follow-up. Withdrawals for lack of efficacy were more in the placebo group (5.7%) compared to Xyzal 2.5, 5, and 10 mg groups (4.8%, 3.8%, and 1.8%), respectively.

Dose-ranging study in adult and adolescent patients with PAR (A265):

Study A265 was double-blind, placebo-controlled, parallel group in design conducted in 53 centers in France and Germany in patients 12 years of age and older with at least a 2

year history of PAR and documented sensitivity to house dust mites. The study was conducted in 2000 and 2001. The study had a 7-day (approximate) screening period, followed by 4-week double blinded treatment period. The treatment groups were Xyzal 2.5 mg, Xyzal 5 mg, and Xyzal 10 mg, and placebo, all administered once daily in the evening. The primary efficacy variable was reflective patient scoring of four symptoms, (Total Nasal Symptom Score, rTSS - rhinorrhea, nasal pruritus, sneezing, and ocular pruritis) once daily in the PM on a four point scale (0=absent, 1=mild, 2=moderate, and 3=severe). Instantaneous scores were not recorded. Other efficacy variables included global evaluation of efficacy and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Safety assessment included recording of adverse events, vital signs, clinical laboratory measures, and physical examinations. The primary efficacy endpoint was the difference from placebo in the mean change from baseline of the average PM rTSS over the 4 weeks of treatment. The study was designed to have 118 patients per treatment arm to give 90% power to detect a 0.85 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05. A total of 521 patients were randomized approximately equally to the four treatment groups and 482 patients (93%) completed the study. Of the 521 randomized patients 2 patients did not take any study medication. Withdrawals for lack of efficacy were more in the placebo group (5.5%) compared to Xyzal 2.5, 5, and 10 mg groups (3.0%, 1.6%, and 1.5%), respectively.

Single dose level study in adult and adolescent patients with SAR (A268)

Study A268 was double-blind, placebo-controlled, parallel group in design conducted in 20 centers in South Africa in patients 12 to 71 years of age and older with at least a 2 year history of SAR and documented sensitivity to grass pollen or weed pollen or both. The study was conducted in 2000 and 2001. The study had a 7-day (approximate) screening period, followed by 2-week double blinded treatment period. The treatment groups were Xyzal 5 mg, and placebo, all administered once daily in the evening. The primary efficacy variable was reflective patient scoring of four symptoms, (Total Nasal Symptom Score, rTSS - rhinorrhea, nasal pruritus, sneezing, and ocular pruritus) once daily in the PM on a four point scale (0=absent, 1=mild, 2=moderate, and 3=severe). In this study patients also recorded instantaneous symptoms scores one hour before dosing. Other efficacy variables included instantaneous patient scoring of the same four symptoms, iTSS (instantaneous total symptom score), global evaluation of efficacy, and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Safety assessment included recording of adverse events, vital signs, clinical laboratory measures, and physical examinations. The primary efficacy endpoint was the difference from placebo in the mean change from baseline of the average of PM rTSS over the 2 weeks of treatment. The study was designed to have 116 patients per treatment arm to give 95% power to detect a 1.0 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05. A total of 237 patients were randomized approximately equally to the two treatment groups and 232 patients (94%) completed the study. Of the 237 randomized patients 1 patient did not take any study medication. There were no preferential discontinuations in any treatment groups.

Single dose level study in adult and adolescent patients with SAR (A222)

Study A222 was double-blind, placebo-controlled, parallel group in design conducted in 49 centers in France in patients 12 to 65 years of age and older with at least a 2 year history of SAR and documented sensitivity to grass pollen or weed pollen or both. The study was conducted in 2000 and 2001. The study had a 7-day (approximate) screening period, followed by 1-week double blinded treatment period. The treatment groups were Xyzal 5 mg, cetirizine 10 mg, and placebo, all administered once daily in the evening. The primary efficacy variable was reflective patient scoring of four symptoms, (Total Nasal Symptom Score, rTSS - rhinorrhea, nasal pruritus, sneezing, and ocular pruritus) once daily in the PM on a four point scale (0=absent, 1=mild, 2=moderate, and 3=severe). Other efficacy variables included investigator global evaluation of improvement. Safety assessment included recording of adverse events, vital signs, clinical laboratory measures, and physical examinations. The primary efficacy endpoint was the difference from placebo in the mean change from baseline of the average of PM rTSS over the 1 week of treatment. The intent of the study was to show equivalence between Xyzal and cetirizine and the protocol had a predefined equivalence margin using 90% CI of the difference between the adjusted means. The study was designed to have 137 patients in placebo arm and 274 patients in each active treatment groups to give 90% power to detect a 1.0 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05. A total of 803 patients were randomized to the study and 6 did not take study medication. Of the remaining 797 patients, 160 received placebo and the other 637 were approximately equally divided between the 2 active treatment groups. Withdrawals were greater in the placebo group (6.3%) than in the Xyzal or cetirizine groups (2.8% or 1.3%), respectively.

Single dose level study in adult and adolescent patients with PAR (A266)

Study A266 was double-blind, placebo-controlled, parallel group in design conducted in 26 centers in South Africa in patients 12 to 71 years of age and older with at least a 2 year history of SAR and documented sensitivity to house dust mite. The study was conducted in 2000. The study had a 7-day (approximate) screening period, followed by 6-week double blinded treatment period. The treatment groups were Xyzal 5 mg, and placebo, all administered once daily in the evening. The primary efficacy variable was reflective patient scoring of four symptoms, (Total Nasal Symptom Score, rTSS - rhinorrhea, nasal pruritus, sneezing, and ocular pruritus) once daily in the PM on a four point scale (0=absent, 1=mild, 2=moderate, and 3=severe). Instantaneous scores were not recorded. Other efficacy variable included global evaluation of efficacy. Safety assessment included recording of adverse events, vital signs, clinical laboratory measures, ECG, and physical examinations. The primary efficacy endpoint was the difference from placebo in the mean change from baseline of the average of PM rTSS over the first 4 weeks of treatment. The study was designed to have 125 patients per treatment arm to give 95% power to detect a 1.0 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05. A total of 294 patients were randomized approximately equally to the two treatment groups and 276 patients (94%) completed the study. Withdrawals

for lack of efficacy were greater in the placebo group (5.6%) than in the Xyzal group (1.3%).

Single dose level study in adult and adolescent patients with SAR (A306)

Study A306 was double-blind, placebo-controlled, parallel group in design conducted in 53 centers in Belgium, France, and Italy in patients 12 to 68 years of age and older with at least a 2 year history of SAR and documented sensitivity to grass pollen or weed pollen or both. The study was conducted in 2004. The study had a 7-day (approximate) screening period, followed by a 16-week double blinded treatment period. The treatment groups were Xyzal 5 mg, and placebo, all administered once daily in the evening. The intent of the study was to compare the efficacy of Xyzal started 8 weeks preceding the anticipated onset of allergy season to Xyzal started during the onset of allergy season. To address the intention of the study there were three treatment groups: placebo for the first 8 weeks followed by Xyzal for the next 8 weeks, Xyzal for 16 weeks, and placebo for 16 weeks. The primary efficacy variable was reflective patient scoring of four symptoms, (Total Nasal Symptom Score, rTSS - rhinorrhea, nasal pruritus, sneezing, and ocular pruritus) once daily in the PM on a four point scale (0=absent, 1=mild, 2=moderate, and 3=severe). Safety assessment included recording of adverse events, vital signs, clinical laboratory measures, and physical examinations. The primary efficacy endpoint was the difference from placebo in the mean change from baseline of the average of PM rTSS over the first 12 weeks of treatment. The study was designed to have 116 patients per treatment arm to give 95% power to detect a 1.0 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05. A total of 463 patients were randomized approximately equally to the three treatment groups and 391 patients (85%) completed the study. There were more discontinuations due to adverse events in the group treated with Xyzal for 16 weeks (6%) compared to the placebo group (3%) treated for 16 weeks.

Single dose level long-term study in adult and adolescent patients with PAR (A264)

Study A264 was double-blind, placebo-controlled, parallel group in design conducted in 53 centers in Belgium, France, Germany, Italy, and Spain in patients 18 to 70 years of age with at least a 2 year history of PAR and documented sensitivity to house dust mites. The study was conducted in 2001 and 2002. The study had a 7-day (approximate) screening period, followed by 6-months double blinded treatment period. The treatment groups were Xyzal 5 mg, and placebo, both administered once daily in the evening. The primary efficacy variables were the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), and reflective patient scoring of five symptoms (Total Nasal Symptom Score, rTSS - rhinorrhea, nasal pruritus, sneezing, nasal congestion, and ocular pruritus) once daily in the PM on a four point scale (0=absent, 1=mild, 2=moderate, and 3=severe). Other efficacy variables included quality of life assessed by SF-66 questionnaire, and rTSS over weeks 1, 3, 4, and 5, and over month 6. Safety assessment included recording of adverse events, vital signs, clinical laboratory measures, and physical examinations. The primary efficacy endpoints were the difference from placebo in the mean change from baseline of the average RQLQ and rTSS over the first 4 weeks of treatment. The

study was designed to have 250 patients per treatment arm to give 87% power to detect a 0.36 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05. A total of 551 patients were randomized approximately equally to the four treatment groups and 421 patients (76%) completed the study. Of the 521 randomized patients 2 patients did not take any study medication. Withdrawals for lack of efficacy were greater in the placebo (16.5%) than the Xyzal group (7.6%). Additionally, 8 patients in the Xyzal group withdrew due to somnolence or fatigue compared to 1 in the placebo group for the same reason.

EEU pharmacodynamic comparative single dose level study in adult and adolescent patients with SAR (A379)

Study A379 was randomized, double-blind, placebo-controlled, parallel group in design conducted in a single center in Kingston, Ontario, Canada, in patients 16 years of age and older with SAR with sensitivity to ragweed. The study was conducted in 2004. This study was primarily designed to provide pharmacodynamic efficacy link of Xyzal to 2X dose of cetirizine. The design of the study also allowed assessment of pharmacodynamic onset of action for Xyzal. Eligible patients were primed in EEU, and patients who met the eligibility criteria of a predefined minimum symptom score were exposed to the allergen on the test day and administered a single dose of Xyzal 5mg or cetirizine 10 mg or placebo. Efficacy was assessed by frequent patient scoring of six symptoms, Major Symptom Complex, MSC, (rhinorrhea, nasal pruritus, sniffles, nose blows, sneezing, and watery eyes) on a six point scale (0=absent, 1=a little, 2=moderate, and 3=quite a bit, 4=sever, and 5=very severe) following study medication administration. On the day of dosing (day 1) MSC was scored every 30 minutes following study medication administration for a total of 10 scores. On the next day (day 2) MSC was scored every 30 minutes for a total of 16 scores. The primary efficacy endpoint was the difference from placebo in the mean change from baseline in the MSC score during day 2. A total of 570 patients were randomized and 563 completed the study.

EEU pharmacodynamic comparative dose ranging study in adult and adolescent patients with SAR (A412)

Study A412 was conducted in 2006 to address the Agency comment at the pre-IND meeting that an optimum study design to link efficacy of a dose of Xyzal to 2X dose cetirizine, two doses of each product need to be compared in the same study and show comparable dose response for the two products. This study was similar in design and conduct to study A379 and was also carried out in the same center in Kingston, Ontario, Canada. The major difference was that the study drugs and doses were Xyzal 2.5 mg, Xyzal 5 mg, cetirizine 5 mg, and cetirizine 10 mg. MSC was scored on the day of dosing (day 1) every 30 minutes following study medication administration for a total of 10 scores. On the next day (day 2) MSC was scores every 30 minutes for a total of 10 scores. The primary efficacy endpoint was the difference from placebo in the mean change from baseline in the MSC score during day 1. A total of 551 patients were randomized and 564 completed the study.

Single dose level study in pediatric patients with SAR (A303)

Study A303 was double-blind, placebo-controlled, parallel group in design conducted in 28 centers in France and Germany in patients 6 to 12 years of age and older with at least a 1 year history of SAR and documented sensitivity to grass pollen or weed pollen or both. The study was conducted in 2002. The study had a 7-day (approximate) screening period, followed by 6-week double blinded treatment period. The treatment groups were Xyzal 5 mg, and placebo, all administered once daily in the evening. The primary efficacy variable was reflective patient scoring of four symptoms, (Total Nasal Symptom Score, rTSS - rhinorrhea, nasal pruritus, sneezing, and ocular pruritus) once daily in the PM on a four point scale (0=absent, 1=mild, 2=moderate, and 3=severe). Other efficacy variables included global evaluation of efficacy, and the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ). Safety assessment included recording of adverse events, vital signs, and physical examinations. The primary efficacy endpoint was the difference from placebo in the mean change from baseline of the average of PM rTSS over the first 2 weeks of treatment. The study was designed to have 146 patients per treatment arm to give 90% power to detect a 0.8 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05. A total of 177 patients were randomized approximately equally to the two treatment groups and 145 patients (82%) completed the study. Withdrawals due to lack of efficacy were greater in the placebo group (10.2%) than in the Xyzal group (5.6%).

Single dose level study in pediatric patients with PAR (A304)

Study A304 was double-blind, placebo-controlled, parallel group in design conducted in 25 centers in South Africa in patients 6 to 12 years of age and older with at least a 1 year history of PAR and documented sensitivity to house dust mites. The study was conducted in 2002. The study had a 7-day (approximate) screening period, followed by 4-week double blinded treatment period. The treatment groups were Xyzal 5 mg, and placebo, all administered once daily in the evening. The primary efficacy variable was reflective patient scoring of four symptoms, (Total Nasal Symptom Score, rTSS - rhinorrhea, nasal pruritus, sneezing, and ocular pruritus) once daily in the PM on a four point scale (0=absent, 1=mild, 2=moderate, and 3=severe). Other efficacy variable included global evaluation of efficacy, and the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ). Safety assessment included recording of adverse events, vital signs, and physical examinations. The primary efficacy endpoint was the difference from placebo in the mean change from baseline of the average of PM rTSS over the first 2 weeks of treatment. The study was designed to have 146 patients per treatment arm to give 90% power to detect a 0.8 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05. A total of 306 patients were randomized approximately equally to the two treatment groups and 297 patients (97%) completed the study. There were no preferential discontinuations in any treatment groups.

Design and conduct of the main CIU efficacy and safety studies:

Dose ranging study in adult and adolescent patients with CIU (A270)

Study A270 was double-blind, placebo-controlled, parallel group in design conducted in 35 centers in France in patients 18 years of age and older with at least a history of CIU (defined as urticaria for at least 3 times per week for at least 6 weeks during the previous 3 months). The study was conducted in 2001 and 2002. The study had a 7-day (approximate) screening period, followed by 4-week double blinded treatment period. The treatment groups were Xyzal 2.5 mg, Xyzal 5 mg, and Xyzal 10 mg, and placebo, all administered once daily in the evening. The primary efficacy variable was reflective patient scoring of pruritus severity score once daily in the PM on a four point scale (0=absent, 1=mild, 2=moderate, and 3=severe). Other efficacy variables included reflective patient scoring of number of wheals and size of wheals on the same four point scale. Safety assessment included recording of adverse events, vital signs, clinical laboratory measures, and physical examinations. The primary efficacy endpoints were the difference from placebo in the mean change from baseline of the average of PM pruritus severity score over the first weeks and 4 weeks of treatment. The study was designed to have 64 patients per treatment arm to give 90% power to detect a 0.5 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05. A total of 257 patients were randomized approximately equally to the four treatment groups and 202 patients (78%) completed the study. There were more patients discontinuing from the placebo treatment groups compared to the active treatment groups. The primary reason for discontinuation was lack of efficacy.

Single dose level study in adult and adolescent patients with CIU (A269)

Study A269 was similar in design and conduct to study A270. This study was conducted in 2001 in 19 centers in Germany and Switzerland in patients 18 years of age and older with at least a history of CIU. The major difference was that there were two treatment groups, Xyzal 5 mg, and placebo. The study was designed to have 77 patients per treatment arm to give 90% power to detect a 0.5 unit mean difference for the primary efficacy endpoint at a two-sided alpha-level of 0.05. A total of 166 patients were randomized approximately equally to the two treatment groups and 124 patients (74.7%) completed the study. There were more patients discontinuing from the placebo treatment groups compared to the active treatment groups. The primary reason for discontinuation was lack of efficacy.

Efficacy findings and conclusions:

The submitted studies support efficacy of Xyzal in patients with SAR, PAR, and CIU, at a dose of 5 mg administered once daily in the evening for ages 12 years and older, and at a dose of 2.5 mg administered once daily in the evening for ages 6 to 11 years. For ages 12 years and older 2.5 mg dose may be adequate in some patients. The dose and dosing frequency are supported by the efficacy studies, pharmacodynamic EEU studies

comparing efficacy of Xyzal and cetirizine, and is also consistent with the dose and dosing frequency of the racemate cetirizine.

Adults and adolescents 12 years of age and older:

The studies that primarily support the SAR and PAR indications in patients 12 years of age and older are 1 dose ranging study in SAR patients (A217), 2 dose ranging studies in PAR patients (A219, A265), 1 single dose level study in SAR patients (A268), and 1 single dose level study in PAR patients (A266). These studies have features that the Division typically expects for allergic rhinitis studies, including at least 2 weeks of treatment for SAR studies, 4 weeks of treatment of PAR studies, and patient centered clinically relevant efficacy measures for this drug class.

In the 3 dose ranging studies (A217, A219, A265) a general trend of dose-related increase in efficacy was observed for the primary efficacy variable, and all doses of Xyzal demonstrated statistically significant difference from placebo (Table 2). In the two single dose level multi-dose studies in SAR and PAR patients (A268, A266) Xyzal 5 mg was statistically significantly superior to placebo (Table 3). In study A268, pre-dose iTNSS, which is a measure of end-of-dosing interval efficacy, there was a statistically significant difference between Xyzal 5 mg and placebo (Table 3). Further support of efficacy is provided by studies A222, A306, and A264. In these studies Xyzal 5 mg was statistically significantly superior to placebo (Table 3). Study A222 was 1 week in duration, which is short for a SAR study. Study A306 was conducted to compare the efficacy of Xyzal started 8 weeks preceding the anticipated onset of allergy season to Xyzal started on the onset of allergy season. The study did not show any difference between Xyzal started before the onset of season compared to Xyzal started on the onset of allergy season, but showed that Xyzal 5 mg was statistically significantly superior to placebo (Table 3). Study A264 was of 6 months in duration, which primarily showed long-term safety of Xyzal. But this study also assessed efficacy in an acceptable way at 4 weeks, which showed that Xyzal 5 mg was statistically superior to placebo. Secondary efficacy variables generally trended along with the primary efficacy variable in all efficacy studies. RQLQ was assessed in some of the studies, and none reached the threshold of clinical significance plus statisticall significance (Table 3).

Table 2. Dose ranging studies, mean change from baseline in rTSS

Variable	Treatment	n	Mean Difference from Placebo	
			Point Estimate	95% CI
A217, SAR adult study, 2 week				
rTSS, PM	Xyzal 2.5 mg	116	- 0.91	-0.27, -1.55
	Xyzal 5 mg	115	-1.11	-0.47, -1.75
	Xyzal 10 mg	118	-1.61	-0.96, -2.25
	Placebo	118		
A219, PAR adult study, 4 week				
rTSS, PM	Xyzal 2.5 mg	105	-0.81	-0.18, -1.45
	Xyzal 5 mg	103	-0.56	-0.07, 1.20
	Xyzal 10 mg	109	-1.21	-0.58, -1.84
	Placebo	104		

Variable	Treatment	n	Mean Difference from Placebo Point Estimate	95% CI
A265, PAR adult study, 4 week				
rTSS, PM	Xyzal 2.5 mg	133	-1.17	-0.71, -1.63
	Xyzal 5 mg	127	-1.22	-0.76, -1.69
	Xyzal 10 mg	129	-1.10	-0.64, -1.57
	Placebo	128		

Table 3. Single dose level studies, mean changes from baseline in selected efficacy variables

Variable	Treatment	n	LS Mean Difference from Placebo Point Estimate	95% CI
A268, SAR adult study, 2 week				
rTSS, PM	Xyzal 5 mg	118	-0.89	-0.30, -1.47
	Placebo	117		
iTSS, AM	Xyzal 5 mg	118	-0.73	-0.17, -1.28
	Placebo	117		
RQLQ	Xyzal 5 mg	118	-0.15	-0.48, 0.17
	Placebo	117		
A222, SAR adult study, 1 week				
rTSS, PM	Xyzal 5 mg	317	-1.73	-1.26, -2.19
	Cetirizine 10 mg	315	-1.88	-1.42, -2.35
	Placebo	158		
A266, PAR adult study, 4 week				
rTSS, PM	Xyzal 5 mg	150	-1.22	-0.76, -1.69
	Placebo	142		
A306, SAR adult study, 8+8 week, efficacy at 12 week				
rTSS, PM	Xyzal+Xyzal 5 mg	148	-0.65	-0.27, -1.03
	Placebo+Xyzal	150	Not reported	Not reported
	Placebo+Placebo	155		
A264, PAR study, 4 weeks				
RQLQ	Xyzal 5 mg	257	-0.48	-0.29, -0.67
	Placebo	252		
rTSS, PM	Xyzal 5 mg	276	-1.14	-0.75, -1.52
	Placebo	271		
A303, SAR pediatric study, 6 week				
rTSS, PM	Xyzal 5 mg	87	-1.29	-0.66, -1.92
	Placebo	87		
A304, PAR pediatric study, 4 week				
rTSS, PM	Xyzal 5 mg	154	-0.69	-0.27, -1.12
	Placebo	152		

Individual symptoms assessed in these studies generally trended in the direction expected for an antihistamine. The individual components of the primary efficacy variable in most of the studies were rhinorrhea or nasal discharge, nasal pruritus, sneezing, and ocular pruritus. Nasal congestion was also measured in these studies with the same rigor, but was not included to form the composite of the primary efficacy variable in most of the studies. This is reasonable because antihistamines are not expected to have a positive effect on nasal congestion and for that reason antihistamines are combined with a decongestant when relief of nasal congestion is also desired. Table 4 shows mean

changes of individual symptoms from selected studies. As expected, Xyzal 5 mg consistently positively impacted all individual symptoms except nasal congestion.

Table 4. Mean change from baseline in individual symptom scores with Xyzal 5 mg from selected studies

Study	Treatment period	rTSS	Sneezing	Nasal discharge	Nasal pruritus	Ocular pruritus	Nasal congestion
A217	2 weeks	-1.11	-0.31	-0.30	-0.25	-0.30	-0.05
A265	4 weeks	-1.22	-0.38	-0.32	-0.26	0.23	-0.02
A268	2 weeks	-0.89	-0.37	-0.20	-0.13	-0.21	+0.09
A266	4 weeks	-1.22	-0.35	-0.34	-0.30	-0.30	-0.28

UCB conducted two EEU pharmacodynamic comparative single dose level studies (A379, A412) in adult and adolescent patients with SAR to link Xyzal 5 mg to cetirizine 10 mg. Study A412 was conducted to specifically address the Division's comment at the pre-IND meeting that there were no studies that compared two doses of Xyzal and two doses of cetirizine to tightly link the two products showing similarity in dose-response efficacy curves. The Division mentioned that such a study would be of value to link the two products. The two EEU pharmacodynamic studies showed that all doses of Xyzal and cetirizine were statistically superior to placebo (Table 5). Study A412 showed efficacy of both doses of the two drugs but did not show consistent dose-response.

It is worth noting that the clinical program that UCB conducted to support the allergic rhinitis indication was rather large for a single isomer of an approved racemate. From an efficacy standpoint a limited program would have sufficed. The first interaction that UCB had with the Division was at the pre-IND meeting when all the efficacy studies were already completed.

Table 5. EEU pharmacodynamic comparative studies, mean change from baseline in MSC

Variable	Treatment	n	Mean Difference from Placebo Point Estimate	95% CI
A379				
MSC, Day 2	Xyzal 5 mg	236	-5.22	-3.94, -6.50
	Cetirizine 10 mg	233	-4.88	-3.60, -6.15
	Placebo	95		
A412				
MSC, Day 1	Xyzal 2.5 mg	116	-3.35	-2.09, -4.61
	Xyzal 5 mg	119	-3.25	-2.00, -4.50
	Cetirizine 5 mg	119	-4.13	-2.88, -5.38
	Cetirizine 10 mg	119	-3.74	-2.49, -4.99
	Placebo	78		

Two studies support the CIU indication in patients 18 years of age and older with CIU. These were the dose ranging study A270 and the single dose level multi-dose study A269. These studies have features that the Division typically expects for CIU studies,

including at least 4 weeks of treatment, and patient centered clinically relevant efficacy measures to assess the pruritus component and the wheal component of the disease. As shown in Table 6 there was a general trend in dose dependent increase in efficacy and statistically significant difference between Xyzal and placebo for all the doses.

Table 6. CIU studies, mean change from baseline in selective efficacy variables over 4 weeks

Variable	Treatment	n	Mean Difference from Placebo Point Estimate	95% CI
A270, CIU dose ranging study				
Pruritus sev, PM	Xyzal 2.5 mg	69	- 0.82	-0.53, -1.11
	Xyzal 5 mg	62	-0.91	-0.62, -1.21
	Xyzal 10 mg	55	-1.11	-0.81, -1.41
	Placebo	60		
No of wheals, PM	Xyzal 2.5 mg	69	- 0.61	-0.30, -0.93
	Xyzal 5 mg	64	-0.69	-0.37, -1.01
	Xyzal 10 mg	56	-0.88	-0.55, -1.21
	Placebo	61		
A269, CIU single dose level study				
Pruritus sev, PM	Xyzal 5 mg	82	-0.62	-0.38, -0.86
	Placebo	80		
No of wheals, PM	Xyzal 5 mg	82	-0.46	-0.20, -0.73
	Placebo	80		

Pediatric:

UCB conducted efficacy studies (A303, A304) in SAR and PAR patients ages 6 to 12 years with Xyzal 5 mg. Both the studies showed efficacy (data not shown in this review), which is expected because 5 mg was efficacious in patients 12 years of age and older. UCB did not conduct efficacy studies with lower doses of Xyzal. 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 12 years of age and older. Therefore, the dosing recommendation for ages 6 to 12 years will be 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. This Division has used this rationale in the past for other oral antihistamines. The two studies A303 and A304 provide ample safety data for Xyzal in the 6 to 12 year age group.

UCB did not conduct efficacy studies in CIU patients under the age of 18 years. Efficacy for CIU also can be extrapolated to lower age group based on the reasoning mentioned above for allergic rhinitis. The indicated age for CIU will also be 6 years and above because there are pharmacokinetic data for dosing recommendation, and safety data in allergic rhinitis and other related diseases with Xyzal.

Onset of action:

The two single-dose EEU studies A379 and A412 provide data for calculation of pharmacodynamic onset of action. Although these studies were conducted to compare efficacy of Xyzal and cetirizine, these studies had frequent recording of efficacy that allow for calculation of onset of action. For regulatory purposes, onset of action is defined as the first time point, replicated in two studies, where the difference in efficacy measure between the active treatment and placebo is statistically significant and the difference persists consistently after that time point. It is also expected that the difference would be clinically meaningful. In the two studies the first replicate time point for onset of action was 1 hour. To place the pharmacodynamic onset of action in clinical context, onset of action was also assessed from the multi-dose studies using daily recording of symptoms. In these studies onset of action was demonstrated after 1 day of dosing. The data that support the onset of action are shown in Dr. Gilbert-McClain's memorandum.

Safety findings and conclusions:

The safety assessment for patients 12 years of age and older was primarily based on 10 multi-dose studies (A217, A219, A265, A268, A222, A266, A306, A264, A270, and A269), and for patients 6 to 12 years of age are based on 2 multi-dose studies (A303, A304) (Table 1). The total number of unique patients exposed to Xyzal in these studies is 2549.

There were no deaths in any of the studies. Serious adverse events were reported by 15 patients, but none of these was related to study drug. A total of 44 patients discontinued because of adverse events. Somnolence or fatigue was the most common cause of discontinuation (3% in Xyzal vs 1% in placebo). Somnolence was also a common adverse event reported (6% in Xyzal 5 mg vs 2% in placebo). There were no trends of abnormality noted in clinical laboratory measures and ECGs. Review of smaller clinical studies, post-marketing experience of countries where Xyzal is marketed did not reveal any findings of concern. These are detailed in Dr. Boucher's and in Dr. Gilbert-McClain's reviews.

Data Quality, Integrity, and Financial Disclosure

A DSI audit was request of 3 study sites in South Africa. These sites were recommended for audit by the clinical team based on large number of subjects enrolled at these sites. The results of the DSI audit showed that in general the sites adhered to the applicable regulations and good clinical practices governing conduct of clinical investigations. During review of the submission no irregularities that would raise concerns regarding data integrity were found. No ethical issues were present. All studies were performed in accordance with accepted clinical standards. The applicant submitted acceptable financial disclosure statements.

Pediatric Considerations

UCB has included children 6 years of age and older in the studies that were submitted with the application. [redacted]

[redacted] The Division has historically taken the position that SAR occurs in children 2 years of age and older and PAR occurs in children 6 months of age and older. Although the lower age cut-off is somewhat arbitrary, there is literature support on the lower age bound (J Allergy Clin Immunol 2000, 106:832).

Labeling

UCB submitted a label in the Physician's Labeling Rule format that generally contains information consistent with other products of this class. The label was reviewed by various disciplines of this Division, and on consult by OSE and DDMAC. Various changes to different sections of the label are recommended to reflect the data accurately and truthfully and better communicate the findings to health care providers. The Division and UCB have agreed to the final version of the label.

Product Name

UCB proposed Xyzal as the trade name for this product. The trade name was reviewed by DMETS or OSE and found to be acceptable. The review teams of Division also find the trade name as acceptable.

Action

UCB submitted adequate data to support approval of Xyzal tablets for symptomatic relief in allergic rhinitis patients and chronic idiopathic urticaria patients 6 years of age and older. The action on this application will be Approval.

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/s/

Badrul Chowdhury
5/25/2007 01:53:16 PM
MEDICAL OFFICER