CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-835/S005
20-346/S002

APPROVAL LETTER

May 15, 1998

NDA 19-835/S-005

Pfizer Inc.
235 East 42nd Street
New York, NY 10017

Attention: Rita A. Wittich
Director, Regulatory Affairs

Dear Ms. Wittich:

Please refer to your supplemental new drug application dated May 29, 1997, received June 3, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyrtec (cetirizine HCl) Tablets.

We acknowledge receipt of your submissions dated January 16, April 28, and May 14, 1998. The user fee goal date for this application is June 3, 1998.

The supplemental application, as amended, provides for the use of Zyrtec in pediatric patients 2-5 years of age for the indications seasonal and perennial allergic rhinitis and chronic idiopathic urticaria.

We have completed the review of this supplemental application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated May 14, 1998. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on May 14, 1998.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplemental NDA 19-835/S-005." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Should a letter communicating important information about this drug product (i.e., a Dear Doctor letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Mrs. Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

May 15, 1998

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APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-835/S005
20-346/S002

FINAL PRINTED LABELING

APPROVED

MAY 15 1998

70-4573-00-2.1

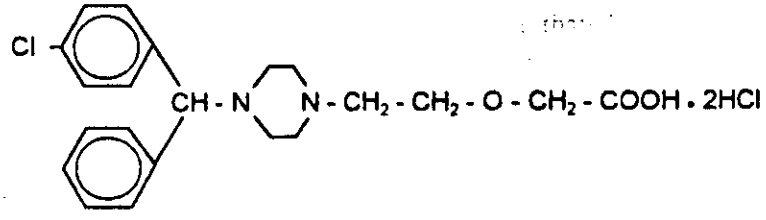
ZYRTEC®

(cetirizine hydrochloride) Tablets and Syrup

For Oral Use

DESCRIPTION

Cetirizine hydrochloride, the active component of ZYRTEC® tablets and syrup, is an orally active and selective H_1-receptor antagonist. The chemical name is (±) - [2- [4- [(4-chlorophenyl)phenylmethyl] -1- piperazinyl] ethoxy]acetic acid, dihydrochloride. Cetirizine hydrochloride is a racemic compound with an empirical formula of $C_{21}H_{25}ClN_2O_3 \cdot 2HCl$. The molecular weight is 461.82 and the chemical structure is shown below:



Cetirizine hydrochloride is a white, crystalline powder and is water soluble. ZYRTEC tablets are formulated as white, film-coated, rounded-off rectangular shaped tablets for oral administration and are available in 5 and 10 mg strengths. Inactive ingredients are: lactose; magnesium stearate; povidone; titanium dioxide; hydroxypropyl methylcellulose; polyethylene glycol; and corn starch.

ZYRTEC syrup is a colorless to slightly yellow syrup containing cetirizine hydrochloride at a concentration of 1 mg/mL (5 mg/5 mL) for oral administration. The pH is between 4 and 5. The inactive ingredients of the syrup are: banana flavor; glacial acetic acid; glycerin; grape flavor; methylparaben; propylene glycol; propylparaben; sodium acetate; sugar syrup; and water.

CLINICAL PHARMACOLOGY

Mechanism of Actions: Cetirizine, a human metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H_1 receptors. The antihistaminic activity of cetirizine has been clearly documented in a variety of animal and human models. *In vivo* and *ex vivo* animal models have shown negligible anticholinergic and antiserotonergic activity. In clinical studies, however, dry mouth was more common with cetirizine than with placebo. *In vitro* receptor binding studies have shown no measurable

affinity for other than H_1 receptors. Autoradiographic studies with radiolabeled cetirizine in the rat have shown negligible penetration into the brain. *Ex vivo* experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H_1 receptors.

Pharmacokinetics:
Absorption: Cetirizine was rapidly absorbed with a time to maximum concentration (Tmax) of approximately 1 hour following oral administration of tablets or syrup in adults. Comparable bioavailability was found between the tablet and syrup dosage forms. When healthy volunteers were administered multiple doses of cetirizine (10 mg tablets once daily for 10 days), a mean peak plasma concentration (Cmax) of 311 ng/mL was observed. No accumulation was observed. Cetirizine pharmacokinetics were linear for the oral doses ranging from 5 to 60 mg. Food had no effect on the extent of cetirizine exposure (AUC) but Tmax was delayed by 1.7 hours and Cmax was decreased by 23% in the presence of food.

Distribution: The mean plasma protein binding of cetirizine is 93%, independent of concentration in the range of 25-1000 ng/mL, which includes the therapeutic plasma levels observed.

Metabolism: A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the feces. Approximately 50% of the radioactivity was identified in the urine as unchanged drug. Most of the rapid increase in peak plasma radioactivity was associated with parent drug, suggesting a low degree of first-pass metabolism. Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The enzyme or enzymes responsible for this metabolism have not been identified.

Elimination: The mean elimination half-life in 146 healthy volunteers across multiple pharmacokinetic studies was 8.3 hours and the apparent total body clearance for cetirizine was approximately 53 mL/min.

Interaction Studies
Pharmacokinetic interaction studies with cetirizine in adults were conducted with pseudoephedrine, antipyrine, ketoconazole, erythromycin and azithromycin. No interactions were observed. In a multiple dose study of theophylline (400 mg once daily for 3 days) and cetirizine (20 mg once daily for 3 days), a 16% decrease in the clearance of cetirizine was observed. The disposition of theophylline was not altered by concomitant cetirizine administration.

Special Populations
Pediatric Patients: When pediatric patients aged 7 to 12 years of age received a single, 5-mg oral cetirizine capsule, the mean Cmax was 275 ng/mL. Based on cross-study comparisons, the weight-normalized, apparent total body clearance was 33% greater and the elimination half-life was 33% shorter in this pediatric population than in adults. In pediatric patients aged 2 to 5 years of age who received 5 mg of cetirizine, the mean Cmax was 660 ng/mL. Based on

cross-study comparisons, the weight-normalized apparent total body clearance was 81 to 111% greater and the elimination half-life was 33 to 41% shorter in this pediatric population than in adults.

Geriatric Patients: Following a single, 10-mg oral dose, the elimination half-life was prolonged by 50% and the apparent total body clearance was 40% lower in 16 geriatric subjects with a mean age of 77 years compared to 14 adult subjects with a mean age of 53 years. The decrease in cetirizine clearance in these elderly volunteers may be related to decreased renal function.

Effect of Gender: The effect of gender on cetirizine pharmacokinetics has not been adequately studied.

Effect of Race: No race-related differences in the kinetics of cetirizine have been observed.

Renal Impairment: The kinetics of cetirizine were studied following multiple, oral, 10-mg daily doses of cetirizine for 7 days in 7 normal volunteers (creatinine clearance 89-128 mL/min), 8 patients with mild renal function impairment (creatinine clearance 42-77 mL/min) and 7 patients with moderate renal function impairment (creatinine clearance 11-31 mL/min). The pharmacokinetics of cetirizine were similar in patients with mild impairment and normal volunteers. Moderately impaired patients had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers.

Patients on hemodialysis (n=5) given a single, 10-mg dose of cetirizine had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal volunteers. Less than 10% of the administered dose was removed during the single dialysis session.

Dosing adjustment is necessary in patients with moderate or severe renal impairment and in patients on dialysis (see **DOSAGE AND ADMINISTRATION**).

Hepatic Impairment: Sixteen patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis), given 10 or 20 mg of cetirizine as a single, oral dose had a 50% increase in half-life along with a corresponding 40% decrease in clearance compared to 16 healthy subjects.

Dosing adjustment may be necessary in patients with hepatic impairment (see **DOSAGE AND ADMINISTRATION**).

Pharmacodynamics: Studies in 69 adult normal volunteers (ages 20-61 years) show that ZYRTEC at doses of 5 and 10 mg strongly inhibits the skin wheal and flare caused by the intradermal injection of histamine. The onset of this activity after a single 10-mg dose occurs within 20 minutes in 50% of subjects and within one hour in 95% of subjects; this activity persists for at least 24 hours. ZYRTEC at doses of 5 and 10 mg also strongly inhibits the wheal and flare caused by intradermal injection of histamine in 19 pediatric volunteers (ages 5-12 years) and the activity persists for at least 24 hours. In a 35-day study in children ages 5

to 12, no tolerance to the antihistaminic (suppression of wheal and flare response) effects of ZYRTEC was found. The effects of intradermal injection of various other mediators or histamine releasers are also inhibited by cetirizine, as is response to a cold challenge in patients with cold-induced urticaria. In mildly asthmatic subjects, ZYRTEC at 5 to 20 mg blocked bronchoconstriction due to nebulized histamine, with virtually total blockade after a 20-mg dose. In studies conducted for up to 12 hours following cutaneous antigen challenge, the late phase recruitment of eosinophils, neutrophils and basophils, components of the allergic inflammatory response, was inhibited by ZYRTEC at a dose of 20 mg.

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.

In a four-week clinical trial in pediatric patients aged 6 to 11 years, results of randomly obtained ECG measurements before treatment and after 2 weeks of treatment showed that ZYRTEC 5 or 10 mg did not significantly increase QTc versus placebo. The effects of ZYRTEC on the QTc interval at doses higher than the 10 mg dose have not been studied in children less than 12 years of age. The effect of ZYRTEC on the QTc interval in children less than 6 years of age has not been studied.

In a six-week, placebo-controlled study of 186 patients (aged 12-64 years) with allergic rhinitis and mild to moderate asthma, ZYRTEC 10 mg once daily improved rhinitis symptoms and did not alter pulmonary function. In a two-week, placebo-controlled clinical trial, a subset analysis of 65 pediatric (6 to 11 years) allergic rhinitis patients with asthma showed ZYRTEC did not alter pulmonary function. These studies support the safety of administering ZYRTEC to pediatric and adult allergic rhinitis patients with mild to moderate asthma.

Clinical Studies: Nine multicenter, randomized, double-blind, clinical trials comparing cetirizine 5 to 20 mg to placebo in patients 12 years and older with seasonal or perennial allergic rhinitis were conducted in the United States. Five of these showed significant reductions in symptoms of allergic rhinitis, 3 in seasonal allergic rhinitis (1 to 4 weeks in duration) and 2 in perennial allergic rhinitis for up to 8 weeks in duration. Two 4-week multicenter, randomized, double-blind, clinical trials comparing cetirizine 5 to 20 mg to

placebo in patients with chronic idiopathic urticaria were also conducted and showed significant improvement in symptoms of chronic idiopathic urticaria. In general, the 10-mg dose was more effective than the 5-mg dose and the 20-mg dose gave no added effect. Some of these trials included pediatric patients aged 12 to 16 years. In addition, four multicenter, randomized, placebo-controlled, double-blind 2-4 week trials in 534 pediatric patients aged 6 to 11 years with seasonal allergic rhinitis were conducted in the United States at doses up to 10 mg.

INDICATIONS AND USAGE

Seasonal Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with seasonal allergic rhinitis due to allergens such as ragweed, grass and tree pollens in adults and children 2 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, nasal pruritus, ocular pruritus, tearing, and redness of the eyes.

Perennial Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with perennial allergic rhinitis due to allergens such as dust mites, animal dander and molds in adults and children 2 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, postnasal discharge, nasal pruritus, ocular pruritus, and tearing.

Chronic Urticaria: ZYRTEC is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 2 years of age and older. It significantly reduces the occurrence, severity, and duration of hives and significantly reduces pruritus.

CONTRAINDICATIONS

ZYRTEC is contraindicated in those patients with a known hypersensitivity to it or any of its ingredients or hydroxyzine.

PRECAUTIONS

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.

Drug-Drug Interactions: No clinically significant drug interactions have been found with theophylline at a low dose, azithromycin, pseudoephedrine, ketoconazole, or erythromycin. There was a small decrease in the clearance of cetirizine caused by a 400-mg dose of theophylline; it is possible that larger theophylline doses could have a greater effect.

Carcinogenesis, Mutagenesis and Impairment of Fertility: In a 2-year carcinogenicity study in rats, cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately

15 times the maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately 10 times the maximum recommended daily oral dose in children on a mg/m^2 basis). In a 2-year carcinogenicity study in mice, cetirizine caused an increased incidence of benign liver tumors in males at a dietary dose of 16 mg/kg (approximately 6 times the maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately 4 times the maximum recommended daily oral dose in children on a mg/m^2 basis). No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 2 times the maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately equal to the maximum recommended daily oral dose in children on a mg/m^2 basis). The clinical significance of these findings during long-term use of ZYRTEC is not known.

Cetirizine 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 rats.

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 maximum recommended daily oral dose in adults on a mg/m^2 basis).

Pregnancy Category B: In mice, rats, and rabbits, cetirizine was not teratogenic at oral doses up to 96, 225, and 135 mg/kg, respectively (approximately 40, 180 and 220 times the maximum recommended daily oral dose in adults on a mg/m^2 basis). There are no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, ZYRTEC should be used in pregnancy only if clearly needed.

Nursing Mothers: In mice, cetirizine causes 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/m^2 basis). Studies in beagle dogs indicate that approximately 3% of the dose is excreted in milk. Cetirizine has been reported to be excreted in human breast milk. Because many drugs are excreted in human milk, use of ZYRTEC in nursing mothers is not recommended.

Geriatric Use: In placebo-controlled trials, 186 patients aged 65 to 94 years received doses of 5 to 20 mg of ZYRTEC per day. Adverse events were similar in this group to patients under age 65. Subset analysis of efficacy in this group was not done.

Pediatric Use: The safety of ZYRTEC, at daily doses of 5 or 10 mg, has been demonstrated in 376 pediatric patients aged 6 to 11 years in placebo-controlled trials lasting up to four weeks and in 254 patients in a non-placebo-controlled 12-week trial. The safety of cetirizine has been demonstrated in 168 patients aged 2 to 5 years in placebo-controlled trials of up to 4 weeks duration. On a mg/kg basis, most of the 168 patients received between 0.2 and 0.4 mg/kg of cetirizine HCl.

The effectiveness of ZYRTEC for the treatment of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria in pediatric patients aged 2 to 11 years is based on an extrapolation

of the demonstrated efficacy of ZYRTEC in adults in these conditions and the likelihood that the disease course, pathophysiology and the drug's effect are substantially similar between these two populations. The recommended doses for the pediatric population are based on a cross-study comparison of the pharmacokinetics and pharmacodynamics of cetirizine in adult and pediatric subjects and on the safety profile of cetirizine in both adult and pediatric patients at doses equal to or higher than the recommended doses. The cetirizine AUC and Cmax in pediatric subjects aged 2 to 5 years who received a single dose of 5 mg of cetirizine syrup and in pediatric subjects aged 6 to 11 years who received a single dose of 10 mg of cetirizine syrup were estimated to be intermediate between that observed in adults who received a single dose of 10 mg of cetirizine tablets and those who received a single dose of 20 mg of cetirizine tablets.

The safety and effectiveness of cetirizine in pediatric patients under the age of 2 years have not yet been established.

ADVERSE REACTIONS

Controlled and uncontrolled clinical trials conducted in the United States and Canada included more than 6000 patients aged 12 years and older, with more than 3900 receiving ZYRTEC at doses of 5 to 20 mg per day. The duration of treatment ranged from 1 week to 6 months, with a mean exposure of 30 days.

Most adverse reactions reported during therapy with ZYRTEC were mild or moderate. In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in patients receiving ZYRTEC 5 or 10 mg was not significantly different from placebo (2.9% vs. 2.4%, respectively).

The most common adverse reaction in patients aged 12 years and older that occurred more frequently on ZYRTEC than placebo was somnolence. The incidence of somnolence associated with ZYRTEC was dose related, 6% in placebo, 11% at 5 mg and 14% at 10 mg. Discontinuations due to somnolence for ZYRTEC were uncommon (1.0% on ZYRTEC vs. 0.6% on placebo). Fatigue and dry mouth also appeared to be treatment-related adverse reactions. There were no differences by age, race, gender or by body weight with regard to the incidence of adverse reactions.

Table 1 lists adverse experiences in patients aged 12 years and older which were reported for ZYRTEC 5 and 10 mg in controlled clinical trials in the United States and that were more common with ZYRTEC than placebo.

Table 1.
Adverse Experiences Reported in Patients Aged 12 Years and Older in Placebo-Controlled United States ZYRTEC Trials (Maximum Dose of 10 mg) at Rates of 2% or Greater (Percent Incidence)

Adverse Experience	ZYRTEC (N=2034)	Placebo (N=1612)
Somnolence	13.7	6.3
Fatigue	5.9	2.6
Dry Mouth	5.0	2.3
Pharyngitis	2.0	1.9
Dizziness	2.0	1.2

In addition, headache and nausea occurred in more than 2% of the patients, but were more common in placebo patients.

Pediatric studies were also conducted with ZYRTEC. More than 1300 pediatric patients aged 6 to 11 years with more than 900 treated with ZYRTEC at doses of 1.25 to 10 mg per day were included in controlled and uncontrolled clinical trials conducted in the United States. The duration of treatment ranged from 2 to 12 weeks. Placebo-controlled trials up to 4 weeks duration included 168 pediatric patients aged 2 to 5 years who received cetirizine, the majority of whom received single daily doses of 5 mg.

The majority of adverse reactions reported in pediatric patients aged 2 to 11 years with ZYRTEC were mild or moderate. In placebo-controlled trials, the incidence of discontinuations due to adverse reactions in pediatric patients receiving up to 10 mg of ZYRTEC was uncommon (0.4% on ZYRTEC vs. 1.0% on placebo).

Table 2 lists adverse experiences which were reported for ZYRTEC 5 and 10 mg in pediatric patients aged 6 to 11 years in placebo-controlled clinical trials in the United States and were more common with ZYRTEC than placebo. Of these, abdominal pain was considered treatment-related and somnolence appeared to be dose-related, 1.3% in placebo, 1.9% at 5 mg and 4.2% at 10 mg. The adverse experiences reported in pediatric patients aged 2 to 5 years in placebo-controlled trials were qualitatively similar in nature and generally similar in frequency to those reported in trials with children aged 6 to 11 years.

Table 2.
Adverse Experiences Reported in Pediatric Patients Aged 6 to 11 Years in Placebo-Controlled United States ZYRTEC Trials (5 or 10 mg Dose) Which Occurred at a Frequency of ≥ 2% in Either the 5-mg or the 10-mg ZYRTEC Group, and More Frequently Than in the Placebo Group

Adverse Experiences	Placebo (N=309)	ZYRTEC	
		5 mg (N=161)	10 mg (N=215)
Headache	12.3%	11.0%	14.0%
Pharyngitis	2.9%	6.2%	2.8%
Abdominal pain	1.9%	4.4%	5.6%
Coughing	3.9%	4.4%	2.8%
Somnolence	1.3%	1.9%	4.2%
Diarrhea	1.3%	3.1%	1.9%
Epistaxis	2.9%	3.7%	1.9%
Bronchospasm	1.9%	3.1%	1.9%
Nausea	1.9%	1.9%	2.8%
Vomiting	1.0%	2.5%	2.3%

The following events were observed infrequently (less than 2%), in either 3982 adults and children 12 years and older or in 659 pediatric patients aged 6 to 11 years who received ZYRTEC in U.S. trials, including an open adult study of six months duration. A causal relationship of these infrequent events with ZYRTEC administration has not been established.

Autonomic Nervous System: anorexia, flushing, increased salivation, urinary retention.

Cardiovascular: cardiac failure, hypertension, palpitation, tachycardia.

Central and Peripheral Nervous Systems: abnormal coordination, ataxia, confusion, dysphonia, hyperesthesia, hyperkinesia, hypertonia, hypoesthesia, leg cramps, migraine, myelitis, paralysis, paresthesia, ptosis, syncope, tremor, twitching, vertigo, visual field defect.

Gastrointestinal: abnormal hepatic function, aggravated tooth caries, constipation, dyspepsia, eructation, flatulence, gastritis, hemorrhoids, increased appetite, melena, rectal hemorrhage, stomatitis including ulcerative stomatitis, tongue discoloration, tongue edema.

Genitourinary: cystitis, dysuria, hematuria, micturition frequency, polyuria, urinary incontinence, urinary tract infection.

Hearing and Vestibular: deafness, earache, ototoxicity, tinnitus.

Metabolic/Nutritional: dehydration, diabetes mellitus, thirst.

Musculoskeletal: arthralgia, arthritis, arthrosis, muscle weakness, myalgia.

Psychiatric: abnormal thinking, agitation, amnesia, anxiety, decreased libido, depersonalization, depression, emotional lability, euphoria, impaired concentration, insomnia, nervousness, paroniria, sleep disorder.

Respiratory System: bronchitis, dyspnea, hyperventilation, increased sputum, pneumonia, respiratory disorder, rhinitis, sinusitis, upper respiratory tract infection.

Reproductive: dysmenorrhea, female breast pain, intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis.

Reticuloendothelial: lymphadenopathy.

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.

Special Senses: parosmia, taste loss, taste perversion.

Vision: blindness, conjunctivitis, eye pain, glaucoma, loss of accommodation, ocular hemorrhage, xerophthalmia.

Body as a Whole: accidental injury, asthenia, back pain, chest pain, enlarged abdomen, face edema, fever, generalized edema, hot flashes, increased weight, leg edema, malaise, nasal polyp, pain, pallor, periorbital edema, peripheral edema, rigors.

Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy. Hepatitis with significant transaminase elevation and elevated bilirubin in association with the use of ZYRTEC has been reported.

In foreign marketing experience the following additional rare, but potentially severe adverse events have been reported: anaphylaxis, cholestasis, glomerulonephritis, hemolytic anemia, hepatitis, orofacial dyskinesia, severe hypotension, stillbirth, and thrombocytopenia.

DRUG ABUSE AND DEPENDENCE

There is no information to indicate that abuse or dependency occurs with ZYRTEC.

OVERDOSAGE

Overdosage has been reported with ZYRTEC. In one adult patient who took 150 mg of ZYRTEC, the patient was somnolent but did not display any other clinical signs or abnormal blood chemistry or hematology results. In an 18 month old pediatric patient who took an overdose of ZYRTEC (approximately 180 mg), restlessness and irritability were observed initially; this was followed by drowsiness. Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. There is no known specific antidote to ZYRTEC. ZYRTEC is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested. The acute minimal lethal oral doses were 237 mg/kg in mice (approximately 95 times the maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately 55 times the maximum recommended daily oral dose in children on a mg/m^2 basis) and 562 mg/kg in rats (approximately 460 times the maximum recommended daily oral dose in adults on a mg/m^2 basis, or approximately 270 times the maximum recommended daily oral dose in children on a mg/m^2 basis). In rodents, the target of acute toxicity was the central nervous system, and the target of multiple-dose toxicity was the liver.

DOSAGE AND ADMINISTRATION

Adults and Children 12 Years and Older: The recommended initial dose of ZYRTEC is 5 or 10 mg per day in adults and children 12 years and older, depending on symptom severity. Most patients in clinical trials started at 10 mg. ZYRTEC is given as a single daily dose, with or without food. The time of administration may be varied to suit individual patient needs.

Children 6 to 11 Years: The recommended initial dose of ZYRTEC in children aged 6 to 11 years is 5 or 10 mg (1 or 2 teaspoons) once daily depending on symptom severity. The time of administration may be varied to suit individual patient needs.

Children 2 to 5 Years: The recommended initial dose of ZYRTEC syrup in children aged 2 to 5 years is 2.5 mg (½ teaspoon) once daily. The dosage in this age group can be increased to a maximum dose of 5 mg per day given as 1 teaspoon (5 mg) once daily, or as ½ teaspoon (2.5 mg) given every 12 hours, depending on symptom severity and patient response.

Dose Adjustment for Renal and Hepatic Impairment: In patients 12 years of age and older with decreased renal function (creatinine clearance 11-31 mL/min), patients on hemodialysis (creatinine clearance less than 7 mL/min), and in hepatically impaired patients, a dose of 5 mg once daily is recommended. Similarly, pediatric patients aged 6 to 11 years with impaired renal or hepatic function should use the lower recommended dose. Because of the difficulty in reliably administering doses of less than 2.5 mg (½ teaspoon) of ZYRTEC syrup and in the absence of pharmacokinetic and safety information for cetirizine in children below the age of 6 years with impaired renal or hepatic function, its use in this impaired patient population is not recommended.

HOW SUPPLIED

ZYRTEC® tablets are white, film-coated, rounded-off rectangular shaped containing 5 mg or 10 mg cetirizine hydrochloride.

5 mg tablets are engraved with "ZYRTEC" on one side and "5" on the other.
Bottles of 100: NDC 0069-5500-66
10 mg tablets are engraved with "ZYRTEC" on one side and "10" on the other.
Bottles of 100: NDC 0069-5510-66

STORAGE: Store at room temperature 59° to 86°F (15° to 30°C).

ZYRTEC® syrup is colorless to slightly yellow with a banana-grape flavor. Each teaspoonful (5 mL) contains 5 mg cetirizine hydrochloride. ZYRTEC® syrup is supplied as follows:

120 mL amber glass bottles	NDC 0069-5530-47
1 pint amber glass bottles	NDC 0069-5530-93

STORAGE: Store at 41° to 86°F (5° to 30°C).

Cetirizine is licensed from UCB Pharma, Inc.

Manufactured/Marketed by

Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

Marketed by

UCB Pharma, Inc.
Smyrna, GA 30080

70-4573-00-2.1

Printed in U.S.A.
Revised May 1998

T Scott

PROJECT MANAGER LABELING REVIEW

NDA(s): 19-835/S-005
20-346/S-002

PRODUCT: Zyrtec (cetirizine HCl) Tablets and Syrup

SPONSOR: Pfizer

SUBMISISON DATE: May 14, 1998

COMMENTS

The Division sent labeling comments to Pfizer via facsimile (fax) on May 8, 1998. A teleconference was then held between representatives of Pfizer and the Division to discuss additional changes (see minutes of teleconference dated May 12, 1998). Pfizer subsequently sent in revised draft labeling on May 14, 1998.

I have reviewed the draft labeling dated May 14, 1998, and found that the changes requested by the Division, and the changes agreed to during the May 12, 1998, teleconference were made with the following exceptions.

1. In the INDICATIONS AND USAGE section, in the last sentence of the first paragraph, the fax sent by the Division had erroneously omitted "redness of the eyes." This was included in the most recently approved labeling, and Pfizer re-instated it in the May 14, 1998, submission.

Since this had been an error by the Division, this change is acceptable.

2. In the ADVERSE REACTIONS section, the following changes were made.

   a. In the second paragraph, Pfizer changed "5 mg or 10 mg" to "5 or 10 mg."

   b. The wording "the majority of reported adverse events" was changed to "the majority of adverse events reported."

   c. The wording "receiving up to Zyrtec 10 mg" was changed to "receiving up to 10 mg of Zyrtec."

All of these changes are editorial, and do not effect the meaning of the labeling, therefore they are acceptable.

3. Throughout the label where the wording "x to y years of age" had been used, or where an age range had been included in parenthesis, Pfizer changed the wording to "aged x to y years."

This is an editorial change, and does not effect the meaning of the labeling, therefore it is acceptable.

/S/

Gretchen Trout
Project Manager

CONCUR:

/S/ 5/14/98

Peter Honig
Medical Team Leader

Non-CONCUR

_____

cc: Orig. NDA 19-835
Orig. NDA 20-346
Div. Files
HFD-570/Trout
HFD-570/Nicklas
HFD-570/Honig

REVIEW

APPEARS THIS WAY
ON ORIGINAL

12 Page(s) Redacted

Draft Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-835/S005
20-346/S002

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	NDA 20,346, NDA 19.835	APPLICATION TYPE:	NDA
SPONSOR:	Pfizer	PRODUCT/PROPRIETARY NAME:	Zyrtec
		USAN / Established Name:	cetirizine
CATEGORY OF DRUG:	anithistamine	ROUTE OF ADMINISTRATION:	syrup/tablet
MEDICAL REVIEWER:	Nicklas	REVIEW DATE:	8 May 1998

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
15 May 1997 (syrup)	16 May 1997	supplemental NDA	see overview below
29 May 1997 (tablets)	31 May 1997	supplemental NDA	see overview below
16 Jan 1998	20 Jan 1998	labeling revision	see overview below
28 April 1998	30 April 1998	information request response	see overview below

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
none	none	none

APPEARS THIS WAY
ON ORIGINAL

Overview of Application/Review: The studies in this pediatric supplement were, with the exception of study 62, performed with an oral 10 mg/ml solution formulation which is significantly different than the marketed syrup and tablet formulations. The sponsor has no PK study directly linking the oral solution formulation used in studies in patients 2-5 years of age and the syrup or tablet formulation. Nevertheless, based on cross-study comparisons between the 10 mg/ml oral solution and the tablet formulation and the 10 mg/ml oral solution and the syrup formulation in adults, as well as a cross-study comparison of the PK data in children 2-5 years and older children and adults, there is sufficient data to determine the appropriate dose and dosing interval for this age group.

This submission contains 4 studies which evaluated the effect of cetirizine on dermatologic conditions in patients 1-16 years of age, 2 studies assessing the effectiveness of cetirizine in the treatment of perennial allergic rhinitis (PAR) and 2 studies evaluating the effectiveness of cetirizine in the treatment of seasonal allergic rhinitis (SAR). Except for study 89 where patients with SAR received 5 mg of cetirizine daily as a single dose for 2 weeks, and possibly study 125 where patients with SAR received a dosage of 2.5 mg bid for 4 weeks compared to oxatomide (an antihistamine marketed in Europe), cetirizine was not shown to be efficacious. There are sufficient numbers of patients included in these studies, where there was no evidence of increased or unexpected adverse events, to support a claim for the safety of cetirizine in patients 2-5 years of age.

The pathophysiology, symptomatology, clinical course and treatment of chronic urticaria, SAR and PAR are essentially the same in adults and children. There is no basis, moreover, for concluding that cetirizine would have a different concentration-effect relationship in children and in adults. Therefore, since the tablet and syrup formulations have been approved for use in patients 6 years of age and older, this NDA would be approvable for the indications proposed, despite insufficient data from the submitted studies, provided there was sufficient PK data linking the tablet and syrup formulations with the 10 mg/ml oral solution formulation used to provide the data which would support an appropriate dose and dosing interval for patients 2-5 years of age. After careful review, we believe that there is sufficient data to link the tablet and syrup formulations to the 10 mg/ml oral solution formulation.

However, based on a cross-study comparison of the PK data in patients 2-5 years of age who received the 10 mg/ml oral solution formulation, with the PK data from studies in older children and adults, the initial dosage for patients 2-5 years of age should be 2.5 mg given once a day. It would be acceptable, however, to increase the dose to 2.5 mg bid or 5 mg given once daily, if the patient's symptoms were not controlled with a dose of 2.5 mg given once daily and no adverse event occurred from administration of the lower dose.

This supplemental NDA is approvable for the reasons noted above, provided the labeling is changed to indicate that the initial dosage of cetirizine in patients 2-5 years of age should be 2.5 mg given once daily.

Outstanding Issues: Revised labeling should be submitted by the sponsor.

Recommended Regulatory Action: approvable with labeling changed noted above.	N drive location:
New Clinical Studies: _____ Clinical Hold	_____ Study May Proceed
NDAs:	
Efficacy / Label Supp.: ___X___ Approvable	_____ Not Approvable
Signed: Medical Reviewer: R. Nicklas	Date: 5/8/98
Medical Team Leader: /S/	Date: 5/14/98

See Team Leader Memo

/S/ 5/14/98

TABLE OF CONTENTS

Abstract of NDA 20,346

The studies in this pediatric supplement were, with the exception of study 62, performed with an oral 10 mg/ml solution formulation which is significantly different than the marketed syrup formulation. The sponsor has no pharmacokinetic study directly linking the oral solution formulation used in studies in patients 2-5 years of age and the syrup formulation. Nevertheless, based on cross-study comparisons between the 10 mg/ml oral solution and the tablet formulation and the 10 mg/ml oral solution and the syrup formulation in adults, as well as a comparison of the PK data in children 2-5 years and older children and adults, there is sufficient data to determine the appropriate dose and dosing interval for this age group.

This submission contains 4 studies which evaluated the effect of cetirizine on dermatologic conditions in patients 1-16 years of age. In study 59, there was no statistically significant difference between cetirizine and placebo in regard to cutaneous manifestations of atopic dermatitis. In study 127, a dose of 2.5 to 5.0 mg of cetirizine given once daily was effective in alleviating pruritus associated with atopic dermatitis, although ceterizine did not appear to improve the lesions of atopic dermatitis. In study 128, there were only 4 patients 2-5 years of age with chronic urticaria, who received cetirizine, and the efficacy demonstrated was likely driven by larger than recommended doses given to older children in the study. In study 62, there was no statistically significant difference between cetirizine and placebo in terms of efficacy in the treatment of atopic dermatitis. Therefore, the studies submitted by the sponsor do not support an indication claim for cetirizine in the treatment of chronic urticaria or any other dermatologic condition.

This submission contains 2 studies assessing the effectiveness of cetirizine in the treatment of perennial allergic rhinitis (PAR) in patients < 3-16 years of age. In study 65, no statistically significant difference was seen between cetirizine and placebo in regard to efficacy. In study 126, cetirizine was only superior to placebo in terms of nasal congestion. Therefore, these studies do not support a claim for the effectiveness of cetirizine in the treatment of PAR.

This submission contains 2 studies evaluating the effectiveness of cetirizine in the treatment of seasonal allergic rhinitis in patients 2-6 years of age. In study 89, in 54 patients over 2 weeks receiving 5 mg of cetirizine per day given as a single dose, a statistically significantly greater efficacy was seen with cetirizine

than with placebo. In study 125, comparable efficacy was seen with cetirizine and oxatomide, an antihistamine marketed in Europe, but there was no placebo control. Study 89, and probably study 125, support a claim for the efficacy of cetirizine in patients 2-5 years of age with seasonal allergic rhinitis.

The studies submitted by the sponsor can be used to support the safety of cetirizine in patients 2-5 years of age. Although 12 lead ECGs were not performed in these studies, a difference in cardiac effect in this age group, compared with older patients, would not be anticipated.

Since the pathophysiology, symptomatology, clinical course and treatment of chronic urticaria, seasonal allergic rhinitis and perennial allergic rhinitis are essentially the same in children and adults, since there is no basis for concluding that cetirizine would have a different concentration-effect relationship in children than in adults, and since efficacy and safety have been demonstrated in patients 6 years of age and older, this NDA is approvable for the indications proposed, despite insufficient data from the submitted studies. There is sufficient PK data linking the tablet formulation and the 10 mg/ml oral solution as well as the syrup and oral formulation in adults to determine the dose and dosing interval that would be appropriate for this age group.

There are data that demonstrate that cetirizine has a different pharmacokinetic profile in children 2-5 years of age than in older children or adults. The Cmax and Tmax (at least in one study in terms of the latter) are greater in this age group than in older children or adults, while the half-life is shorter and associated with more rapid clearance. Nevertheless, for the same milligram dose, the AUC in children 2-5 years of age is about twice that seen in children 6-12 years of age (see table below). Based on cross-study comparisons, weight-normalized total body clearance was 81-111% greater in patients 2-5 years of age and the elimination half-life was 33-41% shorter than in adults.

COMPARISON OF MEAN VALUES (Cross-study comparison)

Patient population	Cmax	Tmax (hrs)	T1/2 (hrs)	Cl	AUC
Study 120 (5 mg)	606	1.9	5.5	1.3	4772
Study 122 (5 mg)	660	1.1	4.9	1.4	4009
6-12 years (5 mg)	275	1.1	6.0	0.9	2201
adults 10 mg	350	1.1	9.4	0.6	-
adults 20 mg	890	0.7	10.6	0.8	-
elderly 10 mg	360	1.3	11.8	0.6	-

Cmax in ng/ml, Cl in ml/min/kg, AUC in ng.hr/ml

Based on the pharmacokinetic data in patients 2-5 years of age, a dosage of 2.5 mg per day would appear to be the most appropriate initial dose rather than a dose of 5 mg given once a day or a dose of 2.5 mg given bid, as proposed by the sponsor. However, the efficacy and safety of cetirizine in patients 2-6 years of age with seasonal allergic rhinitis was demonstrated in study 89 after administration of a single daily dose of 5 mg of cetirizine, using the 10 mg/ml oral solution. Based on a comparison of pharmacokinetic data in patients 2-5 years of age who received the 10 mg/ml oral solution, with the pharmacokinetic data from studies in older children and adults, as well as a comparison of data from studies in adults using the syrup formulation and the 10 mg/ml oral solution formulation (see Biopharm review and table below), it would be acceptable to increase the dose of cetirizine in this age group to 2.5 mg bid or 5 mg once daily, if symptoms were not controlled with a dose of 2.5 mg once daily and no adverse event occurred from administration of the lower dose.

CPK 17 - Zyrtec syrup (10 mg) UCB 113 - oral solution (20 mg)(10 mg/ml)

MEAN (SD)

parameter	syrup	oral solution	p-value
Cmax; dose normalized	315 (611)	411 (65)	0.001
Cmax; body weight normalized	342 (60)	389 (65)	0.02
Tmax	0.73 (0.44)	0.63 (0.22)	0.3
AUC; dose normalized	2671 (498)	3264 (842)	0.1
AUC; body weight normalized	3119 (466)	3078 (569)	0.8

CONCLUSIONS

1. The pathophysiology, symptomatology, clinical course and treatment of chronic idiopathic urticaria are the same in children and adults. The incidence is lower in children but the degree to which the incidence is lower is unknown. Chronic urticaria can be considered the same disease in adults and children.

2. The pathophysiology, symptomatology, clinical course and treatment of seasonal and ~~perennial~~ allergic ~~rhinitis are the same~~ in children and adults. Seasonal and perennial allergic rhinitis can be considered to be the same disease in adults and children.

3. There are data which indicate that cetirizine pharmacokinetically acts differently in children 2-5 years of age than in older children or adults. For a given milligram dose, the Cmax and Tmax are greater in this age group than in older children or adults, while the half-life is shorter and associated with more rapid clearance. The AUC is about twice that seen in children 6-12 years of age. The adult dose of cetirizine is 5-10 mg given once a day. The sponsor proposes a dose of 5 mg once daily or 2.5 mg bid in patients 2-5 years of age. Based on the different pharmacokinetic profile of cetirizine in patients 2-5 years of age, the initial dosage should be 2.5 mg once daily in this age group (see Biopharm review), although a dose of 2.5 mg bid or 5 mg daily would be acceptable if no response was seen with a dose of 2.5 mg once a day and no adverse effect had been noted with this dosage. The labeling will need to be revised to reflect this determination.

4. The sponsor has submitted one study (89) which supports the efficacy of cetirizine in patients 2-6 years of age with seasonal allergic rhinitis. The other studies submitted by the sponsor, including one other study in patients with seasonal allergic rhinitis, studies in patients with perennial allergic rhinitis and various dermatologic conditions do not support the efficacy of cetirizine in patients 2-5 years of age for these conditions. The studies submitted by the sponsor can be used to <u>support</u> the safety of cetirizine in patients 2-5 years of age.

5. Approval of cetirizine for use in patients 2-5 years of age with seasonal or perennial allergic rhinitis as well as chronic urticaria is dependent upon the fact that these conditions are not different in this age group, compared with older children or adults and that there is adequate PK data to insure that the proposed dosage for this age group is safe and effective.

6. This pediatric supplement to NDA 20,346 is approvable, provided the sponsor changes the labeling to indicate that the initial dosage for cetirizine syrup or tablets in patients 2-5 years of age is 2.5 mg once a day. A dose of 2.5 mg bid or 5 mg once a day can be used if a dose of 2.5 mg once a day is not effective and no adverse event occurred after administration of such a dose.

INTEGRATED SUMMARY OF SAFETY

1. There were 168 patients 2-5 years of age who received cetirizine for varying periods of time compared to 139 patients in this age range who received placebo. Of the 168 patients who received cetirizine, 119 were given a total daily dose of 5 mg.

2. There were 32 of 168 (19%) of cetirizine treated patients 2-5 years of age who experienced at least one adverse event compared to 29 of 139 (21%) placebo patients.

3. The most common adverse events experienced by patients 2-5 years of age who received cetirizine were: a) coughing [5 (3%) as compared to 1 (1%) placebo patient]; b) fever [5 (3%) as compared to 2 (1%) placebo patients]; c) rhinitis [4 (2%) compared to no placebo patients]; d) otitis media (3; 2 placebo patients); and e) somnolence (3; 3 placebo patients).

4) There were 26 patients out of 119 patients 2-5 years of age who received 5 mg of cetirizine per day (22%) who experienced an adverse event. There were 6 out of 32 patients in this age group who received 10 mg of cetirizine per day (19%), who experienced an adverse event.

5) There was one 3 year old patient who died from fulminant hepatic failure after 2 doses of cetirizine. Two consultants were asked to review this case and one concluded that cetirizine was a possible/probable cause of the event. The other consultant concluded that there was no relationship between cetirizine and the event. The latter consultant based his conclusion on the following factors: a) the exposure to cetirizine was small; b) the time relationship to the onset of symptoms was inconsistent with an idiosyncratic reaction; and c) the clinical picture was consistent with non-A-G viral hepatitis.

6) There are two reports of overdose with cetirizine in children less than 6 years of age. One was an 18 month old child who ingested 180 mg and developed restlessness, irritability and drowsiness but no ECG changes. The other was a 28 month child who was given 50 mg of cetirizine and developed sedation and pruritus.

7) There are no reports of treatment-related adverse events in patients 2-5 years of age that were not seen in older children and/or adults.

8) Serious adverse events reported in adults from sources other than clinical studies included: a) muscle weakness or pain (2); b) thrombocytopenia (2); c) atrial/nodal arrhythmia (5); d) urticaria (4); e) hypokalemia; f) ventricular tachycardia; g) confusion; h) gastrointestinal manifestations (3); i) anticholinergic reaction; j) dyspnea, loss of consciousness (2), urticaria; k) convulsion (2); l) stroke; m) nervous breakdown; n) confusion and CNS changes; o) pulmonary edema (2); p) Guillain-Barre syndrome; q) dystonia; r) depression; s) syncope (3*); t) cholestatic hepatitis (2); u) possible MI; v) hepatic necrosis (2); w) epistaxis; x) cardiac arrest (2); y) microcytic anemia; z) anaphylaxis;

* prolongation of the QTc interval - 1

9) In the Periodic Adverse Drug Experience Report of 7 Jan 1998 and in adverse reaction reports submitted during 1997, the following types of adverse events were reported: 1) hemolytic anemia (2); 2) arrhythmias (7); and 3) syncope (4). All of these reports were in adults.

ADVERSE DRUG REPORTING FOR ZYRTEC SYRUP/TABLETS

1. Report 9712976: 4 year old male; past history of WPW and VSD, congenital corrected by surgery, but no history of arrhythmias; received 5 mg of Zyrtec syrup on 4 days and developed supraventricular arrhythmia with aberrant ventricular conduction and broadening of the QTc interval, requiring hospitalization for 5 days and treatment with Flecainide.

2. Report 9714093: 20 year old female; receiving fenoterol, fluticasone and other medications, including 10 mg Zyrtec per day, collapsed with ventricular fibrillation. She was successfully resuscitated but had QTc prolongation (0.51 msec) on admission and hypokalemia.

3. Report 1718094: 28 year old female; taking Zyrtec 10 mg daily developed cardiac dysrhythmia with bradycardia (HR = 50-60 bpm). Another report of female patient of unknown age with bradycardia (40 bpm) associated with dizziness and lightheadedness (report 9718278).

4. Report 9717382: 19 year old female; Zyrtec 10 mg daily; 2 syncopal episodes with seizure-like activity; no previous history of convulsive disorder; another report (9715901) of young woman who developed 2 syncopal episodes while receiving Zyrtec.

5. Two patients on Zyrtec reported to have thrombocytopenia (reports 9704475 and 9704075).

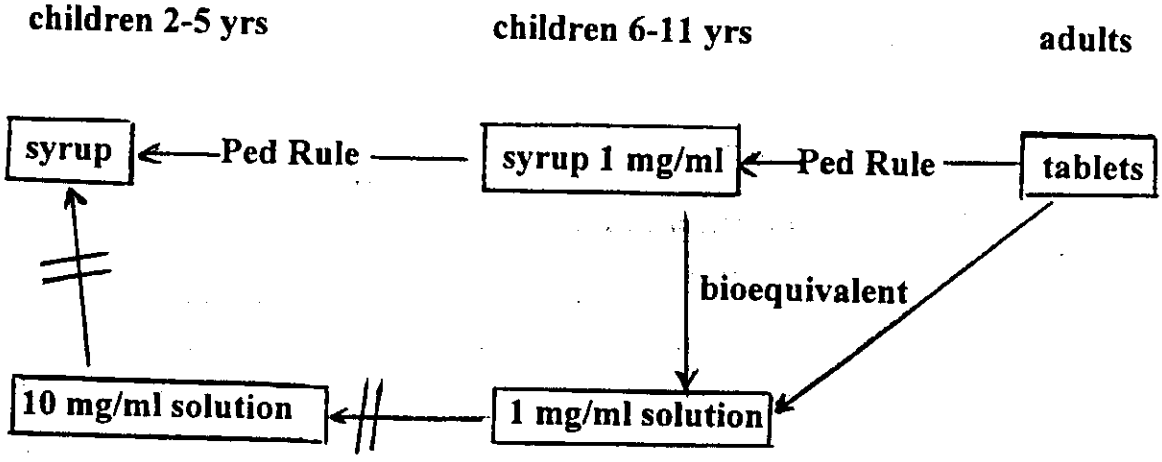
6. Report 9709493: 64 year old female; Zyrtec 10 mg daily; syncope; on hospitalization had hypokalemia and bradycardia with ECG findings of supraventricular and ventricular ectopic beats and short run of ventricular tachycardia.

7. Report 9708617: 73 year old female; after second dose of Zyrtec 10 mg daily developed pulmonary edema and after hospitalization was found to have hypokalemia and developed Torsade de Pointes associated with lightheadedness.

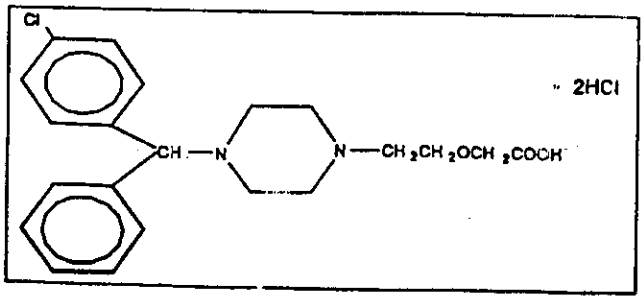
I. BACKGROUND: This submission contains data which the sponsor feels supports the use of cetirizine (Zyrtec) syrup in patients 2-5 years of age for the treatment of 1) seasonal allergic rhinitis; 2) perennial allergic rhinitis; and 3) chronic idiopathic urticaria. The sponsor believes that: 1) this data supports the conclusion that allergic rhinitis and chronic idiopathic urticaria are not different clinically in adults and children 2-5 years of age; 2) this data supports the conclusion that cetirizine does not act differently in adults and children 2-5 years of age; and 3) that there is adequate pharmacokinetic data to support the dosing recommendations in children 2-5 years of age.

Cetirizine was initially approved in a tablet formulation for patients 12 years of age and older. On 20 September 1995, it was approved in the syrup formulation (1 mg/ml) based on the pediatric rule for patients 6-11 years of age with seasonal and perennial allergic rhinitis for administration of a dose of 5-10 mg as a single daily dose. This formulation was not approved at that time for patients 6-11 years of age with chronic urticaria based on the contention that chronic urticaria in this age group was not the same as chronic urticaria in adults. Subsequently, the sponsor submitted justification for extrapolation of data on chronic urticaria in adults to patients 6-11 years of age, so that the labeling indicates that cetirizine syrup is indicated for the treatment of chronic urticaria in patients 6-11 years of age. On 17 June 1997, the sponsor submitted a supplement to the Zyrtec tablet NDA (supplement 005 for NDA 19,835) indicating that the same labeling changes were being proposed for this formulation as for the syrup formulation by cross-referencing the syrup supplement. No additional data was submitted by the sponsor.

In the studies (including PK studies) submitted in this pediatric supplement, a 10 mg/ml oral solution was used. This formulation is significantly different than the marketed syrup formulation. The sponsor has no PK studies linking the 10 mg/ml oral solution formulation and the syrup formulation (see figure below).



Cetirizine hydrochloride, the active component of Zyrtec syrup is an orally active racemic mixture and selective H-2 receptor antagonist, with the chemical structure shown below.



Zyrtec syrup is a colorless to slightly yellow liquid which contains cetirizine hydrochloride at a concentration of 1 mg/mL. It includes the following excipients: banana flavor, glacial acetic acid, glycerin, grape flavor, methylparaben, propylene glycol, propylparaben, sodium acetate, sugar syrup and water. Animal studies have demonstrated the antihistaminic activity of cetirizine, no significant affinity for H-1 receptors and no significant penetration of the blood-brain barrier. In humans, 70% of the drug is recovered in the urine and 10% in the feces. The association of peak plasma levels and the parent compound suggests low first pass metabolism. Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity. The mean plasma protein binding of cetirizine is 93%.

2. **Pharmacokinetics Section: The changes proposed by the sponsor are as follows:**

In pediatric patients aged 2 to 5 years who received 5 mg of cetirizine orally, the maximum mean plasma concentration (C_{max}) obtained was 660 ng/mL. Based on cross-study comparisons of cetirizine pharmacokinetic data in these pediatric patients, weight normalized total body clearance was 81 to 111% greater and the elimination half-life was 33 to 41% shorter than in adults.

COMMENTS: The additional statements are accurate, and therefore, acceptable.

3. **Indications and Usage Section: The changes proposed by the sponsor are as follows:**

Seasonal Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with seasonal allergic rhinitis due to allergens such as ragweed, grass and tree pollens in adults and children 2 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, nasal pruritus, ocular pruritus, tearing and redness of the eyes.

Perennial Allergic Rhinitis: ZYRTEC is indicated for the relief of symptoms associated with perennial allergic rhinitis due to allergens such as dust mites, animal dander and molds in adults and children 2 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, post-nasal discharge, nasal pruritus, ocular pruritus and tearing.

Chronic Urticaria: ZYRTEC is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 2 years of age and older. It significantly reduces the occurrence, severity and duration of hives and significantly reduces pruritus.

COMMENTS: The only change made in this section is the extension of the indication for SAR and PAR, as well as chronic urticaria, down to the age of 2 years. This change for PAR and chronic urticaria is acceptable in terms of efficacy, based NOT on the data submitted by the sponsor in this supplement, but because these conditions are basically the same in this age group and there is adequate PK data to support the proposed dose and dosing interval for patients 2-5 years of age.

4. Dosage and Administration Section: The changes proposed by the sponsor are as follows:

[redacted]

COMMENTS: Based on the pharmacokinetic data in patients 2-5 years of age using the 10 mg/ml oral solution formulation and comparison of this data with pharmacokinetic data in adults when administered the syrup and the 10 mg/ml oral solution formulations, an initial dosage of 2.5 mg once a day is the most appropriate recommendation. The safety data submitted by the sponsor support increasing the dosage to 2.5 mg bid or 5 mg once a day if the patient has not responded to a dosage of 2.5 mg once a day and no adverse event occurred at this dosage.

APPEARS THIS WAY
ON ORIGINAL

II. CLINICAL STUDIES:

A. PHARMACOKINETIC STUDIES:

1. STUDY UCB-120: a single center study done in France

a. Study Characteristics

1) number of patients: 8 (2 patients in each of 4 groups)

2) age range: 2-6 years; divided into 4 groups; ages 2-3 > 3-4 years, >4-5 years and >5-6 years

3) patient population: children undergoing surgery

4) study design: single dose, open, PK study

5) drug administration: 5 mg in solution (UCB) formulation up to 3 hrs before surgery as premedication; the UCB formulation contains propylene glycol, sodium acetate, and purified water; the UCB formulation is different than the Pfzier formulation and has not been tested in any Pfzier sponsored studies; concentration 10 mg/ml solution fasting; 0.5 ml administered directly into mouth or diluted with 10-20 ml of water. Permitted during the study were anesthetic drugs, local anesthetics and paracetamol.

6) periods of study: not adequately described.

7) parameters evaluated:

- ✦ plasma levels before and up to 24 hours after administration of cetirizine; plasma and urinary cetirizine levels were measured by

b. Study Results

1) The mean maximum plasma concentration, i.e. Cmax of 606 ng/ml and the mean AUC of 4772 ng.hr/ml were greater than was seen after a 10 mg dose in adults. The mean elimination half-life was about half of that seen in adults (5.5 hr). Body weight normalized clearance was about twice that seen in adults (1.27 ml/min/kg), but actual clearance was 17.5 ml/min, which is about half that seen in adults. There was no difference within the 2-6 year age group. A mean of 38% of cetirizine was recovered unchanged in the urine, which was less than in adults (see tables below).

Pharmacokinetics of cetirizine
Plasma data

Parameters (units)	Mean ± SD (Range) Total n = 8	95 % confidence interval
C_{max} ($\mu g.l^{-1}$)	606.5 ± 231.3 (196.3 - 856.9)	413 - 800
t_{max} (h)	1.93 ± 1.39 (0.50 - 4.08)	0.77 - 3.09
AUC(0-t) ($\mu g.l^{-1}.h$)	4506.3 ± 1251.1 (2013.56 - 5741.92)	3460 - 5550
lambda, (h^{-1})	0.128 ± 0.020 (0.090 - 0.159)	0.111 - 0.145
C_1 ($\mu g.l^{-1}$)	644.8 ± 226.7 (382.39 - 1086.72)	455 - 834
$t_{1/2}$ (h)	5.85 ± 0.98 (4.37 - 7.69)	4.73 - 6.37
AUC(0-∞) ($\mu g.l^{-1}.h$)	4772.05 ± 1318.4 (2155.93 - 6107.83)	3670 - 5870
MRT or t_2 (h)	8.13 ± 1.31 (6.89 - 10.39)	7.03 - 9.23
*Cl_{app} ($ml.min^{-1}.kg^{-1}$)	1.27 ± 0.80 (0.79 - 3.22)	0.59 - 1.93
*Vd_{app} ($l.kg^{-1}$)	0.60 ± 0.38 (0.37 - 1.52)	0.29 - 0.91
C_{max} normalized ($\mu g/l^{-1}$)	599.3 ± 237 (141.3 - 957.6)	401 - 797
AUC normalized (0-t) ($\mu g.l^{-1}.h$)	4464 ± 1420 (1449.76 - 6089.28)	3270 - 5650
AUC normalized (0-∞) ($\mu g.l^{-1}.h$)	4729 ± 1513 (1552.27 - 6361.57)	3470 - 5990

SD : standard deviation of the variable

* values for clearance and volume of distribution assuming complete absorption

Urinary data : mean values, n = 4 (cases 1, 4, 5, 6)

Parameters	Ae (24) (µg)	Urinary excretion (% of the dose)	Renal Cl ($ml.min^{-1}.kg^{-1}$)
Mean ± SD (range)	1922.5 ± 494.6 (1348.5 - 2486.2)	38.4 ± 9.9 (27.0 - 49.1)	0.42 ± 0.10 (0.33 - 0.53)
95 % confidence interval of the mean	1135 - 2709	22.6 - 54.2	0.26 - 0.59

SD : standard deviation of the variable

2) Individual patient PK data can be seen in the table below. Patients 2 and 4 were 2-3 years of age, patients 1 and 3 were 3-4 years of age, patients 5 and 6 were 4-5 years of age, and patients 7 and 8 were 5-6 years of age.

UCB/Zyrtec : Pharmacokinetic parameters

	Enrolment No.							
	1	2	3	4	5	6	7	8
C_0 ($\mu g.l^{-1}$)	1086.72	382.39	385.08	753.32	721.16	654.13	543.00	632.83
Lambda, (h^{-1})	0.159	0.127	0.090	0.119	0.129	0.146	0.126	0.127
$t_{1/2}$ (h)	4.37	5.47	7.69	5.84	5.37	4.74	5.49	5.47
t_{max} (h)	0.50	4.08	1.58	1.52	0.67	4.08	1.50	1.50
C_{max} ($\mu g.l^{-1}$)	856.9	196.3	504.1	750.9	707.9	389.1	606.7	840.0
AUC_{0-t} ($\mu g.l^{-1}.h$)	5568.41	2013.56	4413.87	5741.92	5206.93	3645.08	4118.77	5341.48
$AUC_{0-\infty}$ ($\mu g.l^{-1}.h$)	5874.80	2155.93	4893.24	6187.83	5458.69	3779.46	4326.12	5580.32
Cl_{app} ($l.h^{-1}$)	0.85	2.32	1.02	0.82	0.92	1.32	1.16	0.90
MRT (h)	6.89	10.38	9.77	8.55	7.50	7.58	7.12	7.26
Vd_{app} (l)	5.36	18.29	11.33	6.89	7.09	9.06	9.15	7.07
Dose ($mg.kg^{-1}$)	0.42	0.42	0.25	0.33	0.29	0.28	0.28	0.26
Cl_{app} ($ml.min^{-1}.kg^{-1}$)	1.18	3.22	0.85	0.81	0.90	1.22	1.07	0.79
Vd_{app} ($l.kg^{-1}$)	0.45	1.52	0.57	0.46	0.42	0.50	0.51	0.37
C_{max} normalised ($\mu g.l^{-1}$)	617.0	141.3	604.9	675.8	722.1	420.2	655.2	957.6
AUC_{0-t} normalised ($\mu g.l^{-1}.h$)	4009.25	1449.76	5296.77	5167.73	5311.07	3936.68	4448.28	6089.28
$AUC_{0-\infty}$ normalised ($\mu g.l^{-1}.h$)	4229.86	1552.27	5871.90	5497.05	5567.87	4081.81	4672.20	6361.87

c. Comments:

1) The formulation used was different than the formulation used in previous efficacy and safety studies but was the same as the formulation used in the efficacy and safety studies in patients 2-5 years of age which are submitted at this time. The drug was also administered differently to different patients, in two patients the content of the syringe was administered directly into the child's mouth and in the other 6 patients the content of the syringe was first diluted in a glass containing 10-20 ml of water and was then drunk by the child. Furthermore, the patients subsequently received general anesthetics, local anesthetics and paracetamol. The potential effect of these concomitant medications on the pharmacokinetics of cetirizine in this age group is not discussed. Nevertheless, the data from this study can be compared to data obtained in previous studies with older children and adults (see table below).

2) Moreover, the PK data in patients 2-5 years of age is somewhat different than that seen in adults and older children; the mean Cmax is substantially greater than the Cmax seen in children 6-12 years of age and elderly patients and greater than that seen in adults after administration of twice the dose (10 mg); the mean Tmax is greater than the mean Tmax in other age groups; the mean half-life is half that of adults and elderly patients and comparable to children 6-12 years of age; clearance appears to be twice as great as that seen in adults; urinary excretion was less in this age group than in other age groups (see table below).

3) The data from studies comparing the syrup formulation and the 10 mg/ml oral solution formulation in adults indicate that 20 mg of the oral solution formulation is associated with phamacokinetic results comparable t o those associated with 10 mg of the syrup formulation. This suggests that the dosage should be less than is proposed (see Biopharm review), e.g. 2.5 mg once daily.

TABLE VI : Comparison of kinetic parameters for cetirizine from various studies (mean and standard deviation)

Parameters / Group		Elderly Subject	Adult	Adult	Children 10-12 years	Children 6-12 years	Children studied group 2-6 years (our study)
Dose	mg	10	20	10	5	5	5
	$mg.kg^{-1}$	0.134	0.295	0.134			0.32 ± 0.07
Pharmaceutical form		tablet	capsule	tablet	tablet	capsule	solution
C_{max} ($\mu g.l^{-1}$)		360 ± 60	890 ± 90	350		275	606.5 ± 231.3
t_{max} (h)		1.3 ± 0.57	0.67 ± 0	1.12 ± 0.53			1.93 ± 1.39
$t_{1/2\beta}$ (h)		11.8 ± 2.6	9.4 ± 1.1	10.6 ± 1.5	6.51	6	5.55 ± 0.98
$^{*}Cl_{tot}$ ($ml.min^{-1}.kg^{-1}$)		0.55 ± 0.11	0.6 ± 0.08	0.6		0.9	1.27 ± 0.80
$^{*}Vd_{ss}$ ($l.kg^{-1}$)				0.6		0.6	0.68 ± 0.30
24-h urinary excretion as a % of the dose		41.9	50.8	56.3	63.7	70.0	38.4 ± 9.9

* Clearance values and volume of distribution assuming total absorption

2. STUDY UCB-122:

a. Study Characteristics

1) number of patients: 8

2) age range: 2-4 years

3) patient population: patients hospitalized for chronic respiratory infection (pneumonia) or allergic condition (allergic rhinitis, asthma and/or eczema)

4) study design: single dose, open

5) drug administration: single dose of 5 mg (10 drops of solution containing 10 mg/ml); fasting

6) periods of study: not adequately described

7) parameters evaluated:

✦ plasma levels of cetirizine: 30, 60, 90, 120 minutes and 4, 6, 8, 12 and 24 hours after drug administration

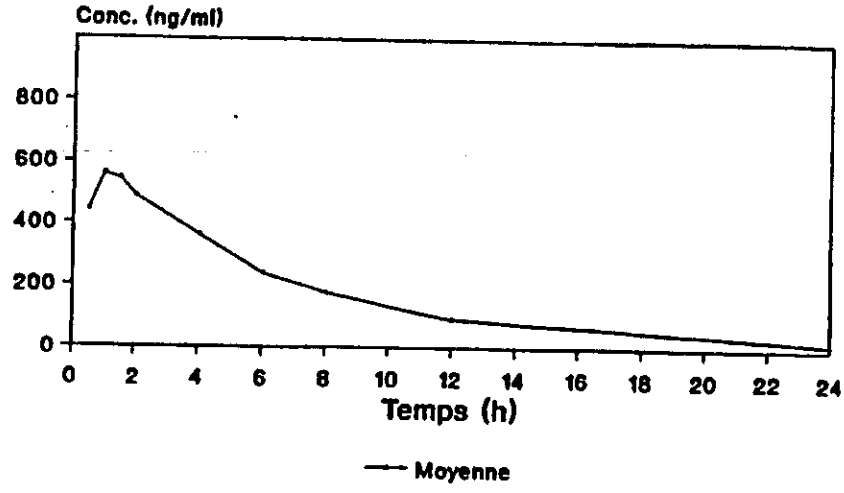
✦ 24 hour urine collection

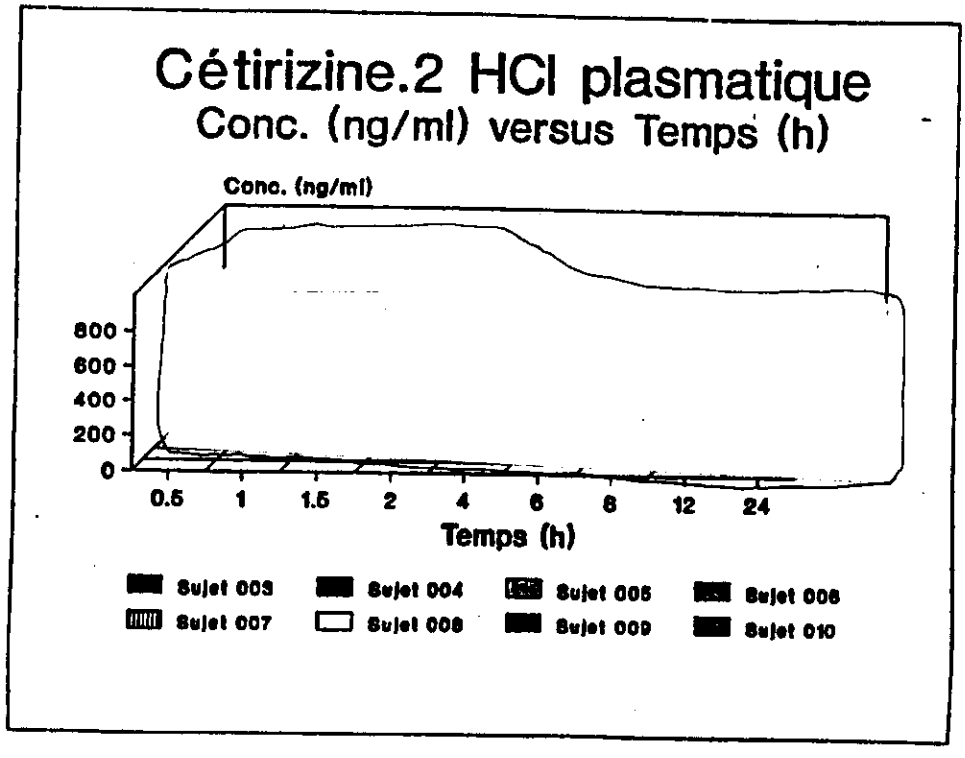
b. Study Results

1) One patient was also taking valproic acid which could have influenced cetirizine PK because of strong plasma protein binding; one urinary collection was not done and two were incomplete.

2) Plasma cetirizine levels can be seen in the figures below.

Cétirizine.2 HCl plasmatique
Conc. (ng/ml) versus Temps (h)





3) Pharmacokinetic data can be seen in the tables below.

TABLE III : PHARMACOKINETIC PARAMETERS

Initials/No.	Obs. C_{max} (ng/ml)	Obs. T_{max} (h)	T 1/2β (h)	AUC 0.5→∞ (ngml^{-1}xh)	Cl/F (ml/min/kg)	V_β/F (l/kg)
/003	862	0.5	4.7	5059	1.02	0.42
/004	737	1.5	4.6	3874	1.49	0.6
/005	744	0.5	6.0	5296	1.02	0.53
/006	413	4	4.7	3027	2.3	0.94
/007	540	1	4.1	2942	1.5	0.53
/008	699	1.5	5.0	3791	1.51	0.66
/009	410	1.5	4.6	3639	1.27	0.51
/010	772	1	5.85	4447	1.72	0.83
Mean (n = 7)	695	1.07	4.94	4150	1.36	0.58
Standard deviation	176	0.45	0.64	832	0.27	0.13
Mean (n = 8)	660	1.44	4.91	4009	1.48	0.63
Standard deviation	191	1.12	0.60	867	0.41	0.18

TABLE IV : URINARY EXCRETION

Initials/No.	Volume (ml)	Period of collection (h)	concentration (µg/ml)	Total excretion (mg/% of dose)
003	469	22	4.76	2.23/44.6
004	215*	21.17	9.13	1.96/39.2
005	130*	21.67	13.78	1.79/35.8
006	705	24	3.15	2.22/44.4
007	320	29.08	5.72	1.83/36.6
008	290	26	5.70	1.65/33
009	**	-	-	-
010	230	24	6.77	1.56/31.2
Mean (n = 6)				1.84/36.7
Standard deviation				0.24/4.8
Mean (n = 7)	-	-	-	1.89/37.8
Standard deviation	-	-	-	0.26/5.2

* Incomplete collection
** Collection not done

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3) A comparison of the pharmacokinetic data from this study and other studies that have been performed can be seen in the table below.

TABLE V : COMPARISON OF RESULTS OBTAINED IN PRESENT STUDY VERSUS RESULTS FROM PREVIOUS STUDIES (extremes, means and standard deviations) *

Origin	Age (years)	n	Weight (kg)	Dose/form	T_{max} (h)	T-1/2 ß (h)	Cl/F (ml/min/kg)	$V_ß$/F (l/kg)	Urine (0-24h) (%)
Present study	2.5 - 3.8 2.8 ± 0.3	7	10.9 - 18.9 15.5 ± 2.6	5 mg drops	0.5 - 1.5 1.07 ± 0.45	4.3 - 6 4.94 ± 0.64	1.02 - 1.72 1.36 ± 0.27	0.42 - 0.83 0.58 ± 0.13	31.2 - 44.6 36.7 ± 4.4
D. Oden reference 5	7 - 12 10.1 ± 1.6	14	24 - 47.6 34.9 ± 7.9	5 mg capsules	0.5 - 2 1.1 ± 0.4	4.5 - 11.3 6.2 ± 1.6	0.68 - 1.13 0.93 ± 0.16	0.37 - 0.64 0.49 ± 0.09	collection limited to 12h
E. Baltes reference 6	10 - 12 10.3 ± 0.7	12	27 - 39 32.6 ± 3.4	5 mg tablets	--	5.2 - 7.7 6.6 ± 0.7	--	--	48.2 - 71.9 61.1 ± 7.3
WTA Watson reference 9	6 ± 0.6* 8 ± 0.6*	10 9	20.5 ± 2.6* 25.4 ± 1.9*	5 mg capsules 10 mg capsules	0.5 - 4 1.4 ± 1.1 0.5 - 1.5 0.8 ± 0.4	4.7 - 9.4 7.1 ± 1.6 4.4 - 10.4 6.9 ± 1.6	0.70 - 1.43 1.04 ± 0.20 0.86 - 1.34 1.10 ± 0.13	0.3 - 1 0.7 ± 0.2 0.4 - 0.9 0.7 ± 0.1	24 - 71 48 ± 15 33 - 69 39 ± 11
C. Harvengt reference 7	21 - 35 26.6 ± 4.1	16	43 - 83 67.7 ± 12.5	20 mg drops	0.12 - 1.05 0.46 ± 0.07	3.75 - 10 6.6 ± 2.1	0.85 - 1.2 0.98 ± 0.17	0.36 - 0.83 0.58 ± 0.13	32.1 - 74.3 53.7 ± 11.8

* extremes not reported in the publication.

COMMENTS: Comparison of means for pharmacokinetic parameters in this study and study 120 shows similar results in patients 2-6 years of age (see table below)

COMPARISON OF MEAN VALUES
(Cross-study comparison)

Patient population	Cmax	Tmax (hrs)	T1/2 (hrs)	Cl	AUC
Study 120 (5 mg)	606	1.9	5.5	1.3	4772
Study 122 (5 mg)	660	1.1	4.9	1.4	4009
6-12 years (5 mg)	275	1.1	6.0	0.9	2201
adults 10 mg	350	1.1	9.4	0.6	-
adults 20 mg	890	0.7	10.6	0.8	-
elderly 10 mg	360	1.3	11.8	0.6	-

Cmax in ng/ml
Cl in ml/min/kg
AUC in ng.hr/ml

The same pattern can be seen in this study as was seen in study 120, i.e. Cmax is significantly higher than seen in other age groups, half-life is significantly shorter and clearance is significantly greater. The time of peak effect is earlier than seen in study 120 and more consistent with the Tmax seen in other age groups. The data from this study suggest that a dose of 2.5 mg per day is adequate to provide efficacy in patients 2-5 years of age (see Biopharm review) In patients who do not respond to 2.5 mg per day, the dose could be increased to 5 mg per day or 2.5 mg bid.

E. DERMATOLOGIC AND UPPER RESPIRATORY ALLERGIC DISEASE

1. Study 59: single center study in Belgium

a. Study Characteristics:

1) number of patients: 48; 24 with cutaneous manifestations; 24 with perennial rhinitis; 12 patients in each group received cetirizine

2) age range: 9 months - 15 years

3) patient population: perennial rhinitis or atopic dermatitis of at least 6 weeks duration; demonstrated IgE-dependent mechanism; not corticosteroid-dependent; off ketotifen and corticosteroids for 15 days and other medications for 4 days

4) study design: double-blind, repetitive dose, placebo-controlled, parallel study

5) drug administration: concentration 10 mg/ml, 0.5 mg per drop; 2.5 mg (5 drops) if patient was < 25 kg, 5 mg if patient was 25-50 kg, and 10 mg if patient was > 50 kg; once a day at night

6) periods of study: 2 weeks of drug administration

7) parameters evaluated:

- ✦ nasal symptoms: nasal obstruction, "rhinitis", "conjunctivitis", sneezing; assessment at baseline and after 2 weeks of treatment; 4 point categorical scale; 0 = none, 3 = severe; graded analog scale; 0 mm = very poor, 100 mm = excellent

- ✦ cutaneous symptoms: pruritus, erythema, papules and edema; assessment at baseline and after 2 weeks of treatment; 4 point categorical scale; 0 = none, 3 = severe; graded analog scale; 0 mm = very poor, 100 mm = excellent
- ✦ global assessment by patient/parent and investigator
- ✦ comparison with previous therapy
- ✦ adverse events
- ✦ laboratory tests; baseline and after treatment

b. Study Results:

1) There was no consistent statistically significant difference between cetirizine and placebo in regard to nasal symptoms, based either on categorical scoring or visual analog scoring. Patients improved after both cetirizine and placebo administration. The lack of any difference in the two treatment groups is due primarily to a very strong placebo response (see tables below).

SYMPTOMS		RESULT				DEVELOPMENT BEFORE/AFTER PROBABILITY		
		BEFORE TREATMENT		AFTER TREATMENT		INTER-GROUPE		C/P
		CETIRIZINE n = 12	PLACEBO n = 12	CETIRIZINE n = 12	PLACEBO n = 12	CETIRIZINE	PLACEBO	
SNEEZING	X	0.9	1.0	0.2	0.5	0.008	NS	NS
	SD	0.9	0.9	0.6	0.7			
CONJUNCTIVITIS	X	0.3	0.3	0.1	0.3	NS	NS	NS
	SD	0.6	0.8	0.3	0.7			
RHINITIS	X	2.3	2.1	1.2	0.9	0.016	0.016	NS
	SD	1.0	0.5	1.4	0.9			
NASAL OBSTRUCT.	X	2.9	2.7	1.8	1.6	0.016	0.039	NS
	SD	0.3	0.5	1.2	1.1			

VISUAL ANALOG SCALE

(from 0 = very poor to 100 = excellent)

(Nasal pathology)

	BEFORE TREATMENT		AFTER TREATMENT		DEVELOPMENT BEFORE → AFTER TREATMENT PROBABILITY	
	CETIRIZINE	PLACEBO	CETIRIZINE	PLACEBO	INTERGROUP	C/P
n	12	12	12	12		
X	14.1	15.5	41.7	50.6	C : 0.017 P : 0.003	NS
SD	10.1	8.3	33.0	33.1		

2) There was no statistically significant difference between placebo and cetirizine in terms of nasal symptomatology, based on global assessment by patient (parent) (p = 1.0) or investigator (p = 0.7).

3) There was no statistically significant difference between cetirizine and placebo in terms of scores of cutaneous manifestations using a categorical scale or using a visual analog scale. Patients improved after both placebo and cetirizine administration. The lack of any difference between the two treatment groups is primarily due to the large placebo effect (see tables below),

	RESULT				DEVELOPMENT BEFORE/AFTER PROBABILITY		
	BEFORE TREATMENT		AFTER TREATMENT		INTER-GROUP		C/P
SYMPTOMS	CETIRIZINE	PLACEBO	CETIRIZINE	PLACEBO			
n	12	12	12	12	CETIRIZINE	PLACEBO	
X	2.6	2.8	1.6	1.5			
PRURITUS					0.039	0.008	NS
SD	0.8	0.4	0.9	1.1			
X	2.5	2.5	1.5	1.8			
ERYTHEMA					0.07	0.125	NS
SD	0.5	0.7	1.3	1.1			
X	0.8	1.1	0.8	0.6			
PAPULES					NS	NS	NS
SD	0.9	1.2	1.1	0.9			
X	0.4	0.1	0.4	0			
OEDEMA					NS	NS	NS
SD	0.9	0.3	0.7	0			

VISUAL ANALOG SCALE

(from 0 = very poor to 100 = excellent)

(Cutaneous pathology)

	BEFORE TREATMENT		AFTER TREATMENT		DEVELOPMENT BEFORE → AFTER TREATMENT PROBABILITY	
	CETIRIZINE	PLACEBO	CETIRIZINE	PLACEBO	INTERGROUP	C/P
n	12	12	12	12		
X	16.1	11.9	40.8	35.9	C : 0.032	NS
SD	12.0	7.4	29.4	24.8	P : 0.008	

4) There was no statistically significant difference between placebo and cetirizine based on global assessment by the patient (parent)($p = 1.0$) or by the investigator ($p = 1.0$).

5) There was no clinically significant difference between placebo and cetirizine based on patient comparison with previous therapy.

6) No adverse events were seen in the cetirizine groups. No significant changes were noted in laboratory tests.

CONCLUSIONS: There was no statistically significant difference in this very small study between cetirizine and placebo in regard to improvement in either nasal/ocular symptoms or cutaneous manifestations. This was due, in large part, to a substantial placebo effect. The study was flawed in a number of ways, including use of prohibited medication, patient selection in the cutaneous group, dose selection (82% responded to doses 20 mg/kg/day or more, 67% responded when given < 20 mg/kg/day), and study methods. This study, therefore, can not be used to support a claim for the efficacy of cetirizine in the treatment of either perennial rhinitis or atopic dermatitis in the age group evaluated.

D. DERMATOLOGIC CONDITIONS

1. STUDY 127: Study of cetirizine in the treatment of eczema-induced pruritus in children; single center study in France

a. Study characteristics:

1) number of patients: 30; 16 patients received cetirizine and 14 patients received placebo

2) age range: 4-8 years

3) patient population: at least a 7 day history of eczema, unrelieved by topical treatment, including corticosteroids; off antihistamines for 5 days

4) study design: placebo controlled, double-blind, parallel, repetitive dose study

5) drug administration: 10 mg/ml concentration; solution delivered by dropper; 0.5 mg per drop; administered once a day in the evening; 2.5 mg (5 drops) if patient is < 25 kg; 5 mg if patient weighs 25-30 kg (0.1-0.24 mg/kg)

6) periods of study: one week of treatment

7) parameters evaluated:

- ✦ evaluation of skin in 7 areas; 1) head and neck; 2) back; 3) thorax and abdomen; 4) upper limbs; and 5) lower limbs; on each of these areas, the investigator evaluated skin lesions using a 4 point scale; 0 = normal skin; 1 = slightly dry skin; 2 = excoriated inflammatory lesions; and 3 = weeping, vesicular or pustular lesions; pruritus was also evaluated using a 4 point scale where 0 = absence and 3 = severe pruritus; visual analog scale could be used.

- ✦ global evaluation by patient and investigator
- ✦ adverse events

b. Study Results:

1) Demographics: There were no significant differences between the two treatment groups.

2) Efficacy: the score in each skin area for eczema lesions, scratching lesions, and history of pruritus decreased after treatment with cetirizine for one week and there was a statistically significant difference from placebo for eczema lesions in 3/7 skin areas, for scratching lesions in 4/7 skin areas and for history of pruritus in 5/7 skin areas (see table below)

Group comparison

	INITIAL VALUES under Cetir.		Placebo			FINAL VALUES under Cetir.		Placebo		
	Mean	sd	Mean	sd	p	Mean	sd	Mean	sd	p
Eczema lesions										
Head and neck	1.63	0.72	1.29	0.91	NS	1.13	0.62	1.14	0.86	NS
Back	1.06	0.8	0.86	0.36	NS	0.81	0.54	0.86	0.36	NS
Thorax and abdomen	0.69	0.7	1	0.39	NS	0.56	0.63	1	0.39	0.03
Right upper limb	1.06	0.68	1.07	0.48	NS	0.69	0.48	1	0.56	NS
Left upper limb	1.06	0.68	1.07	0.46	NS	0.81	0.4	1	0.56	NS
Right lower limb	1.38	0.62	1.71	0.47	NS	1.06	0.44	1.57	0.65	0.02
Left lower limb	1.5	0.73	1.71	0.47	NS	0.94	0.57	1.57	0.65	0.008
Scratching lesions										
Head and neck	0.44	0.63	0.5	0.76	NS	0.19	0.4	0.36	0.63	NS
Back	0.38	0.62	0.21	0.43	NS	0.06	0.25	0.21	0.43	NS
Thorax and abdomen	0.25	0.58	0.29	0.47	NS	0	0	0.21	0.43	NS
RUP	0.31	0.6	0.43	0.76	NS	0	0	0.43	0.76	0.03
LUL	0.31	0.6	0.43	0.76	NS	0	0	0.43	0.76	0.03
RLL	0.56	0.8	0.93	0.83	NS	0.06	0.25	0.71	0.73	0.002
LLL	0.63	0.89	0.93	0.83	NS	0.13	0.34	0.71	0.73	0.007
History of pruritus										
Head and neck	0.75	0.68	0.79	0.8	NS	0.31	0.48	0.71	0.73	NS
Back	0.56	0.63	0.57	0.51	NS	0.25	0.45	0.5	0.52	NS
Thorax and abdomen	0.5	0.63	0.71	0.47	NS	0.19	0.4	0.64	0.5	0.01
RUP	0.63	0.62	0.86	0.66	NS	0.25	0.45	0.79	0.7	0.02
LUL	0.69	0.60	0.86	0.66	NS	0.25	0.45	0.73	0.7	0.02
RLL	0.94	0.68	1.36	0.84	NS	0.38	0.5	1.14	0.86	0.005
LLL	1.	0.73	1.36	0.84	NS	0.38	0.5	1.14	0.86	0.005

Using a visual analog scale, there was a statistically significantly greater degree of improvement based on overall investigator assessment after cetirizine administration compared with placebo administration ($p = 0.001$), as well as patient and investigator global assessment ($p = 0.0008$). In addition, cetirizine better than ketotifen, tritoqualine, mequitazine, terfenadine, cyproheptadine, corticosteroids, or homeopathy by 10/14 patients who received cetirizine as compared with 1/10 placebo patients.

3) safety: There were no adverse events reported in this study.

CONCLUSIONS: **This study supports the sponsor's contention that cetirizine, at a dose of 2.5-5 mg given once a day in children 4-8 years of age, is effective in alleviating pruritus associated with atopic dermatitis, although it is less clear if cetirizine actually improves eczematous lesions. The proposed labeling for this drug product states that "Zyrtec is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 2 years of age and older." Eczema is not urticaria, although there is no data to indicate that pruritus associated with these conditions occurs through different pathophysiologic mechanisms. Therefore, this study can be used to support a claim for relief of pruritus associated with conditions such as atopic dermatitis in children, but not to support a claim that suggests that the effect of cetirizine extends beyond its ability to diminish pruritus. No adverse events were reported in this study. Based on assessment of adverse events, this study supports the safety of cetirizine when administered at a dose of 2.5-5 mg per day to patients 4-8 years of age.**

2. STUDY 128: Study of cetirizine in the treatment of chronic idiopathic urticaria in children; single center study performed in France.

a. Study Characteristics:

1) number of patients: 40 (20 in each treatment group)

2) age range: 3- 16 years

3) patient population: chronic idiopathic urticaria of at least 3 weeks duration not dependent on corticosteroids, off ketotifen and corticosteroids for at least 15 days and other medications for at least 4 days

4) study design: placebo-controlled, double-blind, parallel, repetitive dose study

5) drug administration: 10 mg/ml concentration; solution administered as drops; 0.5 mg per drop; 2.5 mg (5-drops) for patients < 20 kg; 5 mg for patients 20-35 kg, 7.5 mg for patients 35-50 kg, and 10 mg for patients > 50 kg given once daily in the evening

6) periods of study: one week of treatment

7) parameters evaluated:

- ✦ change in pruritus, erythema, skin wheal, and edema evaluated after one week of treatment by the investigator, based on a 4 point categorical scale, where 0 = none, 1 = slight, 2 = moderate, and 3 = severe; a visual analog scale was also used for evaluation by the investigator
- ✦ global evaluation by parent and investigator
- ✦ adverse events

b. Study Results:

1) Demographics: comparable between the two groups.

2) Efficacy: see table below; there was a statistically significantly greater improvement after cetirizine administration for each of the parameters assessed than was seen after placebo administration; note that improvement is reflected in a lower score for the skin manifestations and in a higher score for the patient's condition.

Symptom (scale)		Cetirizine group n = 20 before	Cetirizine group n = 20 after	Placebo group n = 20 before	Placebo group n = 20 after	p
pruritus	mean	2.20	0.9	2	1.85	0
(0-3)	sd	0.41	0.72	0	0.37	
erythema	mean	1.35	0.55	1.20	1.1	0
(0-3)	sd	0.59	0.51	0.41	0.31	
skin wheals	mean	2.15	0.75	2.05	1.85	0
(0-3)	sd	0.37	0.79	0.51	0.67	
edema	mean	0.95	0.30	0.95	0.90	0
(0-3)	sd	0.39	0.47	0.39	0.45	
patient's condition	mean	35.4	72.15	31.8	37.05	0
(0-100)	sd	6.48	23.8	8.55	11.7	

Review of individual patient data, showed that 16/20, 13/20, 16/20, and 13/20 cetirizine patients improved significantly in regard to pruritus, erythema, skin wheal and edema, respectively, compared with 3/20, 1/20, 4/20, and 2/20 placebo patients. Global evaluation by the parent and investigator can be seen in the tables below. There was a statistically significance between the two treatment groups favoring cetirizine. Patients who received cetirizine considered that cetirizine was better than 16/23 previous treatments received, compared to 25/26 previous treatments considered by the placebo group to have been better than placebo.

Evaluation by the patient

	excellent	good	moderate	bad
cetirizine	9	5	2	4
placebo	0	0	3	17
p = 0.0001				

Evaluation by the investigator

	excellent	good	moderate	bad
cetirizine	6	7	3	4
placebo	0	0	3	17
p = 0.0001				

3) safety: no adverse events were reported

CONCLUSIONS: This study supports a claim for the efficacy of cetirizine in the management of urticaria in patients 3-15 years of age, after administration of 2.5 to 10 mg once a day in the evening for one week. The labeling, however, proposes a dose of 5 mg once a day or 2.5 mg every 12 hours for patients 2-5 years of age. There were only 4 patients in this study who were 2-5 years of age. The efficacy of cetirizine was clearly demonstrated in this group, all of whom received a dose of 2.5 mg per day. However, since only 4 patients in this study received a dose which was not greater than the recommended dose for this age group, there is insufficient data from this study alone to conclude that cetirizine at the recommended dose is effective in the management of urticaria in patients 2-5 years of age. Based on assessment of adverse events, this study supports the safety of cetirizine when administered to this age group at the dosse used in this study.

3. STUDY 62: Study of cetirizine in the treatment of atopic dermatitis in children; multicenter study in Germany, Belgium, and France.

a. Study Characteristics:

1) number of patients: 95; 31 received 10 mg/day; 36 received 5 mg/day and 28 received placebo; 8 patients not included in the efficacy analysis (4 in the 10 mg/day group, 1 in the 5 mg/day group and 3 in the placebo group); 3 patients excluded from both the efficacy and safety analysis (1 patient in each of the three treatment groups).

2) age range: 3-6 years

3) patient population: atopic dermatitis; receiving topical antibiotic; minimal score of 4 for pruritus and erythema together; score of 6 for other symptoms based on a five point scale

4) study design: multicenter, double-blind, parallel, placebo-controlled, randomized, repetitive dose study

5) drug administration: 5 mg per day (2.5 mg bid morning and evening) and 10 mg per day (5 mg bid morning and evening); SOLUTION 0.5 mg/ml, 5 ml for 2.5 mg dose and 1 mg/ml, 5 ml for 5 mg dose; topical corticosteroid for rescue; used by 2 placebo patients and 1 patient in each of the two cetirizine treatment groups.

6) periods of study: 1 week of treatment

7) parameters evaluated:

- ✦ pruritus: before and after treatment; 5 point categorical scale where 0 = no pruritus, 4 = very severe pruritus; by investigators and parents separately; parents used a 4 point categorical scale

- ✦ erythema: before and after treatment; 5 point categorical scale where 0 = no erythema, 4 = very severe erythema; by investigators and parents separately; parents used a 4 point categorical scale

- ✦ vesicles, lichenification and crusting: 0 = none, 1 = present

- ✦ global evaluation: at conclusion of study; scale of 0-4, where 0 = deterioration and 4 = no symptoms

- ✦ quality of sleep: by parents

b. Study Results:

1) demographics: there was no significant difference between the three treatment groups.

2) compliance: comparably poor in the three treatment groups.

3) efficacy:

- ✦ Investigator assessment: pruritus was decreased 44% in the 10 mg/day cetirizine group, 39% in the 5 mg/day cetirizine group, and 37% in the placebo group; erythema was decreased 33%, 36% and 34% in the three groups, respectively; for these and other symptoms evaluated, there was no statistically significant difference between the three treatment groups.

- ✦ global assessment by investigator: there was a strong trend favoring cetirizine, with 40% of the 10 mg/day and 46% of the 5 mg/day groups showing good-excellent improvement, compared to 20% of the placebo group, but this difference was not statistically significant.

- ✦ parent assessment: there is a trend favoring cetirizine with a greater decrease in intensity noted in the two cetirizine groups as compared to the placebo group in regard to both pruritus and erythema, although there was no statistically significant difference between the three treatment groups. An earlier and greater degree of improvement was seen in the group which received 10 mg/day of cetirizine.

4) safety: adverse events were reported by 3 patients in the 10 mg/day cetirizine group, 2 patients in the 5 mg/day cetirizine group and 3 patients in the placebo group. One patient receiving 10 mg/day of cetirizine developed mild agitation and one patient developed moderate polydipsia; one patient receiving 5 mg/day of cetirizine developed slight sleepiness and increase in appetite. The number of times that the patient awoke during the night and the state of alertness on waking in the morning was comparable between the three treatment groups. There were no significant changes in the laboratory tests which were performed.

CONCLUSIONS: Even from this brief summary of the data, it appears that the data from this study may have been influenced by lack of compliance, concomitant medication use and possibly other factors, which may have made it less likely that a statistically significant difference could be seen between cetirizine and placebo. Although there are trends favoring cetirizine over placebo, in particular the 10 mg/day dose, there is no statistically significant difference between either dose of cetirizine and placebo in terms of any of the efficacy parameters in this study. Therefore, this study can not be used to support the efficacy of cetirizine in terms of either atopic dermatitis or dermatologic manifestations, such as pruritus, in patients 3-6 years of age at doses of 5-10 mg/day. No unexpected or severe adverse events apparently occurred in this study, and this study, based on limited safety assessment supports the safety of cetirizine at doses of 5-10 mg/day in patients 3-6 years of age.

B. PERENNIAL ALLERGIC RHINITIS (PAR):

1. STUDY UCB-65: Multicenter study in Germany, France, Italy, and The Netherlands

a. Study Characteristics:

1) number of patients: 138 patients enrolled; ITT analysis of 137 patients; 67 patients received cetirizine, 70 patients received placebo

2) age range: see table below;

Age (years)	Placebo	Cetirizine
Age < 3.5	15	9
3.5 ≤ Age < 5.0	25	29
5.0 ≤ Age < 6.5	28	27
6.5 ≤ Age < 8.0	2	1
Age ≥ 8.0	0	1
Total	70	67

3) patient population: PAR; at least one year history; active symptoms of sneezing, rhinorrhea, and nasal congestion; total score at time of screening for these three symptoms of 5 or greater, based on a 4 point scale (0-3)

4) study design: randomized, double-blind, parallel, multicenter, placebo-controlled, repetitive dose study

5) drug administration: 5 mg (10 mg/ml)(10 drops) oral solution given once daily in the evening

6) periods of study: 4 weeks of randomized treatment; visit 1 (day 1); visit 2 (day 12-18)(approximately 2 weeks); and visit 3 (day 26-32)(approximately 4 weeks)

7) parameters evaluated: the primary efficacy variable was the percentage of days where the most severe of 5 rhinitis symptoms (sneezing, rhinorrhea, nasal congestion, nasal pruritus and ocular pruritus) was at most mild, i.e. maximum score of 1 or less for the total treatment period from day 2 on, as recorded in the daily diary by parents; secondary efficacy variables included the cumulative relative frequency of days without symptoms and days with a maximum score of 2 or less, based on 5 symptoms and also 4 symptoms with the exclusion of nasal congestion

- ✦Diary cards: symptom severity recorded each evening by parents; 4 point scale were 0 = none, 1 = slight, 2 = a great deal, and 3 = unbearable; evaluations were made for the 24 hour period since the last recording

- ✦Investigator assessment: at each visit, severity of symptoms was assessed on a 4 point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe

- ✦ global investigator assessment: at final visit compared to baseline on 5 point scale; 0 = worsening, 1 = no change, 2 = slight improvement, 3 = good improvement; 4 = excellent improvement

- ✦ laboratory tests: at baseline and at the conclusion of the study

✦ adverse events: obtained by asking "Have you noticed anything in particular which concerns the health of your child ?" at visits 2 and 3

8) statistical analysis: ITT analysis was used

b. Study Results:

1) Protocol Deviations: There were 3 placebo and 6 cetirizine patients who took prohibited medications during the study. One placebo patient and 3 cetirizine patients were included without a positive test for allergies; there were 11 placebo patients and 7 cetirizine patients who were non-compliant; 9 placebo patients and 12 cetirizine patients failed to complete the study; 2 cetirizine patients were outside the age limits set by the protocol; one placebo patient and 3 cetirizine patients were included without a positive test for IgE antibodies

2) Demographics: there were comparable numbers of patients in each age subdivision except for patients less than 3.5 years of age, in which subdivision there were 15 placebo and 9 cetirizine patients. Otherwise, the demographics were comparable in the two treatment groups.

3) Patient Withdrawals: see table below; there were 3 placebo and 2 cetirizine patients who were withdrawn because of an adverse event; 4 cetirizine patients were withdrawn because of prohibited medication, compared to no placebo patients.

APPENDIX II : PATIENTS WITHDRAWN

CRF NR.	TREATMENT NR.	TREATMENT	REASON
480	446/004	Placebo	Ineligibility
201	439/001	"	Adverse Event
151	452/001	"	Adverse Event
239	441/008	"	Inefficacy
451	447/001	"	Inefficacy
83	449/004	"	Visit schedule
486	446/014	"	Drug compliance
456	447/006	"	Adverse event
233	441/002	"	Personal convenience
153	452/002	Cetirizine	Not known
5602	441/012	"	Adverse Event
54	448/004	"	Averse Event
3853	536/010	"	Inefficacy
458	447/008	"	Visit schedule
3868	537/009	"	Drug compliance
453	447/003	"	Prohibited medication
52	448/002	"	"
78	449/003	"	"
103	450/001	"	"
3882	538/004	"	Inefficacy
3863	537/004	"	Personal convenience

4) Efficacy: See table below, with the results of parent daily evaluation, where PDS = percentage of days with symptoms; PDS = 0 is the percentage of days when the highest score or any of the symptoms was 0; PDS = 1 or less, is the percentage of days when the maximal symptom was 1 or less; PDS = 2 or less, is the percentage of days when the maximal symptom was 2 or less; the primary efficacy variable was PDS = 1 or less. There was no statistically significant difference between mean values for placebo and cetirizine in regard to any of these variables.

There was no consistent trend which favored cetirizine over placebo as can be seen by the table below. Neither investigator visit or global evaluation showed any significant difference between placebo and cetirizine. Therefore, this study can not be used to support a claim for effectiveness of cetirizine in children who have PAR.

Mean symptom score at the visits

	Placebo					Cetirizine				
	Sn	Rh	BN	NP	OP	Sn	Rh	BN	NP	OP
Visit 1	1.74	2.06	2.49	1.14	0.49	1.91	2.09	2.33	1.30	0.72
Visit 2	0.90	1.11	1.48	0.52	0.19	0.91	1.17	1.42	0.62	0.29
Visit 3	0.63	0.96	1.16	0.34	0.18	0.61	0.89	1.15	0.46	0.18
$V_1 - V_2$	0.84	0.94	1.03	0.62	0.31	1.00	0.92	0.89	0.68	0.44
$V_1 - V_3$	1.13	1.09	1.31	0.79	0.30	1.31	1.20	1.15	0.89	0.51

Sn = sneezing
Rh = rhinorrhea
BN = blocked nose
NP = nasal pruritus
OP = ocular pruritus

5) Safety:

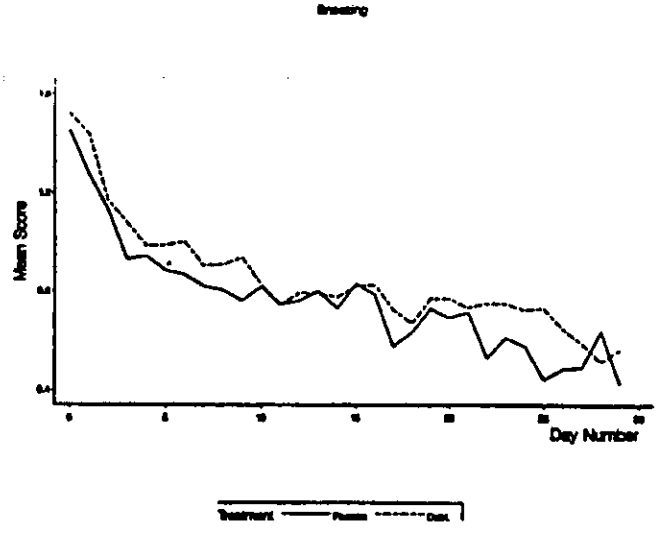
✦ adverse events: see table below; 20 patients in each group reported adverse events; there were 36 AR reports in the placebo group and 41 AR reports in the cetirizine group; 3 placebo and 2 cetirizine patients were withdrawn because of an adverse event; withdrawals in the cetirizine group were due to fever and respiratory infection; there were 2 serious AEs, both in cetirizine patients, Henoch-Schonlein syndrome and respiratory infection requiring hospitalization; in both these cases of serious AEs, a relationship to cetirizine was considered unlikely.

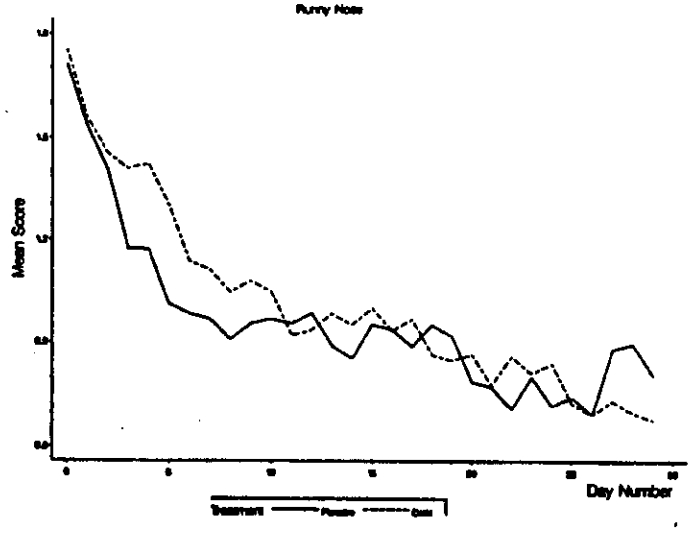
Incidence of Adverse Events
Number of patients and (%)

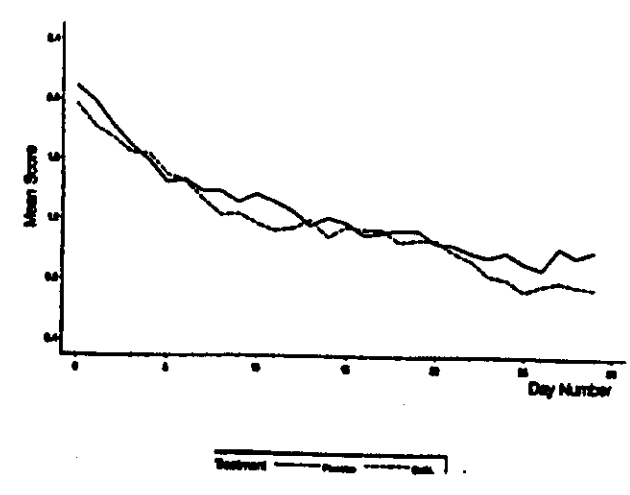
Printed as Body-system/COSTART term	Placebo (n = 70)	Cetirizine (n = 67)
Body as a whole		
Face edema	1 (1.4)	
Fever	2 (2.9)	
Flu syndrome		5 (7.5)
Headache		2 (3.0)
Hostility	1 (1.4)	1 (1.5)
Infection	1 (1.4)	
Pain	2 (2.9)	4 (6.0)
Abdominal pain	1 (1.4)	
		2 (3.0)
Digestive system		
Anorexia	1 (1.4)	
Diarrhea		1 (1.5)
Gastrointestinal disorder		1 (1.5)
Melena	1 (1.4)	
Aphthous stomatitis	1 (1.4)	
Thirst	1 (1.4)	
Vomiting	2 (2.9)	
Hemic and lymphatic system		
Purpura		1 (1.5)
Metabolic and Nutritional Disorders		
Thirst	1 (1.4)	
Nervous system		
Dizziness	1 (1.4)	
Hostility	1 (1.4)	
Hyperkinesia	1 (1.4)	
Somnolence	2 (2.9)	1 (1.5)
Respiratory system		
Asthma	4 (5.7)	4 (6.0)
Bronchitis	2 (2.9)	2 (3.0)
Cough Increased	2 (2.9)	7 (10.4)
Epistaxis	2 (2.9)	
Rhinitis	1 (1.4)	3 (4.5)
Skin and appendages		
Eczema	2 (2.9)	1 (1.5)
Furunculosis		1 (1.5)
Vesiculobullous rash	1 (1.4)	
Sweating		1 (1.5)
Special senses		
Otitis externa	1 (1.4)	
Otitis media	1 (1.4)	3 (4.5)
Abnormal vision		1 (1.5)
Total :	36	41

✦ **laboratory data: no significant changes in laboratory tests were reported.**

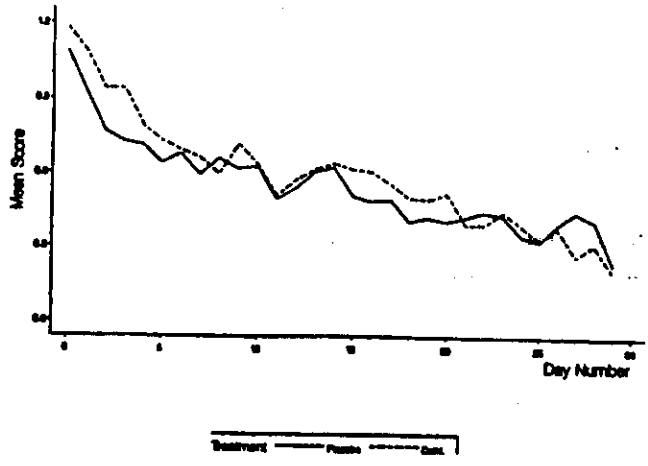
CONCLUSIONS: As can be seen in the figures below, based on mean symptom scores, there was a consistent decrease in the mean score for individual symptoms and for the maximal score for all five symptoms in both treatment groups. There was, however, no significant difference between the two treatment groups, using either an ITT analysis or analysis where 23 patients with major protocol deviations were excluded. There was clearly a strong placebo response. Therefore, this study can not be used to support the efficacy of cetirizine in children with perennial allergic rhinitis. No safety concerns were raised based on AEs and laboratory data from this study.



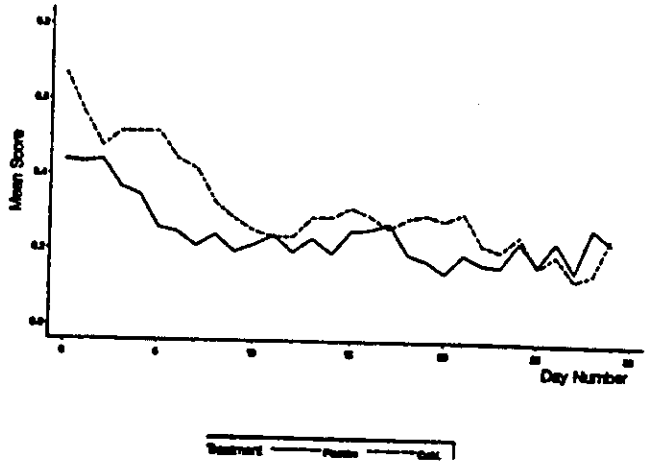




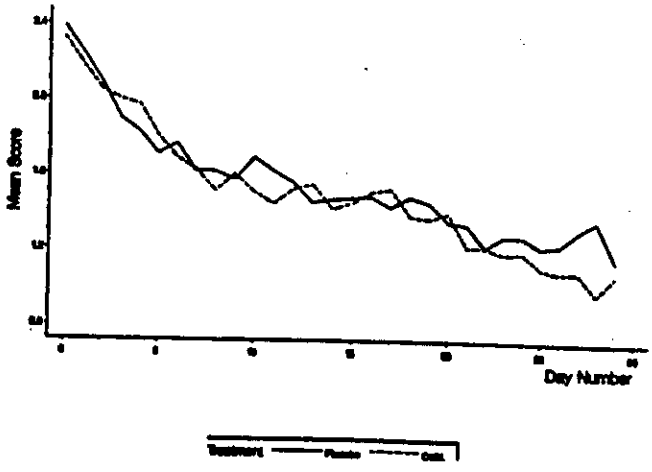
Itchy Nose



Itchy Eyes



Nasal Sx – Symptom Score



2. STUDY UCB-126: Single center study in France

a. Study Characteristics:

1) number of patients: 36 entered; 17 patients received cetirizine, and 19 received placebo

2) age range: 4-16 years

3) patient population: perennial allergic rhinitis; 4 day washout for all medications except ketotifen and corticosteroids, for which the washout was 15 days

4) study design: placebo-controlled, double-blind, repetitive dose, parallel study

5) drug administration: 10 mg/ml solution administered by dropper; 0.5 mg per drop; administered once a day in evening; 2.5 mg (5 drops) if < 20 kg; 5 mg if 20-35 kg; 7.5 mg if 35-50 kg; and 10 mg if > 50 kg; rescue medication was mequitazine

6) periods of study: 1 week of treatment

7) parameters evaluated:

- ✦ investigator assessment after 1 week of treatment; categorical scale for symptoms of nasal obstruction, rhinorrhea, conjunctivitis, sneezing using a 4 point scale (0 = absent, 1 = slight, 2 = moderate, and 3 = severe)

- ✦ investigator assessment using an analog scale between very bad and excellent

- ✦ global evaluation by investigator

- ✦ global evaluation by patient
- ✦ adverse events

b. Study Results:

1) Demographics: comparable between the two groups, except that IgE levels were substantially higher in the cetirizine group than in the placebo group. The effect, if any, that this difference might have on the study results is unclear, since both allergic and non-allergic rhinitis will respond to antihistamines.

2) Efficacy: There was a significant difference in terms of mean symptom scores between cetirizine and placebo only for nasal congestion ($p = 0.04$)(see table below). There was also no significant difference between the two groups in terms of individual patient improvement, except for nasal congestion, where 13/17 cetirizine and 11/19 placebo patients-improved. There was no statistically significant difference between the two groups in terms of either investigator or patient global analysis. The lack of difference between the two treatment groups was primarily due to the large placebo effect that was seen.

Symptoms after treatment

Variables	Cetirizine group (6 girls + 11 boys) n	mean	sd	Placebo group (8 girls + 11 boys) n	mean	sd	p value
Nasal obstruction	17	0.94	0.43	19	1.26	0.45	0.04
Rhinorrhea	17	0.88	0.86	19	1.05	0.85	0.55
Conjunctivitis	17	0.29	0.47	19	0.42	0.51	0.46
Sneezing	17	0.94	0.66	19	1.21	0.86	0.31
Patient's condition	17	55.53	15.1	19	52.47	12.38	0.46

3) Safety: No adverse events were noted in either treatment group.

CONCLUSION: This study can not be used to support a claim for the efficacy of cetirizine in children with PAR since cetirizine was only superior to placebo in terms of nasal congestion. The safety of cetirizine in patients 4-16 years of age who received 2.5-10 mg per day is supported by this study, based on assessment of adverse events.

ABSTRACT
STUDIES OF SEASONAL ALLERGIC RHINITIS

Background: There were two studies performed in children 2-6 years of age with seasonal allergic rhinitis, studies 89 and 125. Data on 54 patients in study 89 and 37 patients in study 125 were analyzed for efficacy.

Methods: Study 89 was a double-blind, placebo-controlled, parallel study with treatment for 2 weeks, while study 125 was a double-blind, active-treatment controlled, parallel study with 4 weeks of randomized treatment. The dose of cetirizine was 5 mg given once a day in study 89 and 2.5 mg bid in study 125, both given as a 10 mg/ml solution.

Both studies evaluated efficacy based on parent and investigator assessment of symptoms and global evaluation by the investigator, but in study 125, inhibition of histamine-induced wheal formation and nasal eosinophil counts were also evaluated as outcome measures. Safety assessment was limited to adverse events in both studies and laboratory tests in study 89.

Results and discussion: The efficacy of cetirizine was demonstrated in both studies. Unfortunately, the results from study 125 are less compelling because there was no placebo control in that study. Evidence of efficacy in the group which received cetirizine was demonstrated after one week of treatment in study 89. Therefore, this 2 week study is adequate to support a claim for efficacy of cetirizine in the treatment of seasonal allergic rhinitis.

Evaluation of safety in these studies was based primarily on adverse events. On the basis of this limited evaluation of safety, no safety concerns were raised by these studies. However, any statement about the safety of cetirizine in the treatment of seasonal allergic rhinitis must be qualified by acknowledging that neither ECGs or vital sign measurements were included in these studies.

In summary, the efficacy of cetirizine was demonstrated in study 89 in 54 patients 2-6 years of age with seasonal allergic rhinitis. The studies submitted by the sponsor are not ideal because of: 1) the relatively small number of patients; 2) the lack of a placebo control in study 125; and 3) the relatively short duration of study 89. Nevertheless, the data is sufficient to support a claim for efficacy. The safety of cetirizine in this patient population, on the other hand, has not been adequately evaluated in these studies.

C. SEASONAL ALLERGIC RHINITIS (SAR):

1. Study UCB 89 (Germany, Belgium, France, Italy):

a. Study Characteristics:

1) number of patients: 107 patients recruited; 107 entered into the study; 106 included in the analysis of efficacy (54 cetirizine patients and 52 placebo patients)

2) age range: 2-6 years (1 patient in the placebo group was 1 year 9 months of age and not included in the analysis)(see table below for distribution by age)

Distribution of patients according to age

AGE	GROUP	
(years)	Cetirizine	Placebo
< 2	-	1 *
2	3	4
3	4	9
4	11	10
5	27	22
6	9	7

3) patient population: SAR; at least 3/5 symptoms (sneezing, rhinorrhea, nasal congestion, nasal pruritus, and ocular pruritus); severity of total symptoms of 6 or greater based on 4 point scale for each symptom (0-3) with 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

4) study design: multicenter, double-blind, placebo-controlled, parallel, randomized, repetitive dose study

5) drug administration: 5 mg cetirizine (10 mg/ml solution given as drops) given with evening meal; 1 ml = 20 drops (5 mg = 10 drops)

6) periods of study: 2 weeks of randomized treatment; there were 3 visits, the baseline visit, and visits after 1 and 2 weeks of treatment

7) parameters evaluated:

EFFICACY

a) parent evaluation (diary cards): sneezing, rhinorrhea, nasal congestion, itching nose, itching eyes; 4 point scale (0-3); percentage of days during which no symptom scored more than mild (score 0 or 1); 0 = none, 1 = mild, 2 = severe, and 3 = unbearable

b) investigator evaluation: comparison of baseline score with score after 1 and 2 weeks of treatment; sneezing, rhinorrhea, nasal congestion, itching nose, itching eyes; 4 point scale (0-3).

c) global evaluation by investigator: at the end of treatment; 5 point scale (0-4)

SAFETY

a) laboratory tests: prior to the study and at its conclusion

b) adverse events

b. Study Results:

1) protocol violations; 6 cetirizine and 2 placebo patients; the study results were not influenced by these protocol violations.

2) demographics: the two study groups were comparable; baseline severity of symptoms was comparable.

EFFICACY

3) percentage of days where no symptoms > 1: 57% of the cetirizine group and 36% of the placebo group (p = 0.002)

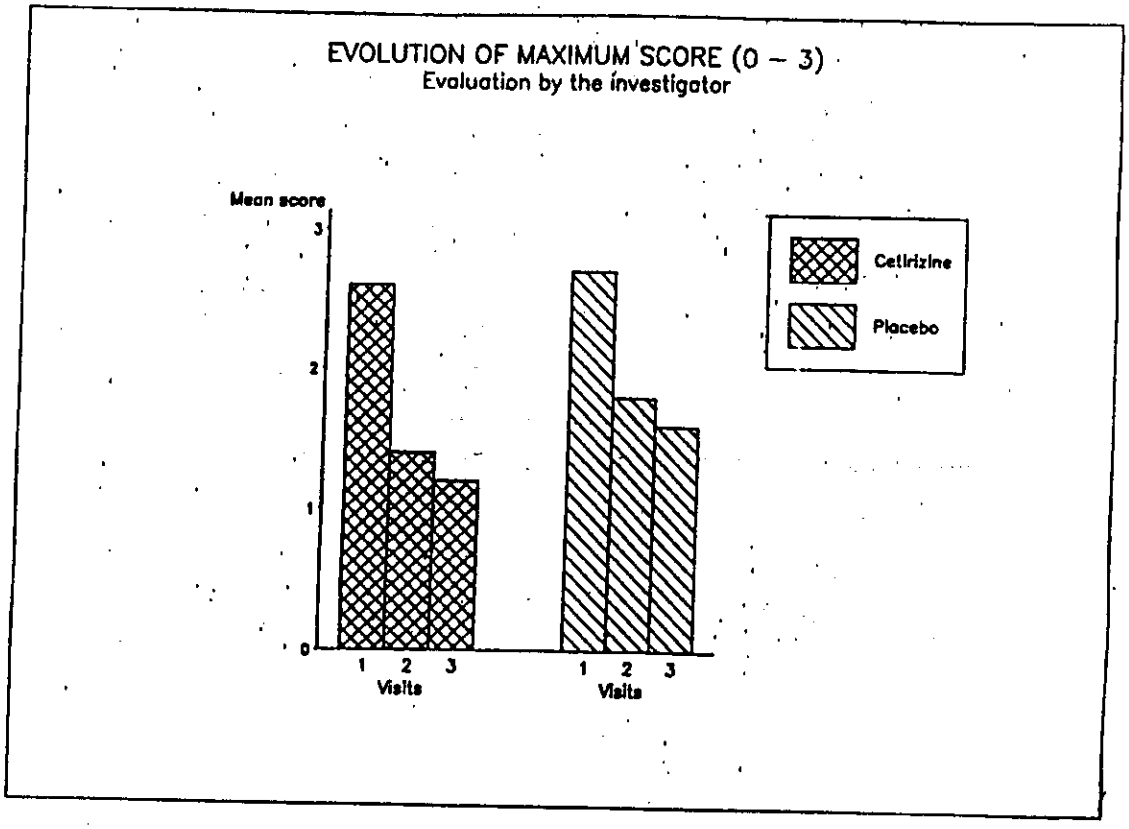
4) days without any symptoms: 10% of study days in the cetirizine group and 4% of study days in the placebo group (p = 0.008)

5) investigator evaluation: mean maximal values for the five symptoms showed a statistically significant difference after 2 weeks of treatment (p = 0.04) and a strong trend after 1 week of treatment (p =0.06)(see table below)

Maximum score for all 5 symptoms

Visits	Cetirizine group			Placebo group			p*
	n	Mean	Standard deviation	n	Mean	Standard deviation	
V_1	54	2,6	0,5	53	2,7	0,5	
V_2	54	1,4	0,8	53	1,8	0,9	
V_3	53	1,2	0,9	53	1,6	0,9	
V_2-V_1	54	- 1,2	0,8	53	- 0,9	0,8	0,064
V_3-V_1	53	- 1,4	0,9	53	- 1,1	0,8	0,04

* p = prob/Ho : cetirizine = placebo (stratified Cochran-Mantal-Haenszel test)



6) Individual symptoms: There was greater improvement for all individual symptoms in the cetirizine group than in the placebo group when evaluated by parents as well as when evaluated by investigators (see tables below).

Evaluation of the daily cards (scale from 0 to 3)

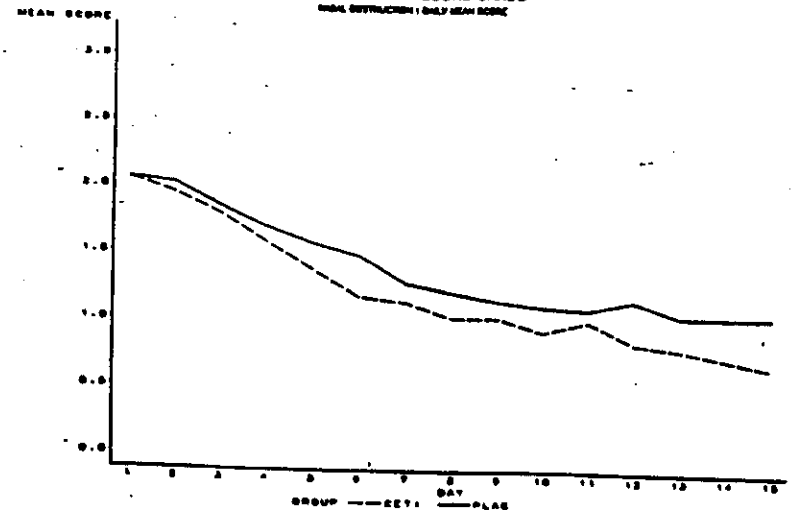
Evolution of the mean scores by symptom and by period

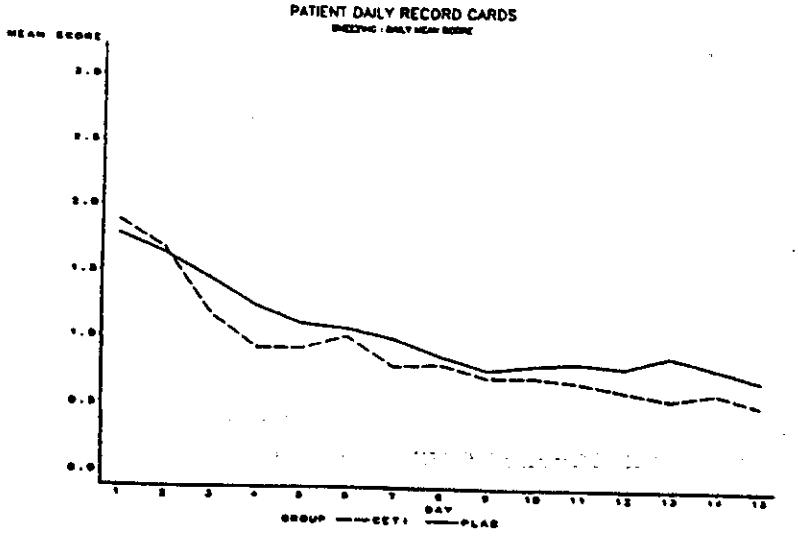
Symptom	Period	Cetirizine group			Placebo group		
		n	Mean	Standard deviation	n	Mean	Standard deviation
sneezing	1 - base	53	- 0,9	0,6	53	- 0,6	0,7
	2 - base	50	- 1,2	0,6	48	- 0,9	0,7
rhinorrhea	1 - base	53	- 0,7	0,7	53	- 0,6	0,7
	2 - base	50	- 1,2	0,8	48	- 1,0	0,7
nasal obstruction	1 - base	53	- 0,7	0,6	53	- 0,5	0,8
	2 - base	50	- 1,2	0,7	48	- 1,0	0,8
nasal pruritus	1 - base	53	- 0,8	0,6	53	- 0,5	0,6
	2 - base	50	- 1,1	0,8	48	- 0,9	0,8
ocular pruritus	1 - base	53	- 0,9	0,6	53	- 0,5	0,7
	2 - base	50	1,1	0,8	48	- 0,9	0,7

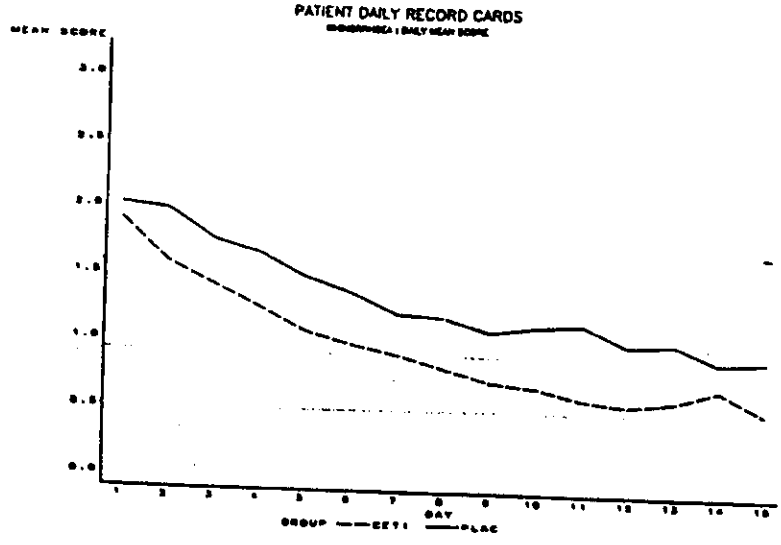
Evaluation of the symptoms by the investigator
mean score per symptom (scale from 0 to 3)

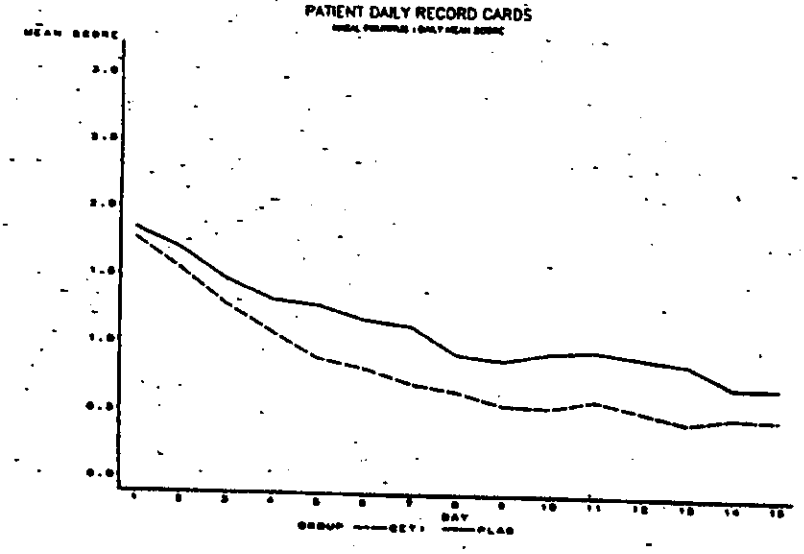
Symptom	Visits	Cetirizine group			Placebo group		
		n	Mean	Standard deviation	n	Mean	Standard deviation
Sneezing	V_1	54	1,9	0,7	53	1,8	0,9
	V_2	54	0,7	0,7	53	1,0	0,8
	V_3	53	0,5	0,7	53	0,9	0,9
	V_2-V_1	54	- 1,1	0,7	53	- 0,8	0,9
	V_3-V_1	53	- 1,3	0,8	53	- 0,9	1,0
rhinorrhea	V_1	54	2,0	0,9	53	2,2	0,6
	V_2	54	0,9	0,8	53	1,4	0,9
	V_3	53	0,7	0,9	53	1,1	1,0
	V_2-V_1	54	- 1,1	0,9	53	- 0,8	0,8
	V_3-V_1	53	- 1,3	1,1	53	- 1,1	1,0
nasal obstruction	V_1	54	2,2	0,9	53	2,2	0,8
	V_2	54	1,1	0,8	53	1,3	1,0
	V_3	53	0,8	0,9	53	1,2	0,9
	V_2-V_1	54	- 1,1	1,0	53	- 0,9	0,9
	V_3-V_1	53	- 1,4	1,1	53	- 1,0	1,0
nasal pruritus	V_1	54	1,7	0,8	53	1,9	0,8
	V_2	54	0,6	0,7	53	1,1	0,9
	V_3	53	0,5	0,7	53	0,9	0,8
	V_2-V_1	54	- 1,1	0,8	53	- 0,8	0,9
	V_3-V_1	53	- 1,2	0,9	53	- 1,1	1,0
ocular pruritus	V_1	54	1,7	0,9	53	1,9	0,9
	V_2	54	0,6	0,8	53	1,0	1,0
	V_3	53	0,4	0,7	53	0,8	1,0
	V_2-V_1	54	- 1,1	1,0	53	- 0,9	0,9
	V_3-V_1	53	- 1,3	1,1	53	- 1,1	1,0

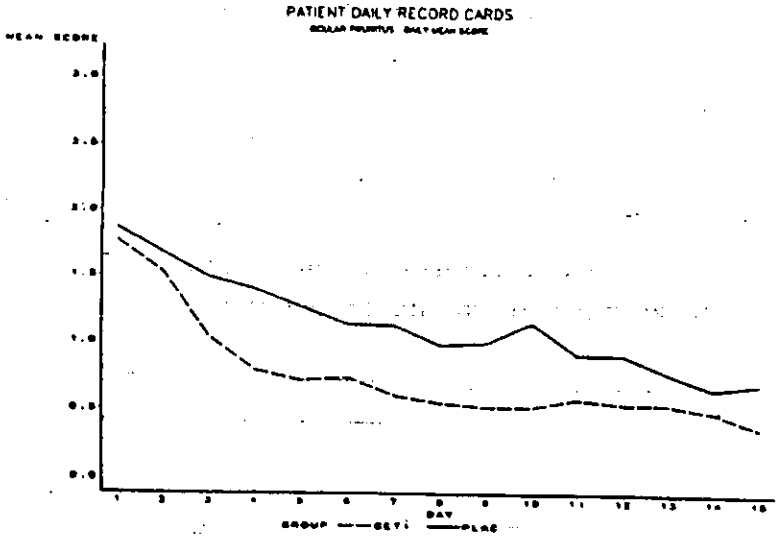
PATIENT DAILY RECORD CARDS











7) <u>global evaluation</u>: 34 patients in the cetirizine group and 24 patients in the placebo group had good/excellent improvement in symptoms (p = 0.04)(see table below)

<u>Frequency distribution of evolutions on treatment</u>

Evolution	Score	Cetirizine group n = 54		Placebo group n = 53		p*
		n	%	n	%	
Aggravation	0	2	3,70	5	9,43	
Status quo	1	7	12,96	11	20,75	
Slight improvement	2	11	20,37	13	24,53	
Good improvement	3	20	37,04	16	30,19	
Excellent improvement	4	14	25.93	8	15,09	
	3 + 4	34	62,97	24	45,28	0,039

* p = prob/Ho : cetirizine = placebo (Cochran-Mantel-Haenszel test)

SAFETY

8) adverse events: reported by 13 patients in the cetirizine group and 11 patients in the placebo group ($p = 0.8$); 6 patients in the cetirizine group had AEs characterized as nervous system events, of which, 3 were mild somnolence; none of the AEs were considered severe. There were 2 patients who developed fever while receiving cetirizine and no placebo patients. No placebo patients developed somnolence.

9) laboratory tests: There were no significant changes in laboratory tests in the cetirizine group, that were not seen with greater frequency in the placebo group and/or at baseline.

MONITORING

10) pollen counts: The pollen counts were sufficiently high at all centers to have produced symptoms. The study results were not influenced by pollen counts.

c. COMMENTS:

1) There was a significant placebo effect in this study, despite reasonable high pollen counts at all sites. Despite this effect, cetirizine produced a statistically significantly greater degree of efficacy than placebo based on most efficacy parameters.

2) The onset of action of cetirizine is seen within the first 2-3 days for ocular pruritus and the overall improvement in symptoms in the cetirizine group is greater after one week of treatment than after two weeks of treatment in the placebo group.

3) There were 14 centers in the study, and 6 centers had only 1-2 patients. There is no indication in the data submitted about how these centers were handled, e.g. were the data from these centers combined and analyzed as one center, was the data analyzed excluding the patients from these centers ?

4) Based on a consistent statistically significant difference between the cetirizine and the placebo groups favoring cetirizine for all outcome variables, this study can be used to support a claim for the efficacy of cetirizine in patients 2-6 years of age with SAR. The failure to demonstrate a clinically significant difference between the two treatment groups is, in large part, due to the significant placebo effect seen in this study.

5) Based on the limited safety evaluation in this study, i.e. adverse events and laboratory testing, there were no safety issues raised by this study.

2. Study UCB 125: Belgium

a. Study Characteristics:

1) number of patients: 39 patients were randomized to receive treatment with cetirizine and 37 patients were randomized to receive treatment with oxatamide (ITT population); all patients were considered valid since violations of the study protocol were not considered serious and, according to the sponsor, did not warrant exclusion of these patients from the valid patient analysis. For 5 patients, the sponsor states that data were partially disregarded in the valid patient population because of intake of prohibited medication (4 patients) and concomitant illness (1 patient). The sponsor does not indicate in which treatment arm these patients were entered.

2) age range: 3-6 years

3) patient population: SAR; 3/5 symptoms (sneezing, rhinorrhea, nasal congestion, nasal pruritus, ocular symptoms) at baseline; total symptom score at least 6 at baseline

4) study design: active-treatment controlled, multicenter, double-blind, double dummy, parallel, randomized, repetitive dose study

5) drug administration: cetirizine 5 mg daily (2.5 mg bid)(5 drops bid)(solution of 10 mg/ml); oxatomide 15 mg daily (7.5 mg bid)(3 ml bid)(solution of 2.5 mg/ml)

6) study periods: 4 weeks of randomized treatment; there were 3 visits; baseline and after 2 (visit 2) and 4 weeks (visit 3) of treatment

7) parameters evaluated:

EFFICACY: Evaluation of efficacy was based primarily on the intent-to-treat population with evaluation from baseline to the last available observation.

a) inhibition of histamine-induced wheals: comparing wheal size at baseline to wheal size after 4 weeks of treatment

b) investigator assessment of symptoms: 4 point scale (0-3); 0 = none, 1 = slight, 2 = moderate, and 3 = serious; at baseline and after 2 and 4 weeks of treatment; the change between baseline and the end of treatment for each of the five symptoms (sneezing, rhinorrhea, nasal congestion, nasal pruritus, and ocular symptoms) and for total symptoms was evaluated as well as change from baseline after 2 weeks of treatment

c) global evaluation by investigator: visual analogue scale 0-100 mm analyzing change from baseline after 4 weeks of treatment; this is the primary efficacy variable

d) nasal brushings for cell counts: at baseline and after 4 weeks of treatment

e) parent assessment of symptoms: 4 point scale (0-3) using same categories as investigator; based on daily diary card; percentage of days with maximal symptom score of 0 (days without symptoms), percentage of days with maximal symptom score of 1 or 0, and percentage of days with maximal symptom score of 2 or less; these evaluations were made for the entire 4 week treatment period as well as each 2 week period; assessment was made once daily; use of rescue medication was also assessed.

SAFETY

a) adverse events

b. Study Results:

1) Patient population: After 4 weeks of treatment, 2 of the cetirizine and 1 of the oxatomide patients were not evaluated, i.e. at visit 3, there were 37 cetirizine and 36 oxatomide patients that were evaluated. The demographics of the two groups were similar except that there were more males in the cetirizine group (67% males) and more females in the oxatomide group (60% females).

2) efficacy:

a) global evaluation: There was improvement in both groups after 2 weeks of treatment which persisted at 4 weeks of treatment. No difference was seen between the two treatment groups (see table below, where treatment A is cetirizine and treatment B is oxatomide).

TABLE 18: VAS ASSESSMENT OF THE GLOBAL NASAL CONDITION
Intention to Treat Population

	Treatment A (N = 39)	Treatment B (N = 37)
Baseline		
Mean	2.92	3.10
Median	3.10	3.10
St. Dev.	1.29	0.99
Minimum		
Maximum		
Number	39	37
Visit 2		
Mean	6.19	6.14
Median	6.50	6.00
St. Dev.	1.81	1.94
Minimum		
Maximum		
Number	39	37
Visit 3		
Mean	7.14	7.10
Median	7.65	7.45
St. Dev.	2.27	2.25
Minimum		
Maximum		
Number	36	36
Last visit		
Mean	6.96	7.02
Median	7.60	7.40
St. Dev.	2.32	2.27
Minimum		
Maximum		
Number	39	37

b) parent assessment in daily diary: see table below. There was no significant difference between the two treatment groups in regard to percentage of days without symptoms, percentage of days with none or slight symptoms or percentage of days without serious symptoms. The use of rescue medication was comparable between the two groups, although there was slightly less rescue medication use in the cetirizine group which, as can be seen in the table above, had a slightly greater reduction in symptoms.

TABLE 21: DRC - WORST SYMPTOM - ENTIRE TREATMENT PERIOD
Intention to Treat Population

	Treatment A (N = 39)	Treatment B (N = 37)
Percentage of days without symptoms		
Mean	11.6	13.7
Median	0.0	3.6
St. Dev.	18.8	20.7
Minimum		
Maximum		
Number	39	37
Percentage of days with no or slight symptoms		
Mean	50.3	53.2
Median	63.0	53.8
St. Dev.	35.7	28.8
Minimum		
Maximum		
Number	39	37
Percentage of days without serious symptoms		
Mean	86.4	87.0
Median	96.3	92.9
St. Dev.	21.9	18.6
Minimum		
Maximum		
Number	39	37

RESULTS OF THE COMPARISON

Mann-Whitney test

No symptoms:	p = 0.506
No or slight symptoms:	p = 0.868
No serious symptoms:	p = 0.638

c) Investigator assessment: There was no statistically significant difference between the two treatment groups for any of the symptoms of rhinitis. There was no statistically significant difference between the two treatment groups in regard to total symptom score (see table below).

TABLE 30: EVOLUTION OF SYMPTOMS OF RHINITIS/CONJUNCTIVITIS
TOTAL SYMPTOM SCORE
Intention to Treat Population

	Treatment A (N = 39)	Treatment B (N = 37)
Baseline		
Mean	9.49	9.59
Median	9.00	10.00
St. Dev.	2.25	2.05
Minimum		
Maximum		
Number	39	37
Visit 2		
Mean	4.10	3.89
Median	4.00	4.00
St. Dev.	2.52	2.08
Minimum		
Maximum		
Number	39	37
Visit 3		
Mean	3.06	3.36
Median	3.00	3.00
St. Dev.	2.60	2.84
Minimum		
Maximum		
Number	36	36
Missing	3	1
Last visit		
Mean	3.26	3.38
Median	3.00	3.00
St. Dev.	2.68	2.80
Minimum		
Maximum		
Number	39	37

RESULTS OF THE COMPARISON

Cochran-Mantel-Haenszel test of the effect of treatment stratified for the baseline value

Visit 2:	p = 0.912
Visit 3:	p = 0.230
Last visit:	p = 0.344

d) skin test response: Wheal size (presumably in mm, although this is not stated) was measured at visits 1 and 3 after epicutaneous injection of 1 mg/ml of histamine phosphate. A greater decrease in mean wheal size was seen in the group which received cetirizine than in the group which received oxatomide, although the mean change in both groups was not statistically significant.

3) safety:

a) Adverse events: see tables below; Treatment A is cetirizine and treatment B is oxatomide; there were no significant adverse events in the cetirizine group.

TABLE 31: ADVERSE EVENTS
Intention to Treat Population

	Treatment A (N = 39)	Treatment B (N = 37)
Adverse events reported		
No	27 (69.2%)	24 (64.9%)
Yes	12 (30.8%)	13 (35.1%)
Adverse events reported with relationship code 'possible', 'very likely', or 'yes'		
No	37 (94.9%)	34 (91.9%)
Yes	2 (5.1%)	3 (8.1%)
Number of adverse events reported		
0	27 (69.2%)	24 (64.9%)
1	9 (23.1%)	9 (24.3%)
2	2 (5.1%)	3 (8.1%)
3	1 (2.6%)	1 (2.7%)

RESULTS OF THE COMPARISON

Adverse events reported:	p = 0.872 *
Adverse events reported with relationship code 'possible', 'very likely', or 'yes':	p = 0.671 +

* = chi-square test
\+ = Fisher Exact test

TABLE 32: ADVERSE EVENTS BROKEN DOWN BY WHO SYSTEM-ORGAN CLASS
Intention to Treat Population

SYSTEM-ORGAN CLASS	Treatment A (N = 39)	Treatment B (N = 37)
CENTRAL & PERIPHERAL NERVOUS SYSTEM	0 (0.0%)	2 (5.4%)
AUTONOMIC NERVOUS SYSTEM	2 (5.1%)	1 (2.7%)
VISION DISORDERS	1 (2.6%)	2 (5.4%)
PSYCHIATRIC DISORDERS	0 (0.0%)	3 (8.1%)
GASTRO-INTESTINAL SYSTEM	4 (10.3%)	2 (5.4%)
RESPIRATORY SYSTEM	10 (25.6%)	7 (18.9%)
PLATELET, BLEEDING & CLOTTING DISORDERS	0 (0.0%)	1 (2.7%)
URINARY SYSTEM	0 (0.0%)	1 (2.7%)
BODY AS A WHOLE	4 (10.3%)	2 (5.4%)
RESISTANCE MECHANISM DISORDERS	7 (17.9%)	10 (27.0%)

e) nasal eosinophils: the mean percentage of eosinophils in the nasal smear cytology at baseline was significantly higher in the group which received cetirizine, which probably accounts for the significantly greater decrease seen after treatment in this group as compared with the oxatomide group.

c. Conclusions: Cetirizine was shown to be as effective as oxatomide, based on all of the outcome variables in this study. There was no placebo control, however. Therefore, this study can not be used to demonstrate conclusively the efficacy of cetirizine. There were no safety concerns raised by this study, although the only parameter analyzed was adverse events.

STUDIES IN CHILDREN LESS THAN 2 YEARS OF AGE

The sponsor has submitted the statistical report of one European PK study (study 123) of a single oral administration of cetirizine at a dose of 0.25 mg/kg (concentration of 10 mg/ml) fasting in infants between the age of 6 months and 2 years. This was an open study in 15 hospitalized patients at two centers who had plasma levels obtained at 30, 60, 90, 120 minutes and 4, 6, 8, 12 and 24 hours. There were 3 patients who experienced a single adverse event, which were "sleepiness", vomiting, and irritability. There were no ECG changes and no significant changes in laboratory tests that were not already present before drug administration. No PK data is provided.

The sponsor has also submitted the report of an European study evaluating the frequency and duration of sleep apnea in 28 allergic infants, 6-24 months of age. This double-blind, crossover, placebo-controlled study utilized a dose of 0.25 mg/kg of cetirizine, at a concentration of 10 mg/ml. There were two patients who experienced adverse events while receiving or after receiving cetirizine, neither of which were considered related to the drug, gastroenteritis and rhinopharyngitis. No significant differences were seen in parameters of sleep apnea.

PUBLICATIONS IN PATIENTS LESS THAN 6 YEARS OF AGE

I. International Journal of Clinical Pharmacology and Therapeutics. 1995; 33:340: Eight children received a single oral dose of 5 mg of cetirizine as a 10 mg/ml solution before a minor surgical proceedure (See review of study 120).

II. Drug Investigations 1992; 4:466: This was a multicenter, double-blind, parallel placebo-controlled study in 138 patients 2-14 years of age with perennial allergic rhinitis who received 2.5 or 5 mg bid over a period of 2 weeks. Patients receiving 10 mg of cetirizine per day had a signficantly greater improvement in symptoms of PAR than patients who received placebo ($p = 0.03$), when assessed by investigators, but not by parents. There was no

statistically significant difference between 5 mg/day of cetirizine and placebo. There were 5 patients who developed sleepiness while receiving cetirizine, compared to 3 placebo patients. No clinically significant changes in laboratory tests were noted.

III. Clin Pharmacol Ther 1993; 53:431: This study done in Belgium was a PK study in 8 patients 2-4 years of age hospitalized with suspected allergic respiratory problems or recurrent respiratory tract infections who had plasma levels measured for up to 24 hours after drug administration. The data supported the conclusion that cetirizine was metabolized faster in young children than in adults (see review of study 122).

IV. Pediatric Allergy and Immunology 1993; 40:157: This European study was performed in 107 patients 2-6 years of age with SAR using a double-blind, parallel, placebo controlled study design. Patients received 5 mg per day of cetirizine or placebo over a period of 2 weeks (see review of study 89).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-835/S005
20-346/S002

CHEMISTRY REVIEW(S)

FEB 7 1998

CHEMIST'S REVIEW

1. ORGANIZATION
HFD-570 DPDP

2. NDA NUMBER
20-346
19-835

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Pfizer Inc.
235 East 42nd Street
New York, NY 10017-5755

4. AF NUMBER

5. SUPPLEMENT(S)
NUMBER(S) DATES(S)
SE1-002 (N20-346) 1/16/98*
SE1-005 (N19-835) 1/16/98*

*Subjects of this review.

6. NAME OF DRUG
Zyrtec® Syrup
Zyrtec® Tablets

7. NONPROPRIETARY NAME
cetirizine HCl syrup and tablets

8. SUPPLEMENT PROVIDES FOR: The supplement provides information in support of the use of cetirizine HCl in children ages 2-5 years old for the indication of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria. The supplement provides updated labeling and an Environmental Assessment.

9. AMENDMENT(S), REPORT(S), ETC.

10. PHARMACOLOGICAL CATEGORY
antihistamine

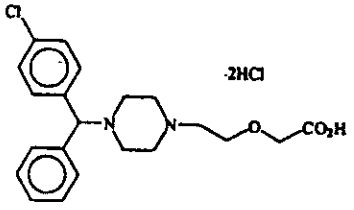
11. HOW DISPENSED
RX X OTC

12. RELATED IND/NDA/DMF
IND
IND
DMF

13. DOSAGE FORM(S)
syrup and tablets

14. POTENCY
5 mg/5 mL (syrup)
5 and 10 mg tablets

CHEMICAL NAME AND STRUCTURE



(±)-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetic acid or (±)-[2-[4-(*p*-Chlorophenybenzyl)-1-piperazinyl]ethoxy]acetic acid

16. RECORDS AND REPORTS
CURRENT YES__NO
REVIEWED YES__NO

17. COMMENTS: No changes were made to the HOW SUPPLIED or the DESCRIPTION sections of the PI. Pfizer claims a categorical exclusion to the environmental assessment analysis requirements as per 21 CFR 25.15 (a), (d).

cc:
Orig. NDA 20-346
HFD-570/div. File
HFD-570/CBertha/2/5/98
HFD-570/GPoochikian
HFD-570/GTrout
R/D Init. by: 2/7/98
F/T by: CBertha/2/5/98
doc # 98-02-05.rev.doc

18. CONCLUSIONS AND RECOMMENDATIONS: In terms of the CMC related information provided in the Environmental Assessment and in the HOW SUPPLIED and DESCRIPTION sections of the labeling, it is recommended that the supplemental application be approved.

19. REVIEWER NAME:
Craig M. Bertha, Ph.D.

SIGNATURE
/S/

DATE COMPLETED
2/5/98

FEB 7 1998

CHEMIST'S REVIEW

1. ORGANIZATION	2. NDA NUMBER
HFD-570 DPDP	20-346 19-835

3. NAME AND ADDRESS OF APPLICANT *(City and State)*	4. AF NUMBER
Pfizer Inc. 235 East 42nd Street New York, NY 10017-5755	

5. SUPPLEMENT(S) NUMBER(S)	DATES(S)
SE1-002 (N20-346)	1/16/98*
SE1-005 (N19-835)	1/16/98*

*Subjects of this review.

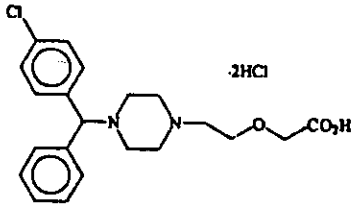
6. NAME OF DRUG	7. NONPROPRIETARY NAME
Zyrtec® Syrup Zyrtec® Tablets	cetirizine HCl syrup and tablets

8. SUPPLEMENT PROVIDES FOR: The supplement provides information in support of the use of cetirizine HCl in children ages 2-5 years old for the indication of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria. The supplement provides updated labeling and an Environmental Assessment.

9. AMENDMENT(S), REPORT(S), ETC.

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
antihistamine	RX X OTC	IND IND DMF
13. DOSAGE FORM(S)	14. POTENCY	
syrup and tablets	5 mg/5 mL (syrup) 5 and 10 mg tablets	

CHEMICAL NAME AND STRUCTURE



(±)-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetic acid or (±)-[2-[4-(p-Chlorophenybenzyl)-1-piperazinyl]ethoxy]acetic acid

16. RECORDS AND REPORTS
CURRENT YES__NO
REVIEWED YES__NO

17. COMMENTS: No changes were made to the HOW SUPPLIED or the DESCRIPTION sections of the PI. Pfizer claims a categorical exclusion to the environmental assessment analysis requirements as per 21 CFR 25.15 (a), (d).

cc:
Orig. NDA 20-346
HFD-570/div. File
HFD-570/CBertha/2/5/98
HFD-570/GPoochikian
HFD-570/GTrout
R/D Init. by: CB 2/7/98
F/T by: CBertha/2/5/98
doc # 98-02-05.rev.doc

18. CONCLUSIONS AND RECOMMENDATIONS: In terms of the CMC related information provided in the Environmental Assessment and in the HOW SUPPLIED and DESCRIPTION sections of the labeling, it is recommended that the supplemental application be approved.

19. REVIEWER NAME:	SIGNATURE	DATE COMPLETED
Craig M. Bertha, Ph.D.	/S/	2/5/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-835/S005
20-346/S002

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

Zyrtec Pediatric Syrup

Claim for Categorical Exclusion According to 21 CFR Part 25.15 (a),(d)

Pfizer Inc claims a categorical exclusion to the environmental analysis requirements in accordance with categorical exclusion criteria 21 CFR Part 25.31 (b): Action on a supplement to NDA; the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. Pfizer Inc claims that to the best of our knowledge no extraordinary circumstances exist.

Preparers:

Jon F. Ericson, Senior Research Scientist, Environmental Sciences Department, Pfizer Central Research Process Research and Development Department. Analytical Chemist with M.S. and 11 years experience in drug metabolism and environmental science.

Patrick Conley, Manager, Process Research and Development, Pfizer Central Research. Chemical Engineer with B.S. in Chemical Engineering and 18 years experience with Pfizer's Production and Process Research and Development

The undersigned official states that the information presented is true, accurate, and complete to the best of Pfizer Inc's knowledge.

Name: Mr. Patrick Conley

Title: Manager, Process Research and Development

Department:
Process Research and Development

Pfizer Central Research Groton, CT
06340

Patrick Conley
Signature

Jan 5, 1998
Date

APPEARS THIS WAY
ON ORIGINAL

The following comment is a result of our review of the clinical pharmacology and biopharmaceutics sections of your supplements to NDA 19-835 (S-005) and NDA 20-346 (S-002) and is being sent to you for your future reference.

For study numbers UCB-122 and UCB-113, [redacted] assay method [redacted] for plasma and urinary cetirizine levels was used. The validation of the above [redacted] assay method is less than satisfactory. Ideally, for quality control of assay, at least three concentration points (instead of 1 or 2 points) should have been used for assessing the inter-day and intra-day variations. For general information on assay validation, please see *Pharmaceutical Research* 9:588-592, 1992.

If you have any questions, please contact me at (301) 827-1058.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

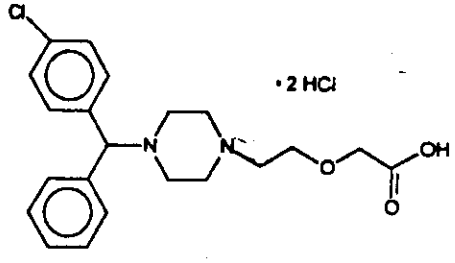
APPLICATION NUMBER: 19-835/S005
20-346/S002

PHARMACOLOGY REVIEW(S)

Trout

APR 20 1998

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

KEY WORDS:	Labeling	
Reviewer Name:	W. Mark Vogel, Ph.D.	
Division Name:	Division of Pulmonary Drug Products	
HFD#:	HFD-570	
Review Completion Date:	20 April, 1998	
Electronic File Number:	not applicable, entered into DFS	
NDA Number:	19-835	20-346
Serial Number:	SE1-005	SE1-002
Submission Date:	29 MAY 97	15 MAY 97
Submission Type:	Pediatric efficacy supplement	
Information to Sponsor:	Yes (✓), No ( )	
Sponsor or Agent:	Pfizer	
Drug: *Generic Name:*	cetirizine HCl	
Trade Name:	Zyrtec tablets (NDA 19-835) and Zyrtec syrup (NDA 20-346)	
CAS Registry Number:	cetirizine - 83881-51-0	cetirizine HCl -83881-52-1
Structure:		
Drug Class:	Antihistamine (H1 histamine antagonist)	
Indication:	Seasonal or perenial allergic rhinitis and chronic urticaria in adults and children aged 2 years and older.	
Route of Administration:	Oral	
Previous Reviews, Dates and Reviewers:	None for current submissions	
Original Preclinical reviews	NDA 19-835, D.H. Jean, 11 APR 1989	
	NDA 20-346, C.J. Sun, 07 DEC 1993	
Preclinical Labeling review:	NDA 20-346, W.M. Vogel, 27 MAR 1996	

Introduction/Drug History: Cetirizine is a human metabolite of hydroxyzine, which has been marketed for many years as an antihistamine and anti-anxiety agent. Zyrtec brand of cetirizine tablets was approved 08 DEC 1995. Zyrtec brand of cetirizine syrup was approved 27 SEP 1996. Both products are currently indicated for adults and children aged 6 years and older. The present submissions are pediatric efficacy supplements to expand the indications for both products to include children aged 2 years and older. No new preclinical data were submitted or requested to support this application. The most recent labeling review for cetirizine was for the syrup (NDA 20-346, by W.M. Vogel, 27 MAR 1996). There have been no substantial changes in the preclinical labeling since the

previous comprehensive labeling review. The present labeling review addresses minor changes in the labeling needed to conform to current Division style with respect to preclinical data as related to recommended doses in adults and children.

LABELING REVIEW

The maximum recommended dose for adults and children 12 years of age and older is 10 mg/day (10 mg/ 50 kg = 0.2 mg/kg). The maximum recommended pediatric doses are 10 mg/day for ages 6-11 years (10 mg/20 kg = 0.5 mg/kg) and 5 mg/day for ages 2-5 years (5 mg/ 12 kg = 0.42 mg/kg). The dose of 10 mg/day in 6 year old children is, thus, the maximum recommended dose in children and labeling calculations for children are based on that dose. Because that was the basis for calculations in the previously approved labeling for the syrup there are only minor changes due to rounding recommended in the safety margins calculated by the sponsor. Reviewer's calculations are attached on page 4, below. The recommended labeling includes safety margins for both adults and children where appropriate. Word order has been changed in several cases and dosage units have been changed from "mg/kg/day" to "mg/kg" to conform to current Division style.

The recommended revised labeling is indicated below:

RECOMMENDATIONS

1. The preclinical sections of the labeling should be revised to read as indicated on pages 2-3 above.

/S/ 20 April 1998
Mark Vogel, Ph.D., Pharmacologist

/S/ April 20, 1998

Original NDA 19-835
Original NDA 20-346
c.c. HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/W.M. Vogel
HFD-570/G. Trout

Preclinical labeling calculations are shown below:

Drug: **Zyrtec (cetirizine) tablets and syrup**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric	6	10	1	10	20	0.50	25	12.50
Adult	>12	10	1	10	50	0.20	37	7.40

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
rat	diet	20	6	120	16.2	9.6	15	10
mouse	diet	16	3	48	6.5	3.84	6	4
mouse	diet	4	3	12	1.6	0.96	2	1/1
extra			—	—	—	—	—	—
extra			—	—	—	—	—	—
Reproduction and Fertility:								
mouse	po	64	3	192	25.9	N/A	25	N/A
extra			—	—	—	N/A	—	N/A
extra			—	—	—	N/A	—	N/A
extra			—	—	—	N/A	—	N/A
Teratogenicity:								
mouse	po	96	3	288	38.9	N/A	40	N/A
rat	po	225	6	1350	182.4	N/A	180	N/A
rabbit	po	135	12	1620	218.9	N/A	220	N/A
extra			—	—	—	N/A	—	N/A
extra			—	—	—	N/A	—	N/A
Overdosage:								
mouse	po	237	3	711	96.1	56.88	95	55
rat	po	562	6	3372	455.7	269.76	460	270
extra			—	—	—	—	—	—
extra			—	—	—	—	—	—
Other:								
extra			—	—	—	—	—	—
extra			—	—	—	—	—	—
extra			—	—	—	—	—	—
extra			—	—	—	—	—	—
extra			—	—	—	—	—	—

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-835/S005
20-346/S002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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MAY - 8 1998

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	SUBMISSION DATE:
20-346 for cetirizine syrup (5 mg/5 ml)	05/15/97 (Serial No. SEI-002) 01/16/98 (Serial No. SEI-002 BL) 04/28/98 (Serial No. SEI-002 BZ)
19-835 for cetirizine tablets (5 and 10 mg)	04/25/95 05/29/97 (Serial No. SEI-005) 01/16/97 (Serial No. SEI-005 BL) 04/28/98 (Serial No. SEI-005 BZ)
BRAND NAME: Zyrtec	
SPONSOR: Pfizer	REVIEWER: Tien-Mien Chen, Ph.D.
TYPE OF SUBMISSION: Pediatric Supplement	Code: 3S

TITLE: "Review of Pediatric Supplement of Zyrtec Syrup For Children 2-5 Years Old"

SYNOPSIS:

Previously, Pfizer's Zyrtec (cetirizine) 5 and 10 mg tablets (NDA 19-835) for adult patients and children 12 years and older and Zyrtec syrup 5 mg/5 ml (NDA 20-346) for children 6-11 years old have been reviewed and approved by the agency on 12/08/95 and 09/27/96, respectively.

Cetirizine, an active metabolite of hydroxyzine, is an orally active and selective H_1-receptor antagonist. It is indicated for **1)** the relief of symptoms associated with seasonal or perennial allergic rhinitis due to allergens such as ragweed, grass and tree pollens and **2)** the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria. The recommended initial dose of Zyrtec for adults and children 12 years and older is 5 or 10 mg per day, depending on symptom severity and that for children 6-11 years old is 5 or 10 mg (1 or 2 teaspoons) QD, depending on symptom severity.

On 05/15/97, the sponsor submitted a pediatric supplement to NDA 20-346 for children 2-5 years old and on 05/29/97, the sponsor further requested to incorporate this pediatric information in NDA 19-835 for Zyrtec tablets. It is the sponsor's intent to incorporate this label information in the combined package insert (PI) for both Zyrtec syrup and tablets. On 01/06/98, the sponsor further submitted their revised PI (11/20/97 version) for review. For this pediatric supplement, the sponsor is seeking approval for a dosing regimen of _ mg syrup (teaspoon) QD or __ mg syrup (teaspoon) BID for children aged 2-5 years old.

Submitted under this pediatric supplement on 05/15/97 were 2 single-dose human pharmacokinetic/bioavailability (PK/Bio) studies, Nos. UCB-120 and UCB-122 in pediatric patients 2 to 5 years old. It was concluded in the previous reviews that in adults, the currently marketed tablet or syrup formulation was equally bioavailable to an oral solution (cetirizine powder in water; 1 mg/ml). However, both Study Nos. UCB-120 and UCB-122 used another oral solution (10 mg/ml; formulation code: 992) which was different from the currently marketed syrup formulation.

Study No. UCB-120 was conducted in 8 (5M+3F) pediatric patients 2 to 5 years old (at approximately 1.5 hr prior to a simple surgery). Their mean (± standard deviation; SD) age and body weight (BW) are 3.9 ± 1.2 years old and 16.4 ± 3.1 kg. Five mg of cetirizine (10 drops of the solution formulation, 10 mg/ml) was employed and the batch of the solution formulation used was No. 79. The study had been submitted previously on 05/12/95 and reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II) on 09/29/95. The assay for cetirizine plasma and urinary levels using an ... method was satisfactory and the study results were found acceptable. Study No. UCB-122 is a new study, therefore, it is reviewed here.

It is noted that in the telecons between the sponsor and HFD-570 on 07/09/97 and 07/14/97, the similarity/dissimilarity between the above oral solution (10 mg/ml, formulation code: 992) and the currently marketed syrup formulation was discussed. The sponsor indicated that there was no direct linkage between the above formulations (specifically the PK data in adults). It was concluded by HFD-570 at the end of the meeting that although the formulations are not the same, they are "similar enough" to support filing of the supplement. However, upon request during the Agency's review, the sponsor further submitted on 04/28/98 additional information on formulation comparisons including data obtained from a UCB study, No. 113 which was submitted on 04/25/95, but was not reviewed previously. Therefore, Study No. UCB-113 and the sponsor's rationale for expected similar PK performance between the syrup formulation and the oral solution (formulation code: 992) are also reviewed.

I. Study No. UCB-113:

This was a single-dose, open-label 2x2 crossover study with a washout period of 1 week. It was to investigate the equivalence of cetirizine drops (oral solution formulation code: 992) and tablets in 16 (14M+4F) healthy adult volunteers. A head-to-head comparison was made in this study between the oral solution (formulation code: 992) and a UCB tablet formulation (which is slightly different from the currently market one in the US, please see Attachment 1 for details). The subjects' mean (± SD) age and BW were 24.6 ± 1.0 years old and 67.7 ± 3.1 kg, respectively. After an overnight fasting, a dose (20 mg) of either 2 x 10 mg tablets or 40 drops of the oral solution was given with a glass of water on an empty stomach.

Venous blood (10 ml each) was collected at time zero (predose) and at 0.5, 1, 1.5, 2, 3, 5, 8, 12, 24, 36, and 48 hr postdose during each treatment phase. Plasma samples were harvested after centrifugation and stored at -18°C until assayed. Urine samples were also collected between 0-6, 6-12, 12-24, 24-48, and 48-72 hr postdose and an aliquot was taken and stored at -18°C until assayed. Plasma and urinary levels of cetirizine were analyzed using a _____ method which was developed by UCB (referred to J. Chromtogra. 430; 149-155, 1988). However, no assay validation report was submitted. Noncompartmental methods were used to obtain PK parameters.

The results of Study UCB-113 are summarized below in **Table 1**. The PK data show that compared to tablets, the oral solution (formulation code: 992) had **1)** slightly higher mean C_{max} (peak plasma level; 5%↑), but shorter T_{max} (time to C_{max}) and **2)** slightly lower AUC (area under the plasma concentration-time curve; 9%↓) and Ae_{0-72} (amount of the dose excreted unchanged in urine; 7%↓). The sponsor concluded that comparable plasma levels were obtained from the intrastudy comparisons except the T_{max}.

Table. 1 Mean (± SD) PK Parameters Obtained From 16 Healthy Volunteers Receiving a 20-mg Dose (Study No. UCB-113)

PK Parameters	2 x 10 mg Tablets	40 drops of an oral solution (10 mg/ml)
C_{max} (ng/ml)	782 ± 174	822 ± 179
T_{max} (hr)	1.09 ± 0.27	0.63 ± 0.22
AUC (ng-hr/ml)	7206 ± 505	6529 ± 421
Ae_{0-72} (% of dose)[a]	70.7 ± 7.8	65.8 ± 13.5

[a]. Amount of drug (in %) excreted unchanged in urine between 0-72 hr postdose.

Reviewer's Comments:

No detailed assay validation report was submitted. Upon request, the information on the compositions of the UCB tablet formulation was submitted on 05/11/98 for review by the sponsor.

II. Sponsor's Responses Submitted on 04/28/98 To The Agency's Requests:

On 04/28/98, the sponsor provided an interstudy comparisons of PK data (in adults) obtained from Study CPK-117 using the currently marketed syrup formulation and Study UCB-113 using the oral solution (formulation code: 992). The results of the interstudy comparisons are summarized below in **Table 2**:

Table 2. **Mean (± SD) PK Parameters Obtained From Adults Receiving the Currently Marketed Syrup and The Oral Solution (Formulation Code: 992)**

Parameters	Zyrtec Syrup (Study CKP-117; n=24)	Oral Solution (Study UCB-113; n=16)	p-Value
Age (yr)	25.0 (± 5.1)	24.6 (± 4.2)	0.829
Weight (kg)	76.7 (± 8.0)	67.8 (± 12.5)	0.009*
C_{max} (ng/ml)[a]	315 (± 61.3)	411 (± 89.4)	0.001*
C_{max} (ng/ml)[b]	342 (± 59.5)	389 (± 64.6)	0.021*
T_{max} (hr)	0.73 (± 0.44)	0.63 (± 0.22)	0.333
AUC (ng-hr/ml)[a]	2871 (± 498)	3264 (± 842)	0.107
AUC (ng-hr/ml)[b]	3115 (± 466)	3078 (± 565)	0.801
$T_{1/2}$ (hr)	9.98 (± 2.54)	8.57 (± 2.07)	0.073

[a]. Normalized to a 10-mg dose.
[b]. Normalized to a 10-mg dose and a BW of 70 kg.
*. Statistically significant ($p<0.05$).

The mean PK parameters obtained form the above interstudy comparison are comparable (after being normalized to dose and weight). The sponsor claimed that the above two formulations could be considered to be bioequivalent (BE). Since no statistical analysis using the Agency's acceptance criteria for assessing BE was provided, the sponsor's claim of BE between the above two formulations can not be verified.

III. Study No. UCB-122:

This was a single-dose, open-label study in 8 (5M+3F) pediatric patients 2 to 5 years old. Their mean (± SD) age and BW were 2.8 ± 0.5 years old and 15.0 ± 2.7 kg, respectively. Five mg of cetirizine (10 drops of the solution formulation, 10 mg/ml) was given under fasting conditions. The batch of the solution formulation used was No. 76.

Nine blood (between 3 to 4 ml) samples were drawn from each child at 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 hr postdose. Urinary samples (0-24 hr) were collected. After centrifugation, plasma was harvested and frozen to -20°C until assayed. An aliquot of urine sample was also stored frozen until assayed. In this study, a method with

was employed for the determination of cetirizine plasma or urinary levels. The above method is different from those used previously. The validation of assay method is summarized below:

The assay method was found less satisfactory. Noncompartmental methods were used for calculation of the PK parameters. The currently marketed syrup formulation and the oral solution formulation (Code: 992) are summarized in **Tables 3** and **4**:

Table 3: Currently Marketed Syrup Formulation (5mg/5ml)

Compositions	Amount (mg)
Cetirizine Dihydrochloride	5.00
Methylparaben, NF	
Propylparaben, NF	
Glacial Acetic Acid, USP	
Sodium Acetate	
Propylene Glycol, USP	
Glycerin, USP	
Purified Water, USP	
Sugar Syrup	
Grape Flavor	
Banana	

Table 4: The Oral Solution Formulation (10 mg/ml, Code: 992)

Compositions	Amount (mg)
Cetirizine Dihydrochloride	10.
Glycerin	
Propylene Glycol	
Methylparaben	
Propylparaben	
Sodium Acetate	
Purified Water	

RESULTS:

Mean cetirizine plasma profile is shown in **Figure 1** below and the PK results of Study Nos. UCB-120 and UCB-122 are summarized in **Table 5** in comparison with those obtained previously.

Figure 1: Mean plasma levels of cetirizine (n=8; Study No. UCB-122)

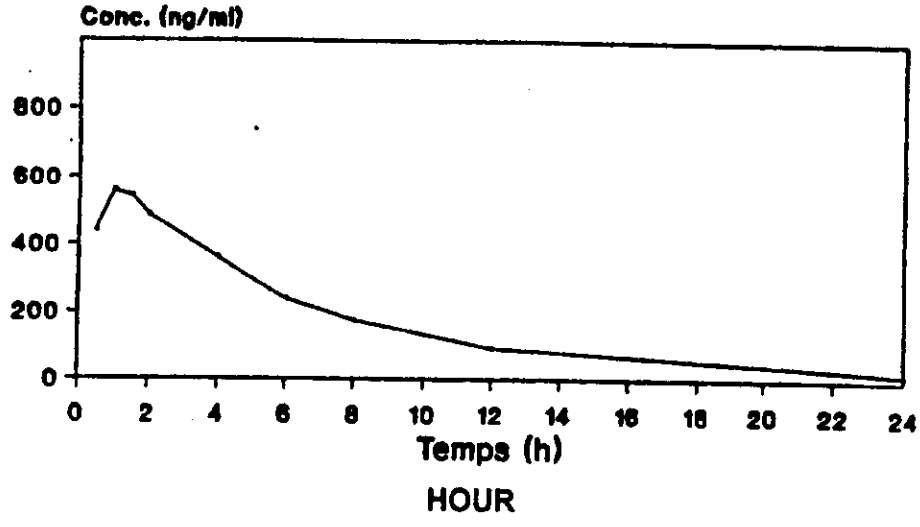


Table 5: Summary of PK Study Results for Cetirizine

PK\Study No.	CPK-1 (Adults)	CPK-17 (Adults)	CPK-11 (Ped. 7-12 yrs)	UCB-120[a] (Ped. 2-5 yrs)	UCB-122[a] (Ped. 2-5 yrs)
Subject Wt (kg)	76 (10; n=17)[b]	77 (10; n=24)	35 (8; n=14)	16.4 (19; n=8)	15.0 (18; n=8)
Single Dose	10 mg tab.	10 mg syrup	5 mg cap.	5 mg sol.[c]	5 mg sol.[c]
C_{max} (ng/ml)	315 (27)	315 (19)	275 (21)	607 (38)	660 (29)
T_{max} (hr)	1.0 (60)	0.73 (60)	1.1 (36)	1.93 (72)	1.44 (78)
$AUC_{0-\infty}$ (ng-hr/ml)	2911 (25)	2871 (17)	2201 (13)	4772 (28)	4120 (23)
$T_{1/2}$ (hr)	8.2 (14)	10 (23)	5.6 (20)	5.55	4.91 (12)
Cl_{app}[d] (ml/min/kg)	1.02 (16)	Ns[e]	1.11 (18)	1.27 (63)	1.48 (29)
Ae_{0-24}[f] (%)	50-60[g]	Ns[e]	64-70	38.4[h] (10)	37.8[i] (14)
Cp_{12} (ng/ml)	NS[e]	78 (18)	52 (16)	117 (29)	94 (32)
Cp_{24} (ng/ml)	NS[e]	31 (26)	14 (30)	32 (19)	19 (47)

a. Submitted under pediatric supplement of NDA 20-346.
b. CV% of the mean and number of subjects.
c. Solution formulation(s) (10 mg/ml) not the same as the to-be-marketed (1 mg/ml).
d. Apparent (or oral) clearance (CL) calculated as Dose/$AUC_{0-\infty}$.
e. Not stated in the study review.
f. Amount (in %) of the total drug excreted unchanged in 0-24 hr urine.
g. Obtained from CPK-4.
h. Obtained from n=4 only.
i. Obtained from n=7 only.

Reviewer's Comments:

Originally, the AUC reported in the study was calculated from time 0.5 hr to infinity ($AUC_{0.5-\infty}$) instead of $AUC_{0-\infty}$. The reason was not provided, however, the $AUC_{0-\infty}$ was recalculated and reported by this reviewer in **Table 5**. The mean difference (3.4%↑) by adding AUC from time zero to 0.5 hr postdose was found to be minor.

The plasma PK data obtained from Study Nos. UCB-120 and UCB-122 show that when compared to adults, the smaller the patients, the greater the systemic exposure (C_{max} and AUC) and the larger the CL_{app} (in ml/min/kg) with shorter terminal half-life ($T_{1/2}$; **Table 5**). The mean Ae_{0-24} values (amount of the total drug excreted unchanged in 0-24 hr urine) obtained from Study Nos. UCB-122 (37.8%) and UCB-120 (38.4%) were smaller than that from adults (50-60%) or from children 7-12 years old (64-70%).

Furthermore, the mean T_{max} obtained from Study No. UCB-120 was 1.93 hr which was much longer than those from other studies.

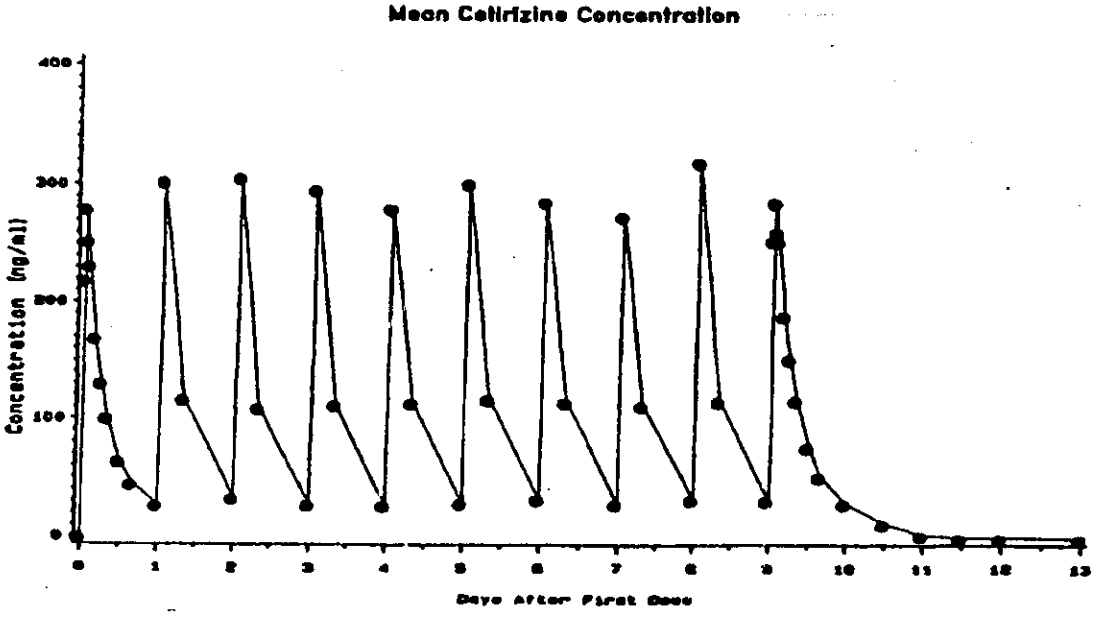
It was not clear to the Agency as to whether **1)** the longer mean T_{max} values obtained from Study UCB-120 and UCB-122 and **2)** the lower mean Ae_{0-24} values than those obtained from adults or children 7-12 years old were due to formulation effects (see **Table 5**). On 04/28/98, the sponsor provided a rationale to justify the differences in T_{max} values. The longer mean T_{max} in these pediatric patients could be due to the anesthesia being employed prior to the surgery in Study No. UCB-120 and/or the differences in sampling schedules. There were 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 60 hr postdose in adults, whereas there were only 0, 0.5, 1.5, 4, 8, 12, and 24 hr postdose in Study UCB-120 and 0, 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 hr postdose in Study UCB-120. For the differences in mean Ae values, the sponsor indicated that the lower mean Ae could be due to incomplete urine collection in this pediatric population. The sponsor concluded that these differences found were unlikely due to formulation effects. The sponsor's rationale is seemingly acceptable.

Finally, the validation of the assay method is less satisfactory. Ideally for quality control of assay, at least three concentration points (instead of 1 or 2 points) should have been used for assessing the interday and intraday variations.

IV. Recommendation of Dosing Regimen for Pediatrics 2-5 years old:

In adults, **1)** the linear kinetics of cetirizine over the dose range of 5 to 60 mg has been demonstrated, **2)** tablet, syrup, and capsule have been shown to be equally bioavailable, and **3)** no significant accumulation (ratio being 1.14) of cetirizine was observed following a daily dose of 10 mg for 10 days (Study No. CPK-4, see **Figure 2** below);

Figure 2: Mean Steady-State Cetirizine Plasma Levels in Adults Receiving 10 mg QD Cetirizine



Under the assumptions that both **1)** disease status and **2)** concentration-response curve of cetirizine are the same in adults, children 6-11 years old, and children 2-5 years old, this reviewer has made the following extrapolations:

A: For single-dose administration, the mean C_{max} and $AUC_{0-\infty}$ values for children 2-5 years old receiving 2.5 mg will be comparable to those for children 6-11 years old receiving 5 mg and also comparable to those for adults receiving 10 mg cetirizine as summarized below:

Single-Dose

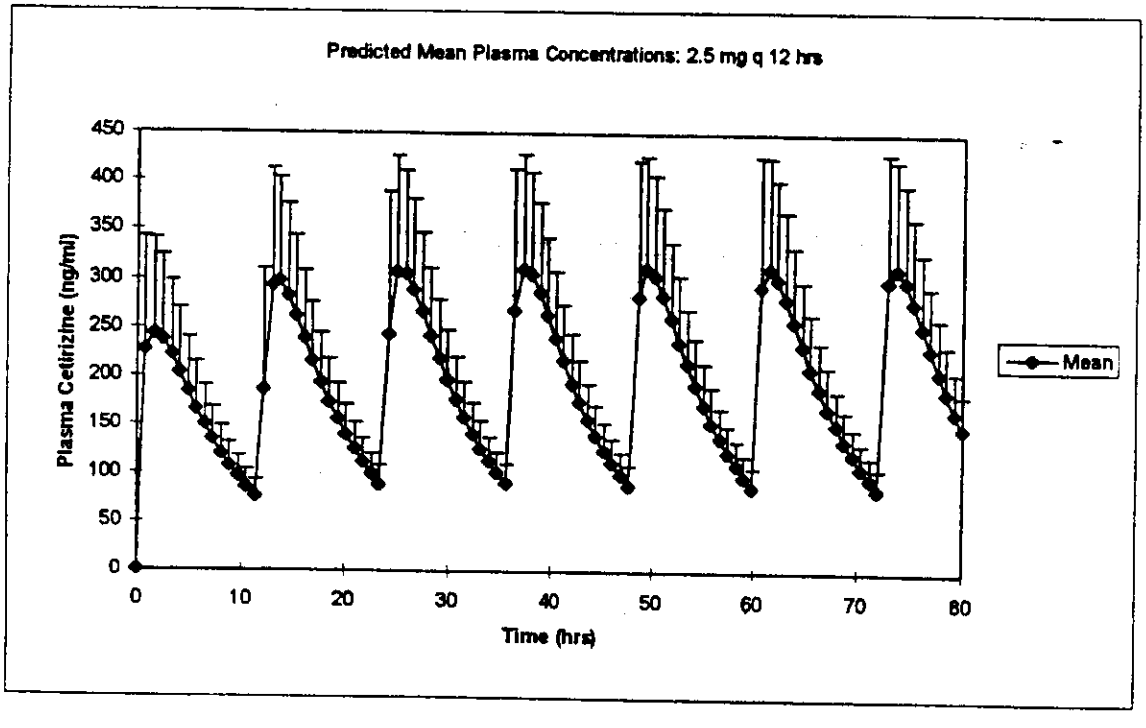
	Adults		Children (6-11 years old)		Children (2-5 years old)
C_{max}:	10 mg	≈	5 mg	≈	2.5 mg
$AUC_{0-\infty}$:	10 mg	≈	5 mg	≈	2.5 mg
($T_{1/2}$:	8-10 hr	>	5.6 hr	≈	5-5.5 hr)

B: For multiple-dose administration, the steady-state mean C_{max} and $AUC_{0-\infty}$ values for children 2-5 years old receiving 2.5 mg QD will be comparable to those for children 6-11 years old receiving 5 mg QD (with little or no accumulation due to a shorter $T_{1/2}$ in these children populations) and also comparable to those for adults receiving 10 mg QD of cetirizine as summarized below:

Multiple-Dose

	Adults		Children (6-11 years old)		Children (2-5 years old)
C_{max}:	10 mg QD	≈	5 mg QD	≈	2.5 mg QD
$AUC_{0-\infty}$:	10 mg QD	≈	5 mg QD	≈	2.5 mg QD
Accumulation ratio:	1.14		Little or no accumulation due to a shorter $T_{1/2}$		

C: Simulation of steady-state mean (± SD) cetirizine plasma levels following oral administration of 2.5 mg BID to children 2-5 years old has been done by this reviewer based on the PK data obtained from Study No. UCB-120:



It should be noted that based on linear kinetics, the steady-state mean AUC_{0-24} values following 5 mg QD and 2.5 mg BID are expected to be the same.

RECOMMENDATION:

The pediatric supplement (Serial No. S-002) to NDA 20-346 Zyrtec (cetirizine) syrup that was submitted by Pfizer on 05/15/97 has been reviewed by OCPB/DPE II. OCPB/DPE II is of the opinion that the human PK/Bio data/information to support the approval of the syrup formulation for pediatrics 2 to 5 years old is rather sparse or incomplete.

Based on linear kinetics and extrapolation, children 2-5 years old could start with 2.5 mg QD and depending on symptom severity, the dose could be increased to 2.5 mg (1/2 teaspoon) BID or 5 mg (one teaspoon) QD. The following General Comment No. 1 and Labeling Comments (pages 11 to 14) as appropriate should be conveyed to the sponsor ASAP.

GENERAL COMMENTS: (No. 1 needs to be sent to the sponsor)

1. For Study Nos. UCB-122 and UCB-113, assay method for plasma and urinary cetirizine levels was used. The validation of the above assay method is less satisfactory.

   Ideally, for quality control of assay, at least three concentration points (instead of 1 or 2 points) should have been used for assessing the interday and intraday variations. For general information on assay validation, please see *Pharmaceutical Research* 9:588-592, 1992.

2. A dosing regimen of 2.5 mg BID for Zyrtec syrup was proposed in the package insert for pediatrics 2-5 years old. However, no clinical or pharmacokinetic studies were conducted employing 2.5 mg BID nor was the simulation of the plasma cetirizine levels using this doing regimen submitted.

3. After administration of a 5-mg oral dose of cetirizine, the systemic exposure (C_{max} and $AUC_{0-\infty}$) of cetirizine in pediatrics 2-5 years old is **1)** approximately 3 to 4-fold higher than that in adults and **2)** approximately 2 to 2.5-fold higher than that in children 7-12 years old.

   Therefore, a reduced oral QD dose (e.g., 2.5 mg or 1/2 teaspoon) is recommended for pediatrics 2-5 years old as the starting dose provided that **1)** the disease status is the same in adults and pediatrics 2 to 5 years old and **2)** the pharmacodynamic and adverse effects of cetirizine are proportional to its systemic exposure (C_{max} and $AUC_{0-\infty}$). Depending on symptom severity, the BID dosing of 2.5 mg syrup (1/2 teaspoon) could be recommended for pediatrics 2 to 5 years old to avoid too high C_{max} and to compensate a shorter $T_{1/2}$ in this population.

2 Page(s) Redacted

Draft

Labeling

/S/

04/17/98

Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Mei-Ling Chen, Ph.D. 04/30/98

FT initialed by Mei-Ling Chen, Ph.D. 5/8/98

cc: NDAs 20-346 and 19-835, HFD-570 (Nicholas, Trout), HFD-870 (M.L. Chen, T.M. Chen), CDR (B. Murphy).

Pediatric Supplement (Serial No. 002)
To NDA 20-346 Zyrtec (cetirizine) Syrup

Attachment 1

Compositions of The Currently Marketed Tablet Formulation and A Tablet Formulation Used in Study UCB-113 (fax on 05/11/98)

	Zyrtec Tablet	Zirtec Tablet
Dosage Form	10 mg	10 mg
Strength	Pfizer	UCB Pharma
Source		
Components	(mg/tablet)	(mg/tablet)
Cetirizine (pharmaceutical grade)	10.00	10.00
Lactose NF		
Lactose		
Starch, Corn, NF		
Corn Starch		
Povidone, USP		
Magnesium Stearate, NF		
Polyethylene glycol		
hydroxypropyl methylcellulose		
polyethylene glycol		
titanium dioxide, USP		

14 Page(s) Redacted

Draft

Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-835/S005
20-346/S002

CORRESPONDENCE

T Trout

MEMORANDUM OF TELECON

DATE: May 6, 1998

APPLICATION NUMBER(s): NDA 19-835/S-005
NDA 20-346/S-002

PRODUCT(s): Zyrtec (cetirizine HCl) Tablets
Zyrtec (cetirizine HCl) Syrup

PARTICIPANTS:

FDA:	Albert Chen	Clin. Pharm. & Biopharm. Reviewer
	Peter Honig	Medical Team Leader
	Richard Nicklas	Medical Reviewer
	Gretchen Trout	Project Manager
	Ramana Uppoor	Clin. Pharm & Biopharm. Team Leader
	Mark Vogel	Pre-Clinical Pharmacology Reviewer
Pfizer:	Stephen Cristo	Regulatory Affairs
	Tom D'Eletto	CSA Medical
	Ben Kramer	PPG Medical
	Kevin Phelan	CSA Project leader
	Larry Samuels	Previous CSA Project Leader

BACKGROUND: The Division requested this teleconference to discuss labeling issues with regard to these supplements, and to discuss what the Division feels is the most appropriate dose for use in children ages 2-5 years. Background material was sent to the sponsor via facsimile on May 5, 1998 (see attachment 1).

The Division informed Pfizer that we feel that 2.5 mg once daily is the most appropriate dose for use in children ages 2-5 years of age, and that 2.5 mg twice daily or 5.0 mg once a day can be used if the initial dose of 2.5 mg once daily is found not to be effective and not to be associated with any adverse event. The Division referred to Table 4 from the May 5, 1998, fax. Specifically in the studies in children ages 2-5 years, the Cmax and AUC was two times greater than seen in children ages 7-12 on 5 mg, and two times greater than seen in adults on 10 mg (four times higher if dose adjusted). Based on the assumptions of linearity and that both the dose response curve and the disease state is similar in adults and children, if 10 mg is effective for adults, and 5 mg is effective in children ages 7-12 years, than 2.5 mg should be effective in children ages 2-5. Pfizer replied that based on the facsimile dated May 5, 1998, and the above statements, they are in agreement with the Division.

The Division informed Pfizer, however, that the approval of the supplements depends on the linkage of the formulations used, and we are still waiting for the information which was requested on

the tablet formulation used in UCB study 113. Pfizer replied that they are in the process of confirming the formulation which was used, and they should be able to provide a table comparing the composition of the formulation used in study UCB-113 to the currently marketed tablet formulation, by Monday or Tuesday (May 11 or 12, 1998). The importance of providing us with this information as soon as possibly (preferably sooner than Monday May 11, 1998) was emphasized to the sponsor.

With regard to the draft labeling comments which were included in the May 5, 1998, facsimile, Pfizer pointed out that a sentence which is in the current package insert had been removed. The sentence would follow the second sentence in the "Absorption" subsection, and reads "No accumulation was observed." The Division replied that the deletion of the sentence was an oversight on our part. However, the Division also reminded Pfizer that comments sent via facsimile are all draft and there may be additional comments.

The Division had also sent pre-clinical labeling comments to Pfizer via facsimile on May 1, 1998, and Pfizer stated that the comments looked reasonable, however, they questioned what assumptions were used for body weight. The Division indicated that we could send via facsimile a table which shows the calculations (see attachment 2).

SUMMARY:

1. The Division feels that the recommended initial dose for children ages 2-5 years should be 2.5 mg once a day. Pfizer agreed.

2. Pfizer will submit information on the composition of the tablet formulation used in UCB study 113 by May 11 or 12, 1998, or earlier if at all possible (NOTE: Pfizer was able to submit a table comparing the tablet formulations via facsimile on May 6, 1998, see Attachment 3).

3. The Division will fax a table with the calculations used for the pre-clinical section of the labeling to Pfizer (NOTE: This was done on May 6, 1998).

4. The Division will send labeling comments to Pfizer as soon as possible so that Pfizer can submit revised labeling prior to the userfee due date of May 16, 1998.

/S/

Gretchen Trout
Project Manager

ATTACHMENT 1

APPEARS THIS WAY
ON ORIGINAL

7 Page(s) Redacted

Draft Labeling

ATTACHMENT 2

APPEARS THIS WAY
ON ORIGINAL

28 Page(s) Redacted

Draft

Labeling

(S)

MEMORANDUM OF TELECON

DATE: April 17, 1998

APPLICATION NUMBER(s): NDA 19-835/S-005
NDA 20-346/S-002

PRODUCT(s): Zyrtec (cetirizine HCl) Tablets
Zyrtec (cetirizine HCl) Syrup

PARTICIPANTS:

FDA:	Albert Chen	Clinical Pharmacology & Biopharmaceutics
	Richard Nicklas	Medical
	Gretchen Trout	Project Manager
Pfizer:	Stephen Cristo	Regulatory Affairs
	Tom Delotto	Clinical Research
	Larry Samuels	Clinical Research

BACKGROUND: The Division requested this teleconference in order to obtain clarification on the formulations used in the various studies submitted in support of these supplements providing for pediatric use of these products.

The Division questioned if the UCB studies 120 and 122 were done with the same formulations, and whether the pharmacokinetic studies used the same formulations as the European studies. Pfizer stated that their understanding is that the formulations are identical however they have asked UCB to confirm this.

Pfizer confirmed that the oral solution used in the studies which were submitted in support of the supplements is different from the currently marketed syrup, and that it differs in the concentration of cetirizine, has
and the are different.

Pfizer did not conduct any studies which looked at a direct comparison between the marketed formulation and the formulation used in the clinical trials. Pfizer does not believe that there are any differences in the characteristics of the kinetics.

The Division explained that we are having difficulty linking the solution used in the clinical studies (UCB-120 and UCB-122) to that of the currently marketed syrup. The Division pointed out that the Tmax is different and the amount excreted in urine unchanged is different, and we don't know if these are due to a formulation effect. The Division requested that Pfizer provide in writing, as soon as possible, a basis for why the difference in inactive ingredients (quantitatively and qualitatively) in the two formulations would not contribute to different absorption

characteristics, and the basis for why they feel that the two formulations would not product a different clinical effect.

CONCLUSION: Pfizer will obtain confirmation from UCB that the formulations used in the UCB studies were the same, and they will provide, in writing, a rationale explaining why they believe that the formulation used in the clinical trials would act no differently than the currently marketed syrup. Pfizer was asked to do this as soon as possible, preferably within the next week.

/S/

Gretchen Trout
Project Manager

cc: Div. Files 19-835, 20-346
Orig. NDAs
HFD-870/Tien-Mien Chen
HFD-870/Mei-Ling Chen
HFD-570/Nicklas
HFD-570/Honig
HFD-570/Trout

/S/ 4/27/98

rd initial by: Chen/4-23-98
Nicklas/4-23-98

TELECON

APPEARS THIS WAY
ON ORIGINAL

Trout

MEMORANDUM OF TELECON

DATE: July 14, 1997

APPLICATION NUMBER(s): NDA 19-835/S-005
NDA 20-346/S-002

PRODUCT: cetirizine

PARTICIPANTS:

Pfizer: Suzanne LoGalbo Regulatory Affairs

FDA: Gretchen Trout Project Manager

BACKGROUND: Reference is made to a teleconference between representatives of the Division and Ms. Suzanne LoGalbo on July 9, 1997, during which data on the differences between the cetirizine solution used in the studies supporting the supplements, and the currently marketed cetirizine syrup, was requested from Pfizer. In a voicemail message to Ms. LoGalbo from Ms. Trout on July 11, 1997, Ms. Trout indicated that this was a possible filing issue,

Pfizer submitted the requested information via facsimile on July 14, 1997 (see attached).

I telephoned Ms. LoGalbo on July 14, 1997, and informed her that Dr. Honig had looked at the data submitted by Pfizer, and determined that the formulations were similar enough to support filing of the supplements. I told Ms. LoGalbo to consider the supplements filed and under review.

Ms. LoGalbo asked several administrative questions with regard to the supplements, and I explained that because the supplements contained clinical data (and the data is necessary to support the changes proposed in the supplements), the supplements would receive a one year review time and that the filing decision had to be made within 60 days of the date of the submission of the supplements. I further explained that although the supplements have different due dates, the Division will take actions on them based on the first due date, since the data supporting the supplements is exactly the same.

/S/

Gretchen Trout
Project Manager

Trout

MEMORANDUM OF TELECON

DATE: July 9, 1997

APPLICATION NUMBER(s): NDA 19-835/S-005
NDA 20-346/S-002

PRODUCT: cetirizine

PARTICIPANTS:

Pfizer:	Suzanne LoGalbo	Regulatory Affairs
FDA:	Craig Bertha	Chemistry Reviewer
	Brad Gillespie	Clinical Pharmacology and Biopharmaceutics Reviewer
	Dick Nicklas	Medical Reviewer
	Gretchen Trout	Project Manager

BACKGROUND: Pfizer submitted a supplement to NDA 20-346 (Zyrtec Syrup) on May 15, 1997, providing for changes in the label to support use in patients 2-5 years of age for seasonal and perennial allergic rhinitis and chronic idiopathic urticaria. On May 29, 1997, Pfizer submitted a supplement to NDA 19-835 (Zyrtec Tablets) for the same changes, cross-referencing to the data submitted in the supplement to NDA 20-346. Following an internal meeting, this teleconference was held to obtain clarification on several issues.

Dr. Nicklas questioned if the marketed syrup and the solution formulations used in the studies for the 2-5 year age group were the same formulation. Ms. LoGalbo replied that they are similar, but not the same. Ms. LoGalbo agreed to find out how the formulations differed, both qualitatively and quantitatively. Ms. LoGalbo did state the studies were conducted with the UCB solution formulation.

Dr. Nicklas then questioned if Pfizer has any data which link the formulations, particularly pharmacokinetic data in adults. Ms. LoGalbo replied that there was no linking data. Ms. LoGalbo questioned if the two formulations were only quantitatively different, would the linking still be an issue. Dr. Nicklas replied that it could still be an issue.

Dr. Nicklas then referred to a report that had been included of a child with fulminant hepatitis. He questioned if there were any physician or hospital records. Ms. LoGalbo agreed to look into obtaining additional information.

FOLLOW-UP: In a later telephone conversation between Ms. LoGalbo and Ms. Trout on the same day, Ms. LoGalbo sated that while she does not yet have anything in writing, she was told verbally by UCB that there was no comparison done between the syrup and the solution in terms of bioavailability. She will be obtaining the data on the qualitative and quantitative differences between the solution and the syrup, and a droplet which was used. Ms. LoGalbo explained that at the current time she did not know if the droplet was the same as the solution, just administered in droplets, or if it was also different. Ms. LoGalbo stated that she would have the information by Friday, July 11, 1997.

With regard to the case of fulminant hepatitis, Ms. LoGalbo stated that there were no hospital records.

/S/

Gretchen Trout
Project Manager

APPEARS THIS WAY
ON ORIGINAL

Team Leader Memorandum

TO: NDA 20,346

FROM: Peter K Honig, MD
Medical Team Leader
Division of Pulmonary Drug Products, HFD-570

/S/ 5/11/98

THROUGH: John K. Jenkins, MD
Division Director
Division of Pulmonary Drug Products, HFD-570

/S/ 5/13/98

RE: Zyrtec® (cetirizine) Syrup

DATE: May 11, 1998

Please refer to previous Team Leader memorandum dated September 17, 1996 regarding the approval of Zyrtec Syrup. Zyrtec Tablets/Syrup is approved for the treatment of seasonal and perennial allergic rhinitis and idiopathic chronic urticaria in patients 6 years of age and older. This action was based on the tenets of the 'Pediatric Rule' (21 CFR 201.57(f)(9)) which was finalized December 13, 1994 and relied on the extrapolation of adult efficacy data to the relevant pediatric population provided that the safety of the drug in the pediatric population can be adequately demonstrated and the appropriate dose can be determined. This application proposes to extend the approved lower age limit for pediatric patients down to 2 years. In support of the application, the sponsor has submitted safety data from 168 children aged 2-5 years who received daily doses of cetirizine for periods up to 4 weeks in studies involving allergic rhinitis and dermatological conditions. The majority of these children (119) received 5 milligrams per day of cetirizine. Cetirizine administered as an oral solution appeared to be well tolerated by this age group. The adverse event profile in this age group was qualitatively similar in nature and quantitatively comparable in frequency to the adverse event profile demonstrated in older children (7-11) and adults. The effect of cetirizine on electrocardiographic intervals was not studied in this age population; however, no arrhythmias or cardiac-related adverse events were reported and the concentration-response relationship of cetirizine on cardiac electrophysiology in this patient population is not likely to differ from adults or older children. Thus, the safety of cetirizine in the pediatric population has been demonstrated.

The question of whether the conditions of allergic rhinitis and idiopathic chronic

urticaria exist in children as young as 2 years of age is debatable. Allergic rhinitis is primarily an IgE-mediated condition. Studies have shown that specific IgE antibodies decline after birth, nadir at 6 months of age, and begin to rise above that baseline by 24 months. Clearly, atopy exists in patients below the age of 2; however, the mean age of early onset of clinically observable respiratory tract allergic conditions (e.g. allergic rhinitis) in this population, in some studies, is 36 months. It is appreciated that the clinical manifestation of allergic disease results from an interrationship between genetic constitution (atopy) and the encountered environment and available data indicate that allergic rhinitis clearly exists by age 3 and, in some individuals, by age 2. Idiopathic chronic urticaria is manifested in patients as young as 2 years of age. Current data do not support the treatment of SAR, PAR, or CIU in patients less than 2 years of age. Therefore, the sponsor's contention that allergic rhinitis and chronic idiopathic urticaria exists in the proposed patient population is valid and the sponsor's proposal not to study such patients (i.e., less than 2 years of age) is acceptable.

The dose of Zyrtec Syrup is based on two, single-dose, pharmacokinetic studies involving children aged 2-5 years who were administered cetirizine solution (10 mg/ml) several hours before surgical procedures. The mean results of these studies and PK studies conducting in older children and adults are summarized in the table below. All PK parameters are normalized for weight.

Parameter	Study CPK 17 Adults	Study CPK 11 Children 7-11	UCB-120 Children 2-5	UCB-122 Children 2-5
Dose	10 mg	5 mg	5 mg	5 mg
Cmax (ng/mL)	315	275	607	660
AUC (ng-hr/mL)	2871	2201	4772	4120
Apparent oral clearance (ml/min/kg)	1.02 (estimated)	1.11	1.27	1.48
Conc at 12 hrs	78	52	117	94
Conc at 24 hrs	31	14	32	19

It can be seen that a single, 5-mg dose of cetirizine would provide for larger exposures and maximum concentrations that those achieved after dosing adults

with a dose of cetirizine that has been shown effective in adequate and well-controlled trials. Assuming linear pharmacokinetics in the pediatric population aged 2-5 years, a single-dose of 2.5 mg would provide Cmax's and AUCs that are more consistent with dosing for adults and older children (i.e. AUC= 2060-2386 ng-hr/mL and Cmax 303-330 ng/mL). Thus, the initial starting dose of cetirizine in this population should be 2.5 mg given once per day. Since, the 5 mg daily dose was well-tolerated and the efficacy of this dose is substantiated in a single-trial of seasonal allergic rhinitis (Study 89), it is reasonable to recommend a dosing range up to 5 mg per day given a single or divided dose. This is consistent with the approved pediatric labeling for children aged 6 to 11 years which recommends daily doses of 5 or 10 milligrams depending on symptom severity.

The remaining problem with the application is the linking of the formulation used in the pediatric PK studies with the approved syrup formulation. The approved tablet and the approved syrup linked by pharmacokinetic, efficacy and safety data. The sponsor has provided a single study in adults which compared the pharmacokinetic performance of the cetirizine solution used in the pediatric PK studies to a cetirizine tablet formulation. This study demonstrated the two formulations to be comparable in PK performance. Although the tablet formulation is not identical in composition to the marketed tablet, it is similar. There are some quantitative differences in major components (e.g. lactose, corn starch, povidone, and magnesium stearate). The major qualitative difference is the substitution of [redacted] for hydroxypropyl methylcellulose [redacted] is a [redacted] which does not change the release characteristics of the drug. In the opinion of this reviewer, these are not a significant differences that would be likely to dramatically alter the absorption or pharmacokinetics of the formulation.

Team Leader Recommendation:

Cetirizine syrup (2.5 mg/day given as a single dose or 5 mg/day given in single or divided doses) should be approved for the treatment of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria in the adult and pediatric population 2 to 5 years of age. Labeling for this product has been integrated into the approved Zyrtec labeling.

/S/

Peter K Honig, MD
Medical Team Leader

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

NDA NO. 20-346 REF NO. 002
NDA SUPPL FOR SE1

Pfizer Pharmaceuticals Group
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 2950 Fax 212 573 1563

Pfizer Pharmaceuticals

May 15, 1997

Suzanne E. LoGalbo
Associate Director—Drug Regulatory Affairs

John J. Jenkins, M.D., Director
Division of Pulmonary Drug Products (HFD-155)
Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852

RE: Zyrtec (cetirizine HCl) Syrup
NDA #20-346
Pediatric Supplement

Dear Dr. Jenkins:

Pursuant to 21 CFR 314.70 and in accordance with 21 CFR 201.57 (f)(9) we are submitting a supplement to our Zyrtec (cetirizine HCl) NDA #20-346 supporting pediatric use in 2-5 year olds for the indications of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria.

The information included in this application supports the similarity of this disease states between adult and children and substantiates the dosing instruction and labeling for safe and effective pediatric use for these indications. Please note that Pfizer hereby requests that this information be incorporated by reference into NDA #19-835; Zyrtec (cetirizine HCl) Tablets. At the time of approval of this supplement it is Pfizer's intent to combine this label information into the combined package insert for both Zyrtec (cetirizine HCl) Tablets and Syrup.

In accordance with the requirements of the Generic Drug Enforcement Act of 1992, and in connection with this application, the best of its knowledge, Pfizer Inc. did not use in any capacity the services of any person debarred under Section 306 of the Federal Food , Drug, and Cosmetic Act.

Please be advised that the applicable user fee for this submission has been remitted in accordance with the Perception Drug User Fee Act of 1992 and that Form 3397 is enclosed as required. The User Fee ID Number is

We look forward to a timely review of this application. If there are any questions regarding the organization or content of this application, please contact Stephen Cristo at (212) 573-7827.

Sincerely,

Suzanne E. LoGalbo

Enclosure
SEL:amw
ZYRTEC6.DOC/1

Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 7827 Fax 212 573 1563

Pfizer Pharmaceuticals

SE1-005
EL

Stephen Cristo
Associate Director—Drug Regulatory Affairs

May 14, 1998

John J. Jenkins, M.D., Director
Division of Pulmonary Drug Products (HFD-155)
Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852

RE: NDA 20-346 Zyrtec (cetirizine HCl) Syrup
NDA 19-835 Zyrtec (cetirizine HCl) Tablets
Efficacy Supplement: Pediatric Ages 2-5 Years
Final Labeling

Dear Dr. Jenkins:

Reference is made to NDA 20-346 for Zyrtec (cetirizine HCl) Syrup with cross reference to NDA 19-835 for Zyrtec (cetirizine HCl) Tablets. Specific reference is made to Pfizer's Efficacy Supplement: Pediatric filed on May 15, 1997 filed in accordance with 21 CFR 201.57(f)(9)(iv). This Supplement provides information in support of the use of cetirizine HCl in children ages 2-5 year olds for the indications of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria.

Enclosed please find Final Labeling incorporating FDA comments faxed to Pfizer on May 8, 1998. Additional changes to the label have been made as a result of a teleconference of May 12, 1998 with Dr. Nicholas, Dr. Honig and Ms. Trout of the Agency and Dr. Phelan, Dr. D'Eletto and Mr. Cristo of Pfizer. We have also incorporated the language faxed to Pfizer on May 13, 1998 for the Dosage and Administration section; Dosage Adjustment for Renal and Hepatic Impairment for pediatric patients under 6 years of age. We have inverted the statements regarding the difficulty in dosing and the absence of information. And lastly, please note that in the PK section under Special Populations; Renal Impairment, we have changed from "Dosing adjustment is ." to "Dosing adjustment is necessary..." This is consistent with the current label. All other changes have been made.

Please do not hesitate to contact me at (212) 573-7827, if you have any questions.

Sincerely,

Stephen Cristo

Stephen Cristo

cc: Gretchen Trout, CSO