DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Robert B. Clark
Vice President, US Regulatory
Pfizer Inc.
Regulatory Affairs
235 East 42nd Street
New York, New York 10017

RE: NDA #21-150
Zyrtec-D 12 Hour® (cetirizine HCl 5 mg/pseudoephedrine HCl 120 mg) Extended Release Tablets
MACMIS ID #11949

Dear Mr. Clark:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional sales aid (Admis #150264) for Zyrtec-D 12 Hour® (cetirizine HCl 5 mg/pseudoephedrine HCl 120 mg) Extended Release Tablets (Zyrtec-D) submitted by Pfizer Inc. (Pfizer) under cover of Form FDA 2253. Additionally, DDMAC has reviewed promotional statements for this drug that appear on a website (www.zyrtec.com) maintained by or on behalf of Pfizer. These materials omit information concerning the risks of Zyrtec-D and, therefore, misbrand the drug within the meaning of the Federal Food, Drug, and Cosmetic Act (the Act) and FDA implementing regulations. See 21 U.S.C. 201(n), 352(a) and (n); 21 C.F.R. 202.1(e)(5). The omission of this risk information is a public health concern because Zyrtec-D is contraindicated for several patient populations, and the ingestion of pseudoephedrine may cause serious adverse health consequences.

Background

According to the Indications and Usage section of the FDA-approved professional labeling (PI):

> ZYRTEC-D 12 HOUR Extended Release Tablets should be administered when both the antihistaminic properties of cetirizine hydrochloride and the nasal decongestant properties of pseudoephedrine hydrochloride are desired.
>
> ZYRTEC-D 12 HOUR Extended Release Tablets are indicated for the relief of nasal and non-nasal symptoms associated with seasonal or perennial allergic rhinitis in adults and children 12 years of age and older.

The Contraindications section of the PI states (in pertinent part):

> Due to its pseudoephedrine component, ZYRTEC-D 12 HOUR Extended Release Tablets are contraindicated in patients with narrow-angle glaucoma or urinary retention, and in patients receiving monoamine oxidase (MAO) inhibitor therapy or within fourteen (14) days of stopping such treatment (see **PRECAUTIONS, Drug Interactions** section). It is also contraindicated in patients with severe hypertension, or severe coronary artery disease, and in those who have shown hypersensitivity or idiosyncrasy to its components, to adrenergic agents, or to other drugs of similar chemical structures. Manifestations of patient idiosyncrasy to adrenergic agents include insomnia, dizziness, weakness, tremor, or arrhythmias.

According to the Warnings section of the PI:

> Sympathomimetic amines should be used judiciously and sparingly in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, renal impairment, or prostatic hypertrophy (see **CONTRAINDICATIONS**). Sympathomimetic amines may produce central nervous system stimulation with convulsions or cardiovascular collapse with accompanying hypotension. The elderly are more likely to have adverse reactions to sympathomimetic amines.

Omission of Risk Information

The sales aid and website fail to reveal facts that are material in light of the representations they make regarding the consequences that may result from using Zyrtec-D as they suggest. Specifically, these materials fail to disclose the contraindications and warnings described above.

Conclusions and Requested Actions

DDMAC requests that Pfizer immediately cease the dissemination of promotional materials for Zyrtec-D the same as or similar to those described above. Please submit a written response to this letter on or before May 6, 2004, describing your intent to comply with this request, listing all promotional materials for Zyrtec-D the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857, facsimile at 301-594-6759. In all future correspondence regarding this matter, please refer to MACMIS ID # 11949 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Zyrtec-D comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Christine Hemler Smith, Pharm.D.
Consumer Promotion Analyst
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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

/s/

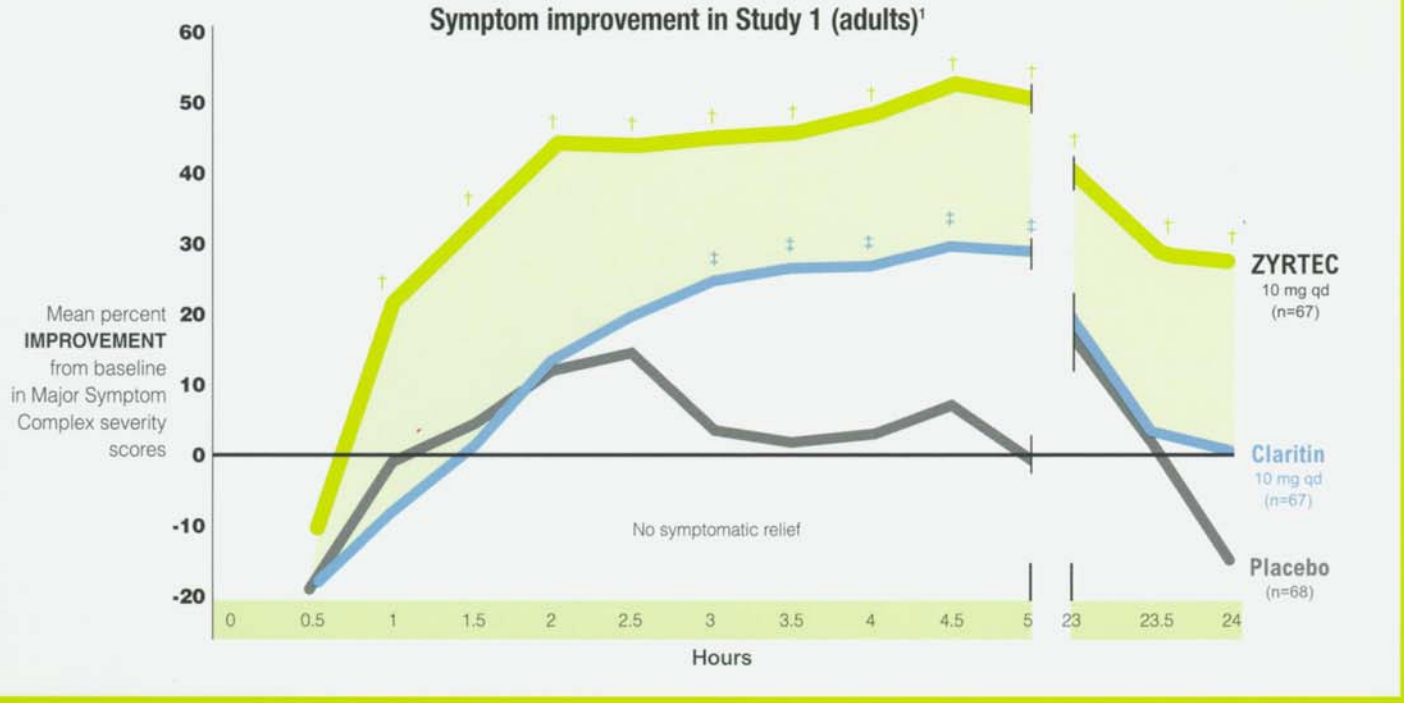
Christine Smith
4/22/04 02:18:09 PM

Preferred on formulary

In two 2-day Environmental Exposure Unit (EEU) studies...

ZYRTEC—differentiated from Claritin® with twice the symptom relief 2X

Demonstrated two times better mean overall symptom relief[1,2]



†$P \leq 0.05$ vs Claritin and placebo. ‡$P \leq 0.05$ vs placebo.

In a controlled Environmental Exposure Unit, 202 patients who tested positive to ragweed pollen **(moderate reaction at screening)** received ZYRTEC tablets 10 mg qd, Claritin tablets 10 mg qd, or placebo to control symptoms of seasonal allergic rhinitis. Patients were exposed to ragweed pollen for one 7-hour and one 6-hour period over 2 days in a classroom setting in which the pollen was delivered at a controlled rate. Major symptom complex included runny nose, sniffles, itchy nose, nose blows, sneezes, and watery eyes. Baseline severity, assessed by patients, was comparable for all groups.[1] Results of a second EEU study confirmed these findings.[2]

Day JH, Briscoe M, Widlitz MD. Cetirizine, loratadine, or placebo in subjects with seasonal allergic rhinitis: effects after controlled ragweed pollen challenge in an environmental exposure unit. *J Allergy Clin Immunol*.1998;101:638-645.

The two well-designed, controlled EEU studies allow the direct comparison of ZYRTEC with Claritin[1,2]

In studies for U.S. approval of ZYRTEC alone, most side effects were mild or moderate. The incidence of somnolence was dose related (in adults: 11% at 5 mg, 14% at 10 mg, and 6% with placebo; in children: 1.9% at 5 mg, 4.2% at 10 mg, and 1.3% with placebo).

Other common side effects versus placebo in adults included fatigue (5.9% vs 2.6%) and dry mouth (5.0% vs 2.3%); in children, headache (11% at 5 mg, 14% at 10 mg vs 12.3%), pharyngitis (6.2% at 5 mg, 2.8% at 10 mg vs 2.9%), and abdominal pain (4.4% at 5 mg, 5.6% at 10 mg vs 1.9%).

References: 1. Day JH, Briscoe M, Widlitz MD. Cetirizine, loratadine, or placebo in subjects with seasonal allergic rhinitis: effects after controlled ragweed pollen challenge in an environmental exposure unit. *J Allergy Clin Immunol*.1998;101:638-645. **2.** Day JH, Briscoe M, Rafeiro E, Chapman D, Kramer B. Comparative onset of action and symptom relief with cetirizine, loratadine, or placebo in an environmental exposure unit in subjects with seasonal allergic rhinitis: confirmation of a test system. *Ann Allergy Asthma Immunol*. 2001;87:474-481.

Rx = ZYRTEC®
cetirizine HCl

Please see full prescribing information in pocket for ZYRTEC 5-mg and 10-mg tablets, 1-mg/mL syrup, and ZYRTEC-D 12 Hour®.

SIKO

Preferred on formulary

Rx = ZYRTEC® cetirizine HCl

Easy dosing for all patients—
adults to infants as young as 6 months

In patients 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, the recommended dosage is as follows:

ZYRTEC tablets and syrup—In patients aged 6 years and older, a dose of 5 mg once daily. In children below the age of 6 years with impaired renal or hepatic function, ZYRTEC is not recommended.

ZYRTEC-D 12 Hour—In patients aged 12 years and older, a dose of one tablet once daily.

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In ZYRTEC studies with infants 6 to 23 months old, side effects overall were similar to placebo and included irritability/fussiness, insomnia, fatigue, and malaise.

In trials for U.S. approval of ZYRTEC-D 12 Hour, the most common side effects which occurred at a rate of 2% or greater included insomnia (4.0% vs 0.6%), dry mouth (3.6% vs 0.4%), and fatigue (2.4% vs 0.9%).

Pseudoephedrine hydrochloride may cause mild CNS stimulation in hypersensitive patients. Nervousness, excitability, restlessness, dizziness, weakness, or insomnia may occur.

ZYRTEC is indicated for relief of symptoms associated with seasonal allergic rhinitis in patients 2 years and older, and perennial allergic rhinitis and chronic idiopathic urticaria in patients 6 months and older. ZYRTEC-D 12 Hour is indicated for the treatment of Seasonal Allergic Rhinitis (SAR) with nasal congestion and Perennial Allergic Rhinitis (PAR) with nasal congestion down to the age of 12 years.

Please see full prescribing information in pocket for ZYRTEC 5-mg and 10-mg tablets, 1-mg/mL syrup, and ZYRTEC-D 12 Hour.

Manufactured/Marketed by
Pfizer U.S. Pharmaceuticals
New York, NY 10017

Marketed by
ucb Pharma
UCB Pharma, Inc.
Smyrna, GA 30080

ZY155716

10% TOTAL RECOVERED FIBER

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