For patients with persistent asthma

Introducing the first multiple-strength inhaled corticosteroid with high topical anti-inflammatory activity

- B.i.d. convenience
- Multiple strengths to minimize the number of puffs per dose
- Relatively rapid onset of action
- Rare reports (<1%) of unpleasant taste[1]

Maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment. Onset of action and degree of symptom relief may vary.

FLOVENT is indicated for the maintenance treatment of asthma as prophylactic therapy for patients ≥12 years of age and for patients requiring oral corticosteroid therapy for asthma, many of whom may be able to reduce or eliminate their requirement for oral corticosteroids over time.

FLOVENT is NOT indicated for the relief of acute bronchospasm.

CAUTION: Adrenal insufficiency may occur when transferring patients from systemic steroids (see WARNINGS).

NEW

Control made convenient

FloVent™ 44 mcg 110 mcg 220 mcg

(fluticasone propionate) Inhalation Aerosol

Custom-tailored treatment for *starting, switching, and sparing*

Reference: 1. Data on file, Glaxo Wellcome Inc.

Please consult Brief Summary of Prescribing Information on adjacent page.

GlaxoWellcome

FloVent™ 44 mcg 110 mcg 220 mcg
(fluticasone propionate) Inhalation Aerosol

For Oral Inhalation Only **BRIEF SUMMARY**

The following is a brief summary only; see full prescribing information for complete product information.

CONTRAINDICATIONS: FLOVENT Inhalation Aerosol is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of these preparations contraindicates their use.

WARNINGS:

Particular care is needed for patients who are transferred from systemically active corticosteroids to FLOVENT Inhalation Aerosol because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although fluticasone propionate inhalation aerosol may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to fluticasone propionate inhalation aerosol. In a trial of 96 patients, prednisone reduction was successfully accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during transfer to inhaled fluticasone propionate. Successive reduction of prednisone dose was allowed only when lung function, symptoms, and as-needed beta-agonist use were better than or comparable to that seen before initiation of prednisone dose reduction. Lung function (forced expiratory volume in 1 second [FEV$_1$] or morning peak expiratory flow rate [AM PEFR]), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to fluticasone propionate inhalation aerosol may unmask conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, and arthritis.

Persons who are on drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Fluticasone propionate inhalation aerosol is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

As with other inhaled asthma medications, bronchospasm may occur with an immediate increase in wheezing after dosing. If bronchospasm occurs following dosing with FLOVENT Inhalation Aerosol, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with FLOVENT Inhalation Aerosol should be discontinued and alternative therapy instituted.

Patients should be instructed to contact their physicians immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with fluticasone propionate inhalation aerosol. During such episodes, patients may require therapy with oral corticosteroids.

PRECAUTIONS:

General: During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Fluticasone propionate will often permit control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of fluticasone propionate inhalation aerosol in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing fluticasone propionate inhalation aerosol.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, fluticasone propionate inhalation aerosol should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

A reduction of growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should closely follow the growth of adolescents taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression if an adolescent's growth appears slowed.

The long-term effects of fluticasone propionate in human subjects are not fully known. In particular, the effects resulting from chronic use of fluticasone propionate on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients have received fluticasone propionate inhalation aerosol on a continuous basis for periods of 3 years or longer. In clinical studies with patients treated for nearly 2 years with inhaled fluticasone propionate, no apparent differences in the type or severity of adverse reactions were observed after long- versus short-term treatment.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids.

In clinical studies with inhaled fluticasone propionate, the development of localized infections of the pharynx with *Candida albicans* has occurred. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while remaining on treatment with fluticasone propionate inhalation aerosol, but at times therapy with fluticasone propionate may need to be interrupted.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, viral or parasitic infections; or ocular herpes simplex.

Information for Patients: Patients being treated with FLOVENT Inhalation Aerosol should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients should use FLOVENT Inhalation Aerosol at regular intervals as directed. Results of clinical trials indicated significant improvement may occur within the first day or two of treatment; however, the full benefit may not be achieved until treatment has been administered for 1 to 2 weeks or longer. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.

Patients should be warned to avoid exposure to chickenpox or measles and, if they are exposed, to consult their physicians without delay.

For the proper use of FLOVENT Inhalation Aerosol and to attain maximum improvement, the patient should read and follow carefully the Patient's Instructions for Use accompanying the product.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone propionate demonstrated no tumorigenic potential in studies of oral doses up to 1,000 mcg/kg (approximately two times the maximum human daily inhalation dose based on mcg/m^2) for 78 weeks in the mouse or inhalation of up to 57 mcg/kg (approximately 1/4 the maximum human daily inhalation dose based on mcg/m^2) for 104 weeks in the rat.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells *in vitro*. No significant clastogenic effect was seen in cultured human peripheral lymphocytes *in vitro* or in the mouse micronucleus test when administered at high doses by the oral or subcutaneous routes. Furthermore, the compound did not delay erythroblast division in bone marrow.

No evidence of impairment of fertility was observed in reproductive studies conducted in rats dosed subcutaneously with doses up to 50 mcg/kg (approximately 1/4 the maximum human daily inhalation dose based on mcg/m^2) in males and females. However, prostate weight was significantly reduced in rats.

Pregnancy: *Teratogenic Effects: Pregnancy Category C:* Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg, respectively (approximately 1/10 and 1/2 the maximum human daily inhalation dose based on mcg/m^2, respectively), revealed fetal toxicity characteristic of potent glucocorticoid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed following subcutaneous doses of 4 mcg/kg (approximately 1/25 the maximum human daily inhalation dose based on mcg/m^2). However, following oral administration of up to 300 mcg/kg (approximately 3 times the maximum human daily inhalation dose based on mcg/m^2) of fluticasone propionate to the rabbit, there were no maternal effects nor increased incidence of external, visceral, or skeletal fetal defects. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY section of full prescribing information).

Less than 0.008% of the administered dose crossed the placenta following oral administration of 100 mcg/kg to rats or 300 mcg/kg to rabbits (approximately 1/2 and 3 times the maximum human daily inhalation dose based on mcg/m^2, respectively).

There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral glucocorticoids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from glucocorticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous glucocorticoid dose and many will not need glucocorticoid treatment during pregnancy.

Nursing Mothers: It is not known whether fluticasone propionate is excreted in human breast milk. Subcutaneous administration of 10 mcg/kg titrated drug to lactating rats (approximately 1/20 the maximum human daily inhalation dose based on mcg/m^2) resulted in measurable radioactivity in both plasma and milk. Because glucocorticoids are excreted in human milk, caution should be exercised when fluticasone propionate inhalation aerosol is administered to a nursing woman.

Pediatric Use: One hundred thirty-seven (137) patients between the ages of 12 and 16 years were treated with fluticasone propionate inhalation aerosol in the US pivotal clinical trials. The safety and effectiveness of FLOVENT Inhalation Aerosol in children below 12 years of age have not been established. Oral corticosteroids have been shown to cause a reduction in growth velocity in children and teenagers with extended use. If a child or teenager on any corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of corticosteroids should be considered (see PRECAUTIONS).

Geriatric Use: Five hundred seventy-four (574) patients 65 years of age or older have been treated with fluticasone propionate inhalation aerosol in US and non-US clinical trials. There were no differences in adverse reactions compared to those reported by younger patients.

ADVERSE REACTIONS: The following incidence of common adverse experiences is based upon seven placebo-controlled US clinical trials in which 1,243 patients (509 female and 734 male adolescents and adults previously treated with as-needed bronchodilators and/or inhaled corticosteroids) were treated with fluticasone propionate inhalation aerosol (doses of 88 to 440 mcg twice daily for up to 12 weeks) or placebo.

Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate in US Controlled Clinical Trials With MDI in Patients Previously Receiving Bronchodilators and/or Inhaled Corticosteroids

Adverse Event	Placebo (n = 475) %	FLOVENT 88 mcg twice daily (n = 488) %	FLOVENT 220 mcg twice daily (n = 95) %	FLOVENT 440 mcg twice daily (n = 185) %
Ear, nose, and throat				
Pharyngitis	7	10	14	14
Nasal congestion	8	8	16	10
Sinusitis	4	3	6	5
Nasal discharge	3	5	4	4
Dysphonia	1	4	3	8
Allergic rhinitis	4	5	3	3
Oral candidiasis	1	2	3	5
Respiratory				
Upper respiratory infection	12	15	22	16
Influenza	2	3	8	5
Neurological				
Headache	14	17	22	17
Average duration of exposure (days)	44	66	64	59

The table above includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in the combined fluticasone propionate inhalation aerosol groups and were more common than in the placebo group. In considering these data, differences in average duration of exposure should be taken into account.

These adverse reactions were mostly mild to moderate in severity, with ≤2% of patients discontinuing the studies because of adverse events. Rare cases of immediate and delayed hypersensitivity reactions, including urticaria and rash and other rare events of angioedema and bronchospasm, have been reported.

Systemic glucocorticoid side effects were not reported during controlled clinical trials with fluticasone propionate inhalation aerosol. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, e.g., Cushing's syndrome, could occur.

Other adverse events that occurred in these clinical trials using fluticasone propionate inhalation aerosol with an incidence of 1% to 3% and which occurred at a greater incidence than with placebo were:

Ear, Nose, and Throat: Pain in nasal sinus(es), rhinitis.
Eye: Irritation of the eye(s).
Gastrointestinal: Nausea and vomiting, diarrhea, dyspepsia and stomach disorder.
Miscellaneous: Fever.
Mouth and Teeth: Dental problem.
Musculoskeletal: Pain in joint, sprain/strain, aches and pains, pain in limb.
Neurological: Dizziness/giddiness.
Respiratory: Bronchitis, chest congestion.
Skin: Dermatitis, rash/skin eruption.
Urogenital: Dysmenorrhea.

In a 16-week study in asthmatics requiring oral corticosteroids, the effects of fluticasone propionate inhalation aerosol, 660 mcg twice daily (n = 32) and 880 mcg twice daily (n = 32), were compared with placebo. Adverse events (whether considered drug-related or nondrug-related by the investigator) reported by more than three patients in either fluticasone propionate group and which were more common with fluticasone propionate than placebo are shown below:

Ear, Nose, and Throat: Pharyngitis (9% and 25%); nasal congestion (19% and 22%); sinusitis (19% and 22%); nasal discharge (16% and 16%); dysphonia (19% and 9%); pain in nasal sinus(es) (13% and 0%); Candida-like oral lesions (16% and 9%); oropharyngeal candidiasis (25% and 19%).
Respiratory: Upper respiratory infection (31% and 19%); influenza (0% and 13%).
Other: Headache (28% and 34%); pain in joint (19% and 13%); nausea and vomiting (22% and 16%); muscular soreness (22% and 13%); malaise/fatigue (22% and 28%); insomnia (3% and 13%).

OVERDOSAGE: There are no data available on the effects of acute or chronic overdosage with FLOVENT Inhalation Aerosol. Inhalation by healthy volunteers of a single dose of 1,760 or 3,520 mcg of fluticasone propionate inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups. Chronic overdosage may result in signs/symptoms of hypercorticism (see PRECAUTIONS). The oral and subcutaneous median lethal doses in rats and mice were >1,000 mg/kg (>2,000 times the maximum human daily inhalation dose based on mg/m^2).

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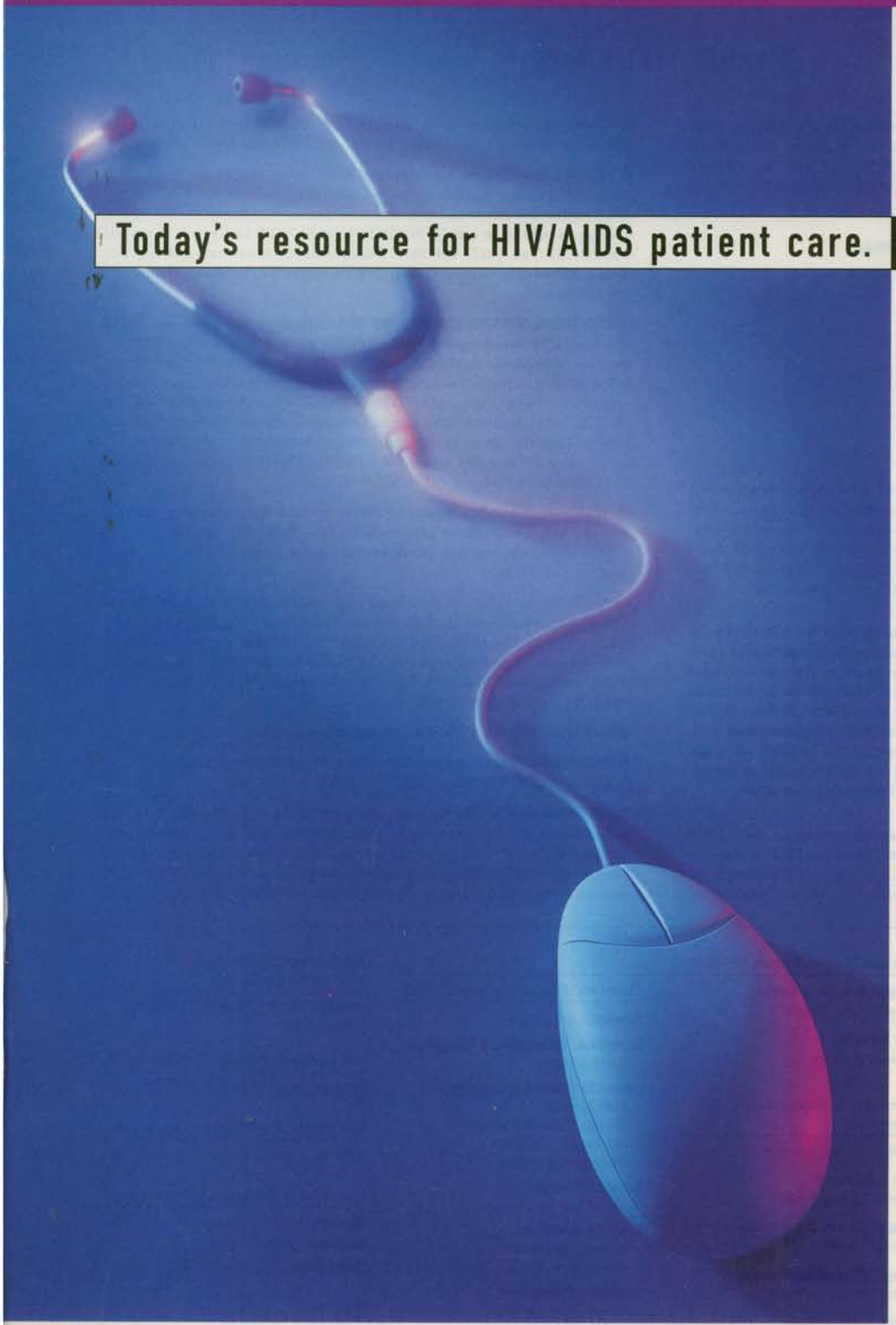

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VOL 5 NO. 9, SEPTEMBER 1996

SPECIAL SELECTION

LETTERS TO THE EDITOR

ORIGINAL CONTRIBUTIONS

American Medical Association
Physicians dedicated to the health of America

Zyrtec™
(cetirizine HCl) tablets

Proven Effective for:

Seasonal Allergic Rhinitis

Perennial Allergic Rhinitis

Chronic Idiopathic Urticaria

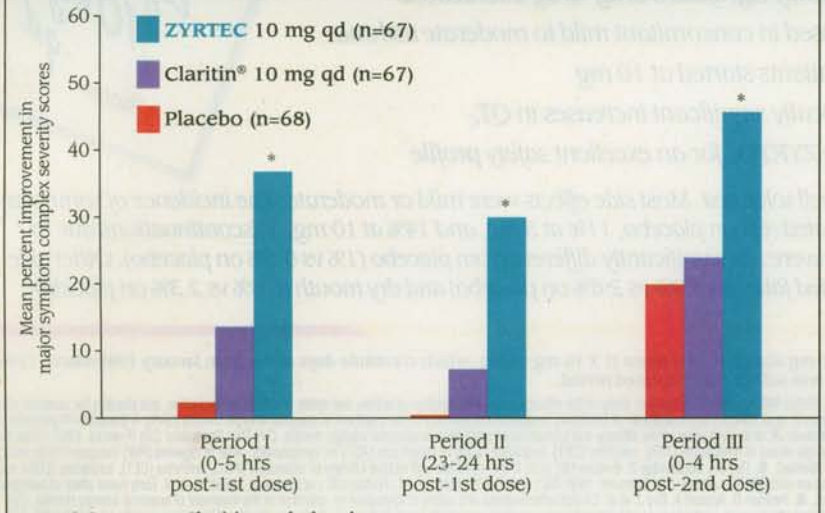
New data confirm...

FAST, EFFECTIVE ALLERGY RELIEF

Please see brief summary of prescribing information on the last page of this advertisement.

ZYRTEC: Efficacy you can count on

Excellent improvement in major symptom severity[1]



*$p \leq 0.01$ versus Claritin and placebo.

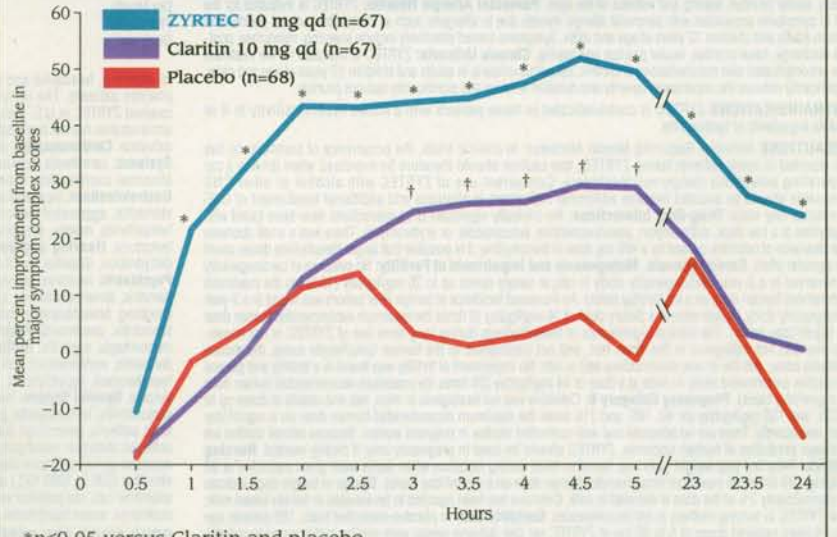
ZYRTEC significantly improved seasonal allergic rhinitis symptoms[1]

In a controlled environmental exposure unit, 202 patients who tested positive to ragweed pollen received either ZYRTEC 10 mg/day, Claritin 10 mg/day, or placebo to control symptoms of seasonal allergic rhinitis. Patients were exposed to ragweed pollen for two 5-hour periods over 2 days in a "classroom-type" setting in which the pollen was delivered to a large seating area at a controlled rate. While fans circulated air, particle counters measured pollen levels throughout the seating area to control exposure level. 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. (Data on file.[1])

ZYRTEC relieved symptoms rapidly[1]

In a separate study by Meltzer et al comparing Zyrtec 10 mg/day and Claritin 10 mg/day in 279 patients with seasonal allergic rhinitis, ZYRTEC's fast-acting, effective relief was confirmed.[2]

Significant relief beginning at 1 hour[1]



*$p \leq 0.05$ versus Claritin and placebo.

†$p < 0.05$ versus placebo.

Once-a-day

Zyrtec™

(cetirizine HCl) tablets

FOR EFFECTIVE ALLERGY RELIEF

Please see reference section for available clinical literature on cetirizine and loratadine.[2-11]

Once-a-day

Zyrtec™ (cetirizine HCl) 5 mg, 10 mg tablets

FOR EFFECTIVE ALLERGY RELIEF

- 2.9 billion patient-days of use*
- No clinically significant drug-drug interactions
- Safely used in concomitant mild to moderate asthma
- Most patients started at 10 mg
- No clinically significant increases in QT_C
- Choose ZYRTEC for an excellent safety profile

ZYRTEC is well tolerated. Most side effects were mild or moderate. The incidence of somnolence was dose related (6% on placebo, 11% at 5 mg, and 14% at 10 mg). Discontinuations due to somnolence were not significantly different from placebo (1% vs 0.6% on placebo). Other side effects included fatigue (5.9% vs 2.6% on placebo) and dry mouth (5.0% vs 2.3% on placebo).

*Based on Total Sector UCB S.A. sales tracking of ZYRTEC 10 mg standard daily doses (1 x 10-mg tablet), which constitute days of use from January 1988-March 1996. Total Sector is defined as all 94 countries in which ZYRTEC was sold during the stated period.

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Due caution should be exercised when driving a car or operating potentially dangerous machinery.

BRIEF SUMMARY

ZYRTEC™ (cetirizine hydrochloride) Tablets **For Oral Use**

(FOR FULL PRESCRIBING INFORMATION, CONSULT PACKAGE INSERT)

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 12 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 12 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 12 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:** No evidence of carcinogenicity was observed in a 2-year carcinogenicity study in rats at dietary doses up to 20 mg/kg/day (15 times the maximum recommended human dose on a mg/m^2/day basis). An increased incidence of benign liver tumors was found in a 2-year carcinogenicity study in male mice at a dietary dose of 16 mg/kg/day (6 times the maximum recommended human dose on a mg/m^2/day 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 the *in vivo* micronucleus test in rats. No impairment of fertility was found in a fertility and general reproductive performance study in mice at a dose of 64 mg/kg/day (26 times the maximum recommended human dose on a mg/m^2/day basis). **Pregnancy Category B:** Cetirizine was not teratogenic in mice, rats and rabbits at doses up to 96, 225, and 135 mg/kg/day (or 40, 180, and 216 times the maximum recommended human dose on a mg/m^2/day basis), respectively. 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:** Retarded pup weight gain was found in mice during lactation when dams were given cetirizine at 96 mg/kg/day (40 times the maximum recommended human dose on a mg/m^2/day 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; use of ZYRTEC in nursing mothers is not recommended. **Geriatric Use:** In placebo-controlled trials, 186 patients age 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:** Safety and effectiveness in children under 12 years of age has not been established.

ADVERSE REACTIONS Controlled and uncontrolled clinical trials conducted in the United States and Canada included more than 6000 patients, 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 mg or 10 mg was not significantly different from placebo (2.9% vs. 2.4%, respectively). The most common adverse reaction that occurred more frequently on cetirizine 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 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 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. The following events were observed infrequently (less than 2%), in 3982 patients who received ZYRTEC in U.S. trials, including an open study of six months duration; a causal relationship with ZYRTEC administration has not been established. **Autonomic Nervous System:** anorexia, urinary retention, flushing, increased salivation. **Cardiovascular:** palpitation, tachycardia, hypertension, cardiac failure. **Central and Peripheral Nervous Systems:** paresthesia, confusion, hyperkinesia, hypertonia, migraine, tremor, vertigo, leg cramps, ataxia, dysphonia, abnormal coordination, hyperesthesia, hypoesthesia, myelitis, paralysis, ptosis, twitching, visual field defect. **Gastrointestinal:** increased appetite, dyspepsia, abdominal pain, diarrhea, flatulence, constipation, vomiting, ulcerative stomatitis, aggravated tooth caries, stomatitis, tongue discoloration, tongue edema, gastritis, rectal hemorrhage, hemorrhoids, melena, abnormal hepatic function. **Genitourinary:** polyuria, urinary tract infection, cystitis, dysuria, hematuria. **Hearing and Vestibular:** earache, tinnitus, deafness, ototoxicity. **Metabolic/Nutritional:** thirst, dehydration, diabetes mellitus. **Musculoskeletal:** myalgia, arthralgia, arthrosis, arthritis, muscle weakness. **Psychiatric:** insomnia, nervousness, depression, emotional lability, impaired concentration, anxiety, depersonalization, paroniria, abnormal thinking, agitation, amnesia, decreased libido, euphoria. **Respiratory System:** epistaxis, rhinitis, coughing, bronchospasm, dyspnea, upper respiratory tract infection, hyperventilation, sinusitis, increased sputum, bronchitis, pneumonia. **Reproductive:** dysmenorrhea, female breast pain, intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis. **Reticuloendothelial:** lymphadenopathy. **Skin:** pruritus, rash, dry skin, urticaria, acne, dermatitis, erythematous rash, increased sweating, alopecia, angioedema, furunculosis, bullous eruption, eczema, hyperkeratosis, hypertrichosis, photosensitivity reaction, photosensitivity toxic reaction, maculopapular rash, seborrhea, purpura. **Special Senses:** taste perversion, taste loss, parosmia. **Vision:** blindness, loss of accommodation, eye pain, conjunctivitis, xerophthalmia, glaucoma, ocular hemorrhage. **Body as a Whole:** increased weight, back pain, malaise, fever, asthenia, generalized edema, periorbital edema, peripheral edema, rigors, leg edema, face edema, hot flashes, enlarged abdomen, nasal polyp. Occasional instances of transient, reversible hepatic transaminase elevations have occurred during cetirizine therapy. A single case of possible drug-induced hepatitis with significant transaminase elevation (500 to 1000 IU/L) and elevated bilirubin has been reported. In foreign marketing experience the following additional rare, but potential severe adverse events have been reported: hemolytic anemia, thrombocytopenia, orofacial dyskinesia, severe hypotension, anaphylaxis, hepatitis, glomerulonephritis, stillbirth, and cholestasis.

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 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. 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 minimal lethal oral dose in rodents is approximately 100 times the maximum recommended clinical dose on a mg/m^2 basis and the liver is the target organ of toxicity.

DOSAGE AND ADMINISTRATION 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. 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, a dose of 5 mg once daily is recommended.

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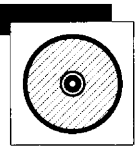

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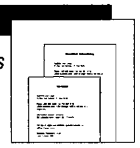

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INDICATIONS AND USAGE

PRECOSE®, as monotherapy, is indicated as an adjunct to diet to lower blood glucose in patients with non-insulin-dependent diabetes mellitus (NIDDM) whose hyperglycemia cannot be managed on diet alone. PRECOSE® may also be used in combination with a sulfonylurea when diet plus either PRECOSE® or a sulfonylurea do not result in adequate glycemic control. The effect of PRECOSE® to enhance glycemic control is additive to that of sulfonylureas when used in combination, presumably because its mechanism of action is different.

In initiating treatment for NIDDM, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling blood glucose and symptoms of hyperglycemia. The importance of regular physical activity when appropriate should also be stressed. If this treatment program fails to result in adequate glycemic control, the use of PRECOSE® should be considered. The use of PRECOSE® must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint.

CONTRAINDICATIONS

PRECOSE® is contraindicated in patients with known hypersensitivity to the drug and in patients with diabetic ketoacidosis or cirrhosis. PRECOSE® is also contraindicated in patients with inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or in patients predisposed to intestinal obstruction. In addition, PRECOSE® is contraindicated in patients who have chronic intestinal diseases associated with marked disorders of digestion or absorption and in patients who have conditions that may deteriorate as a result of increased gas formation in the intestine.

PRECAUTIONS

General

Hypoglycemia: Because of its mechanism of action, PRECOSE® when administered alone should not cause hypoglycemia in the fasted or postprandial state. Sulfonylurea agents may cause hypoglycemia. Because PRECOSE® given in combination with a sulfonylurea will cause a further lowering of blood glucose, it may increase the hypoglycemic potential of the sulfonylurea. Oral glucose (dextrose), whose absorption is not inhibited by PRECOSE®, should be used instead of sucrose (cane sugar) in the treatment of mild to moderate hypoglycemia. Sucrose, whose hydrolysis to glucose and fructose is inhibited by PRECOSE®, is unsuitable for the rapid correction of hypoglycemia. Severe hypoglycemia may require the use of either intravenous glucose infusion or glucagon injection.

Elevated Serum Transaminase Levels: In clinical trials, at doses of 50 mg t.i.d. and 100 mg t.i.d., the incidence of serum transaminase elevations with PRECOSE® was the same as with placebo. In long-term studies (up to 12 months, and including PRECOSE® doses up to 300 mg t.i.d.) conducted in the United States, treatment-emergent elevations of serum transaminases (AST and/or ALT) occurred in 15% of PRECOSE®-treated patients as compared to 7% of placebo-treated patients. These serum transaminase elevations appear to be dose related. At doses greater than 100 mg t.i.d., the incidence of serum transaminase elevations greater than three times the upper limit of normal was two to three times higher in the PRECOSE® group than in the placebo group. These elevations were asymptomatic, reversible, more common in females, and, in general, were not associated with other evidence of liver dysfunction.

In international post-marketing experience with PRECOSE® in over 500,000 patients, 19 cases of serum transaminase elevations > 500 IU/L (12 of which were associated with jaundice) have been reported. Fifteen of these 19 cases received treatment with 100 mg t.i.d. or greater and 13 of 16 patients for whom weight was reported weighed < 60 kg. In the 18 cases where follow-up was recorded, hepatic abnormalities improved or resolved upon discontinuation of PRECOSE®.

Loss of Control of Blood Glucose: When diabetic patients are exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of control of blood glucose may occur. At such times, temporary insulin therapy may be necessary.

Information for Patients: Patients should be told to take PRECOSE® orally three times a day at the start (with the first bite) of each main meal. It is important that patients continue to adhere to dietary instructions, a regular exercise program, and regular testing of urine and/or blood glucose.

PRECOSE® itself does not cause hypoglycemia even when administered to patients in the fasted state. Sulfonylurea drugs and insulin, however, can lower blood sugar levels enough to cause symptoms or sometimes life-threatening hypoglycemia. Because PRECOSE® given in combination with a sulfonylurea or insulin will cause a further lowering of blood sugar, it may increase the hypoglycemic potential of these agents. The risk of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be well understood by patients and responsible family members. Because PRECOSE® prevents the breakdown of table sugar, patients should have a readily available source of glucose (dextrose, D-glucose) to treat symptoms of low blood sugar when taking PRECOSE® in combination with a sulfonylurea or insulin.

If side effects occur with PRECOSE®, they usually develop during the first few weeks of therapy. They are most commonly mild-to-moderate gastrointestinal effects, such as flatulence, diarrhea, or abdominal discomfort and generally diminish in frequency and intensity with time.

Laboratory Tests: Therapeutic response to PRECOSE® should be monitored by periodic blood glucose tests. Measurement of glycosylated hemoglobin levels is recommended for the monitoring of long-term glycemic control.

PRECOSE®, particularly at doses in excess of 50 mg t.i.d., may give rise to elevations of serum transaminases and, in rare instances, hyperbilirubinemia. It is recommended that serum transaminase levels be checked every 3 months during the first year of treatment with PRECOSE® and periodically thereafter. If elevated transaminases are observed, a reduction in dosage or withdrawal of therapy may be indicated, particularly if the elevations persist.

Renal Impairment: Plasma concentrations of PRECOSE® in renally impaired volunteers were proportionally increased relative to the degree of renal dysfunction. Long-term clinical trials in diabetic patients with significant renal dysfunction (serum creatinine >2.0 mg/dL) have not been conducted. Therefore, treatment of these patients with PRECOSE® is not recommended.

Drug Interactions: Certain drugs tend to produce hyperglycemia and may lead to loss of blood glucose control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel-blocking drugs, and isoniazid. When such drugs are administered to a patient receiving PRECOSE®, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from patients receiving PRECOSE® in combination with sulfonylureas or insulin, patients should be observed closely for any evidence of hypoglycemia.

Intestinal adsorbents (e.g., charcoal) and digestive enzyme preparations containing carbohydrate-splitting enzymes (e.g., amylase, pancreatin) may reduce the effect of PRECOSE® and should not be taken concomitantly.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Nine chronic toxicity/carcinogenicity studies were conducted in three animal species (rat, hamster, dog) including two rat strains (Sprague-Dawley and Wistar).

In the first rat study, Sprague-Dawley rats received acarbose in feed at high doses (up to approximately 500 mg/kg body weight) for 104 weeks. Acarbose treatment resulted in a significant increase in the incidence of renal tumors (adenomas and adenocarcinomas) and benign Leydig cell tumors. This study was repeated with a similar outcome. Further studies were performed to separate direct carcinogenic effects of acarbose from indirect effects resulting from the carbohydrate malnutrition induced by the large doses of acarbose employed in the studies. In one study using Sprague-Dawley rats, acarbose was mixed with feed but carbohydrate deprivation was prevented by the addition of glucose to the diet. In a 26-month study of Sprague-Dawley rats, acarbose was administered by daily postprandial gavage so as to avoid the pharmacologic effects of the drug. In both of these studies, the increased incidence of renal tumors found in the original studies did not occur. Acarbose was also given in food and by postprandial gavage in two separate studies in Wistar rats. No increased incidence of renal tumors was found in either of these Wistar rat studies. In two feeding studies of hamsters, with and without glucose supplementation, there was also no evidence of carcinogenicity.

Acarbose showed no mutagenic activity when tested in six *in vitro* and three *in vivo* assays.

Fertility studies conducted in rats after oral administration produced no untoward effect on fertility or on the overall capability to reproduce.

Pregnancy:

Teratogenic Effects: Pregnancy Category B. The safety of PRECOSE® in pregnant women has not been established. Reproduction studies have been performed in rats at doses up to 480 mg/kg (corresponding to 9 times the exposure in humans, based on drug blood levels) and have revealed no evidence of impaired fertility or harm to the fetus due to acarbose. In rabbits, reduced maternal body weight gain, probably the result of the pharmacodynamic activity of high doses of acarbose in the intestines, may have been responsible for a slight increase in the number of embryonic losses. However, rabbits given 160 mg/kg acarbose (corresponding to 10 times the dose in man, based on body surface area) showed no evidence of embryotoxicity and there was no evidence of teratogenicity at a dose 32 times the dose in man (based on body surface area). There are, however, no adequate and well-controlled studies of PRECOSE® in pregnant women. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed. Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers: A small amount of radioactivity has been found in the milk of lactating rats after administration of radiolabeled acarbose. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, PRECOSE® should not be administered to a nursing woman.

Pediatric Use: Safety and effectiveness of PRECOSE® in pediatric patients have not been established.

ADVERSE REACTIONS

Digestive Tract: Gastrointestinal symptoms are the most common reactions to PRECOSE®. In U.S. placebo-controlled trials, the incidences of abdominal pain, diarrhea, and flatulence were 21%, 33%, and 77% respectively in 1075 patients treated with PRECOSE® 50-300 mg t.i.d., whereas the corresponding incidences were 9%, 12%, and 32% in 818 placebo-treated patients. Abdominal pain and diarrhea tended to return to pretreatment levels over time, and the frequency and intensity of flatulence tended to abate with time. The increased gastrointestinal tract symptoms in patients treated with PRECOSE® is a manifestation of the mechanism of action of PRECOSE® and is related to the presence of undigested carbohydrate in the lower GI tract. Rarely, these gastrointestinal events may be severe and might be confused with paralytic ileus.

Elevated Serum Transaminase Levels: See PRECAUTIONS.

Other Abnormal Laboratory Findings: Small reductions in hematocrit occurred more often in PRECOSE®-treated patients than in placebo-treated patients but were not associated with reductions in hemoglobin. Low serum calcium and low plasma vitamin B_6 levels were associated with PRECOSE® therapy but were thought to be either spurious or of no clinical significance.

Caution: Federal law prohibits dispensing without a prescription.

PZ500036BS 4/96 Bay g 5421 PRECOSE®/5202/0/8/USA-1
 6160 Printed in U.S.A.

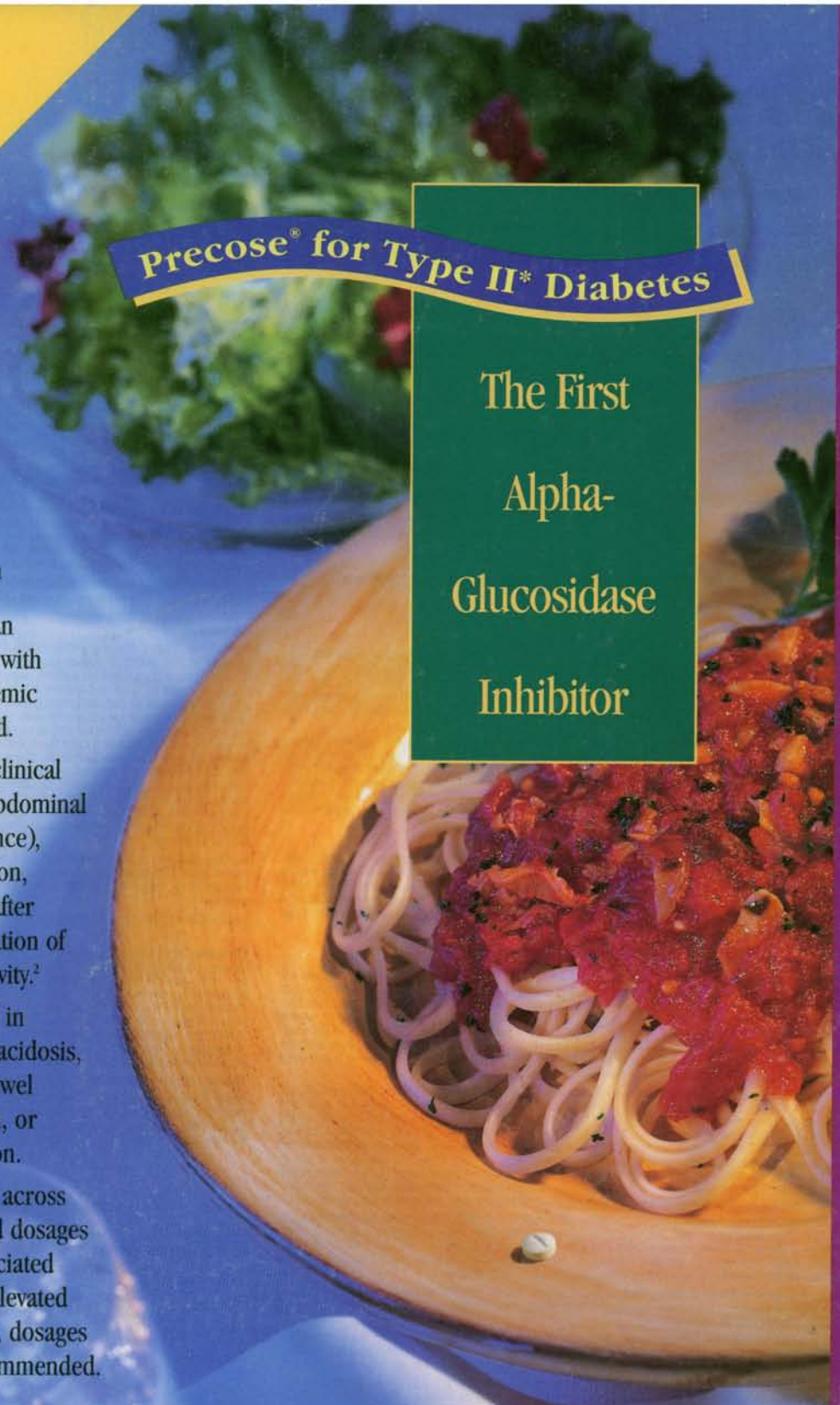
References

1. Precose® (acarbose tablets) Package Insert.
2. Hanefeld M. Acarbose efficacy review. *Practical Diabetes Suppl.* 1993;10(6):S21-S27.

Bayer

Pharmaceutical Division

ANNOUNCING
ALTERNATE DOSING OPTIONS
(see reverse side)



Precose® for Type II* Diabetes

The First Alpha-Glucosidase Inhibitor

Unique, Nonsystemic Mode of Action[1]

Lowers blood glucose as an adjunct to diet – alone or with a sulfonylurea† when glycemic control cannot be achieved.

Majority of side effects in clinical trials were GI in nature (abdominal pain, diarrhea, and flatulence), related to the mode of action, and generally diminished after 4 to 8 weeks due to adaptation of small intestine enzyme activity.[2]

Precose is contraindicated in patients with diabetic ketoacidosis, cirrhosis, inflammatory bowel disease, colonic ulceration, or partial intestinal obstruction.

Because efficacy is similar across dosages ≥ 100 mg *tid*, and dosages > 100 mg *tid* may be associated with an increased risk of elevated serum transaminase levels, dosages > 100 mg *tid* are not recommended.

* Non-insulin-dependent diabetes mellitus.

† Precose itself does not cause hypoglycemia. When used in combination with sulfonylureas, it may increase their hypoglycemic potential. Oral glucose, whose absorption is not inhibited by Precose, should be used instead of sucrose in the treatment of mild to moderate hypoglycemia.

Please see brief summary of Prescribing Information on adjacent page.

50 mg, 100 mg

Precose®
(acarbose tablets)

NIDDM management from the first bite.