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its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn.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).

Made in England June 1996 RL-323 *Glaxo Wellcome Inc. Research Triangle Park, NC 27709*

ARCHIVES OF FAMILY MEDICINE

The ARCHIVES OF FAMILY MEDICINE is a member of the consortium of AMA journals listed below. The ARCHIVES reaches more than 81 500 readers in family and general practice each month, in addition to paid subscribers. The complete text of all AMA journals is available online from Dialog Information Services and Information Access Company.

The Journal of the American Medical Association (JAMA)
Archives of Dermatology
Archives of Family Medicine
Archives of General Psychiatry
Archives of Internal Medicine
Archives of Neurology
Archives of Ophthalmology
Archives of Otolaryngology—Head & Neck Surgery
Archives of Pathology & Laboratory Medicine
Archives of Pediatrics & Adolescent Medicine
Archives of Surgery

The ARCHIVES OF FAMILY MEDICINE (ISSN 1063-3987) is published monthly, except for August and December, by the American Medical Association, 515 N State St, Chicago, IL 60610, and is an official publication of the Association. Periodicals postage paid at Chicago and at additional mailing offices. GST registration number 12622 5556 RT. Canada Post International Publications Mail (Canadian Distribution) Sales Agreement No. 319600. Printed in the USA.

SUBSCRIPTION RATES—The personal subscription rates for the ARCHIVES OF FAMILY MEDICINE are $100 for 1 year (10 issues) in the United States and US possessions; $130 in the Americas; £90 outside the Americas. The institution rates for 1 year are $115 in the United States; $150 in the Americas; £105 outside the Americas. Special rates for residents and medical students are available. Address all subscription communications to: Subscriber Services Center, American Medical Association, PO Box 10946, Chicago, IL 60610. Phone: (800) 262-2350. Fax: (312) 464-5831. E-mail: ama-subs@ama-assn.org. For mailing addresses outside the United States and US possessions, see International Subscription Information.

CHANGE OF ADDRESS—POSTMASTER, send all address changes to ARCHIVES OF FAMILY MEDICINE, c/o Subscriber Services, American Medical Association, 515 N State St, Chicago, IL 60610. Please notify us of address change at least 6 weeks in advance to ensure uninterrupted service. Include both old and new addresses, a recent mailing label, and new ZIP code. For mailing addresses outside the United States and US possessions, see International Subscription Information.

SUBSCRIBER SERVICES—For information about subscribing to any of the AMA publications, change of address, missing issues, or purchasing back issues, please contact Subscriber Services Center, American Medical Association, PO Box 10946, Chicago, IL 60610, or call (312) 670-SUBS (670-7827) between 8:30 AM and 4:30 PM CST. Fax: (312) 464-5831. E-mail: ama-subs@ama-assn.org. For mailing addresses outside the United States and US possessions, see International Subscription Information.

INTERNATIONAL SUBSCRIPTION INFORMATION—Subscriptions outside the United States and US possessions are served according to geographic region. Please address correspondence to the following 2 offices based on delivery address: (1) For delivery in North America, Central America, and South America, contact Subscriber Services Center, AMA, PO Box 10946, Chicago, IL 60610. Phone (312) 670-7827. Fax: (312) 464-5831. E-mail: ama-subs@ama-assn.org. (2) For delivery outside the Americas, contact JAMA & Archives Journals, Reader Services Centre, PO Box 299, London WC1H 9TD, England. Phone: +44(0)171 383 6270. Fax: +44(0)171 383 6402.

REPRINTS—Authors place their reprint order at the time the edited typescript is reviewed and should allow 4 to 6 weeks for delivery following publication. Requests for individual reprints should be sent directly to the author at the address shown in the article.

For bulk reprint orders for distribution by commercial organizations, please contact Wanda Bartolotta, 500 Fifth Ave, #2210, New York, NY 10010. Phone: (212) 354-0050. Fax: (212) 354-1169. E-mail: QGZR06A@Prodigy.com. For reprint orders in limited quantities for distribution by educational organizations, please contact Joseph R. Rekash, 515 N State St, Chicago, IL 60610. Phone: (312) 464-2512. Fax: (312) 464-5835.

WORLD WIDE WEB ADDRESS—http://www.ama-assn.org.

PERMISSIONS—Contact Ada Jimenez-Walker, Permissions Assistant, 515 N State St, Chicago, IL 60610. Phone: (312) 464-2513.

ADVERTISING PRINCIPLES—Each advertisement in this issue has been reviewed and complies with the principles governing advertising in AMA scientific publications. A copy of these principles is available on request. The appearance of advertising in AMA publications is not an AMA guarantee or endorsement of the product or the claims made for the product by the manufacturer.

Publication Staff
Offices: 515 N State St
Chicago, IL 60610

Editorial Processing Department, Specialty Journals

Director: Paula Glitman

Manager: Vickey Golden

Freelance Manager:
Diane L. Cannon

Senior Copy Editor/Atex Specialist:
Paul Frank

Copy Editors:
Mary Kingzette
Barbara Wojtowicz

Editorial Assistant:
Celina Canchola

New Media Editorial Office

New Media Editor:
William M. Silberg

Assistant Editor:
Marty Suter

Production & Distribution Division

Manager, Budgets & Costs:
Bonnie Van Cleven

Office Manager:
Karen Branham

Advertising & Production Department

Director: Vanessa Hayden

Paper & Planning:
Karen Adams-Taylor

Manager, Advertising Services:
Carole Piszker

Manager, Production Services:
Susan Price

Production Associates:
Debbie Camp
Betty Frigerio
Sarah Powell
Jennifer Reiling
Christine M. Wagenknecht
E. Ruth White

Production Assistant:
Jo Anne Turner

Distribution

Distribution Manager: Paul Gasiecki

Electronic Production Department

Director: Linda Knott

Supervisor, Composition & Pagination:
Sandra Lopez

Electronic Production Operators:
Gail Barrett
Brenda Chandler-Haynes
Michael L. Culbert
Mary Ann Kuranda

Graphics Manager:
Charl Richey-Davis

Graphics Operators:
Joe Amft
JoAnne Weiskopf
Alicja Wojcik

Manager, Proofreading:
Teresa H. Omiotek

Proofreaders:
David Antos
Daniel James
Mary Kay Tinerella

Production Assistant:
Ruth Sprague

Database & New Media

Electronic Coordinator:
Mary Ellen Johnston

Database Assistant:
Melanie Parenti

Specialty Journal Division Office

Assistant to the Associate Publisher:
Christine Hearne

Publications Marketing & New Media Division

Assistant to the Publisher, New Media:
Marla Hall

Circulation Processing Department

Director: Beverly Martin

Circulation Development Department

Director: Ann Westerbeke

Licensing & Permissions Department

Director: Norman Frankel
Indexing: Kathy Gaydar
Permissions: Ada Jimenez-Walker

Reprints

Reprint Coordinator: Joseph Rekash

ARCHIVES OF FAMILY MEDICINE

VOL 5 NO. 10, NOVEMBER/DECEMBER 1996

SPECIAL SELECTION

ORIGINAL CONTRIBUTIONS

EDITORIAL

American Medical Association
Physicians dedicated to the health of America

UNITED STATES POSTAL SERVICE™

Statement of Ownership, Management, and Circulation

(Required by 39 U.S.C. 3685)

1. Publication Title	2. Publication No.	3. Filing Date
Archives of Family Medicine	0 0 9 - 5 0 5	9-30-96
4. Issue Frequency	**5. No. of Issues Published Annually**	**6. Annual Subscription Price**
Monthly except for August and December	10	$100.00

7. Complete Mailing Address of Known Office of Publication *(Street, City, County, State, and ZIP+4) (Not Printer)*

515 N. State Street, Chicago, Cook, IL 60610

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*

515 N. State Street, Chicago, Cook, IL 60610

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*

Publisher *(Name and Complete Mailing Address)*

American Medical Association, 515 N. State Street, Chicago, IL 60610

Editor *(Name and Complete Mailing Address)*

Marjorie A. Bowman, M.D., MPA, 515 N. State Street, Chicago, IL 60610

Managing Editor *(Name and Complete Mailing Address)*

None

10. Owner *(If owned by a corporation, its name and address must be stated and also immediately thereafter the names and addresses of stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a partnership or other unincorporated firm, its name and address as well as that of each individual must be given. If the publication is published by a nonprofit organization, its name and address must be stated.) (Do Not Leave Blank.)*

Full Name	Complete Mailing Address
American Medical Association	515 N. State Street, Chicago,IL 60610

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check here. ☒ None

Full Name	Complete Mailing Address
None	

12. For completion by nonprofit organizations authorized to mail at special rates. The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes: *(Check one)*

☒ Has Not Changed During Preceding 12 Months

☐ Has Changed During Preceding 12 Months
(If changed, publisher must submit explanation of change with this statement)

PS Form **3526**, October 1994 *(See Instructions on Reverse)*

13. Publication Name	14. Issue Date for Circulation Data Below
Archives of Family Medicine	9/96

15. Extent and Nature of Circulation	Average No. Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*	10/95-9/96 49102	41226
b. Paid and/or Requested Circulation (1) Sales Through Dealers and Carriers, Street Vendors, and Counter Sales *(Not Mailed)*	n/a	n/a
(2) Paid or Requested Mail Subscriptions *(Include Advertisers' Proof Copies/Exchange Copies)*	25425	23634
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2))*	25425	23634
d. Free Distribution by Mail *(Samples, Complimentary, and Other Free)*	22540	16336
e. Free Distribution Outside the Mail *(Carriers or Other Means)*	0	0
f. Total Free Distribution *(Sum of 15d and 15e)*	22540	16336
g. Total Distribution *(Sum of 15c and 15f)*	47965	39970
h. Copies Not Distributed (1) Office Use, Leftovers, Spoiled	1137	1256
(2) Return from News Agents	0	0
i. Total *(Sum of 15g, 15h(1), and 15h(2))*	49102	41226
Percent Paid and/or Requested Circulation *(15c / 15g x 100)*	53%	59%

16. This Statement of Ownership will be printed in the 11/96 issue of this publication. ☐ Check box if not required to publish.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner — Date

Peter Pappel, Associate Publisher — 9-30-96

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions *(including fines and imprisonment)* and/or civil sanctions *(including multiple damages and civil penalties)*.

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster on or before October 1, annually. Keep a copy of the completed form for your records.
2. Include in items 10 and 11, in cases where the stockholder or security holder is a trustee, the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check box. Use blank sheets if more space is required.
3. Be sure to furnish all information called for in item 15, regarding circulation. Free circulation must be shown in items 15d, e, and f.
4. If the publication had second-class authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or the first printed issue after October, if the publication is not published during October.
5. In item 16, indicate date of the issue in which this Statement of Ownership will be printed.
6. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of second-class authorization.

masking covert folate deficiency in iron deficient subjects with neutrophil hypersegmentation: do suppression tests on lymphocytes and bone marrow. *Br J Haematol.* 1978;39:357-375.
9. Herbert V. Don't ignore low serum cobalamin (vitamin B_{12}) levels. *Arch Intern Med.* 1988;148:1705-1707.
10. Herbert V. The 1986 Herman Award Lecture: nutrition science as a continually unfolding story: the folate and vitamin B12 paradigm. *Am J Clin Nutr.* 1987;46:387-402.
11. Hebert V, Memoli D, McAleer E, Coleman N. What is normal? variation from the individual's norm for granulocyte 'lobe average' and holotranscobalamin II (holo-TC II) diagnoses vitamin B12 deficiency before variation from the laboratory norm. *Clin Res.* 1986;34:718. Abstract.
12. Ardeman S, Chanarin I, Frankland AW. The Pelger-Huet anomaly and megaloblastic anemia. *Blood.* 1963;4:472-476.
13. Davidson WMB, Markson JL. The gastric mucosa in iron deficiency anemia. *Lancet.* 1955;2:639-643.
14. Ikkala E, Siurala M. Gastric lesion in iron deficiency anemia. *Acta Haematol.* 1970;43:228.
15. Taylor KB. Immune aspects of pernicious anemia and atrophic gastritis. *Clin Haematol.* 1976;5:497-519.
16. Oski FA. The non-hematologic manifestations of iron deficiency. *AJDC.* 1979;133:315-322.
17. Dallman PR, Beutler E, Finch CA. Effects of iron deficiency exclusive of anemia. *Br J Haematol.* 1978;40:179-184.
18. MacDonald WC, Rubin CE. Gastric biopsy: a critical evaluation. *Gastroenterology.* 1967;53:143-170.
19. Kapadia CR, Donaldson RM. Disorders of cobalamin (vitamin B12) absorption and transport. *Am Rev Med.* 1985;36:93-110.
20. Rector WG, Fortuin NJ, Conley CL. Nonhematologic effects of chronic iron deficiency. *Medicine.* 1982;42:382-389.
21. Halsted JA, Prasad AS, Madimi M. Gastrointestinal function in iron deficiency anemia. *Arch Intern Med.* 1965;116:2-5.
22. Carmel R, Sinow RM, Siegel ME, Samloff IM. Food cobalamin malabsorption occurs frequently in patients with unexplained low serum cobalamin levels. *Arch Intern Med.* 1988;148:1715-1719.
23. Stenman UF. Intrinsic factor and the vitamin B12 binding proteins. *Clin Haematol.* 1976;5:473-495.
24. Stootsky JA, Oye RK. The changing relationship between clinicians and the laboratory medicine specialist in the managed care era. *Am J Clin Pathol.* 1993;99(suppl 1):S7-S11.
25. Council on Ethical and Judicial Affairs of the American Medical Association. Ethical issues in managed care. *JAMA.* 1995;273:330-335.

50 mg, 100 mg

Precose®
(acarbose tablets)

Dosage and Administration

Taken With the First Bite of Each Main Meal	
Initial dosage:	25 mg *tid* (half of a scored 50-mg tablet *tid*)
Alternate Initial Dosage to Minimize GI Side Effects	
Initial dosage:	25 mg *once daily* (taken with the first bite of the main meal)
Gradually titrate to:	25 mg *tid*
Titrate to:	50 mg *tid*
Maintenance dosage:	50 mg *tid* to 100 mg *tid*
Maximum dosages:	50 mg *tid* for patients ≤ 132 lb 100 mg *tid* for patients > 132 lb

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

PZ500036BS 4/96

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.

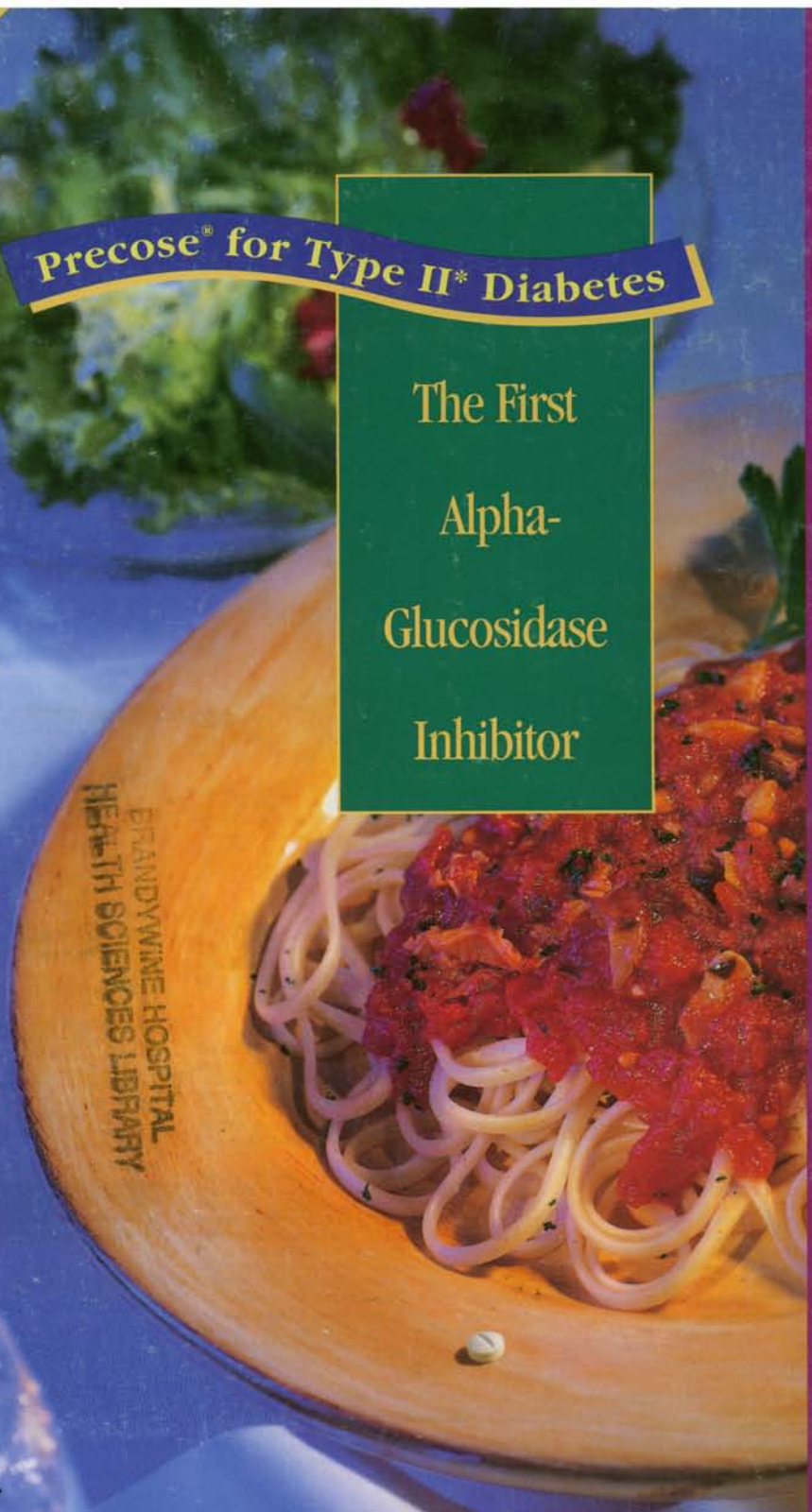
Bayer

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.