

Diabetes

Care

JULY 1995

Original Articles

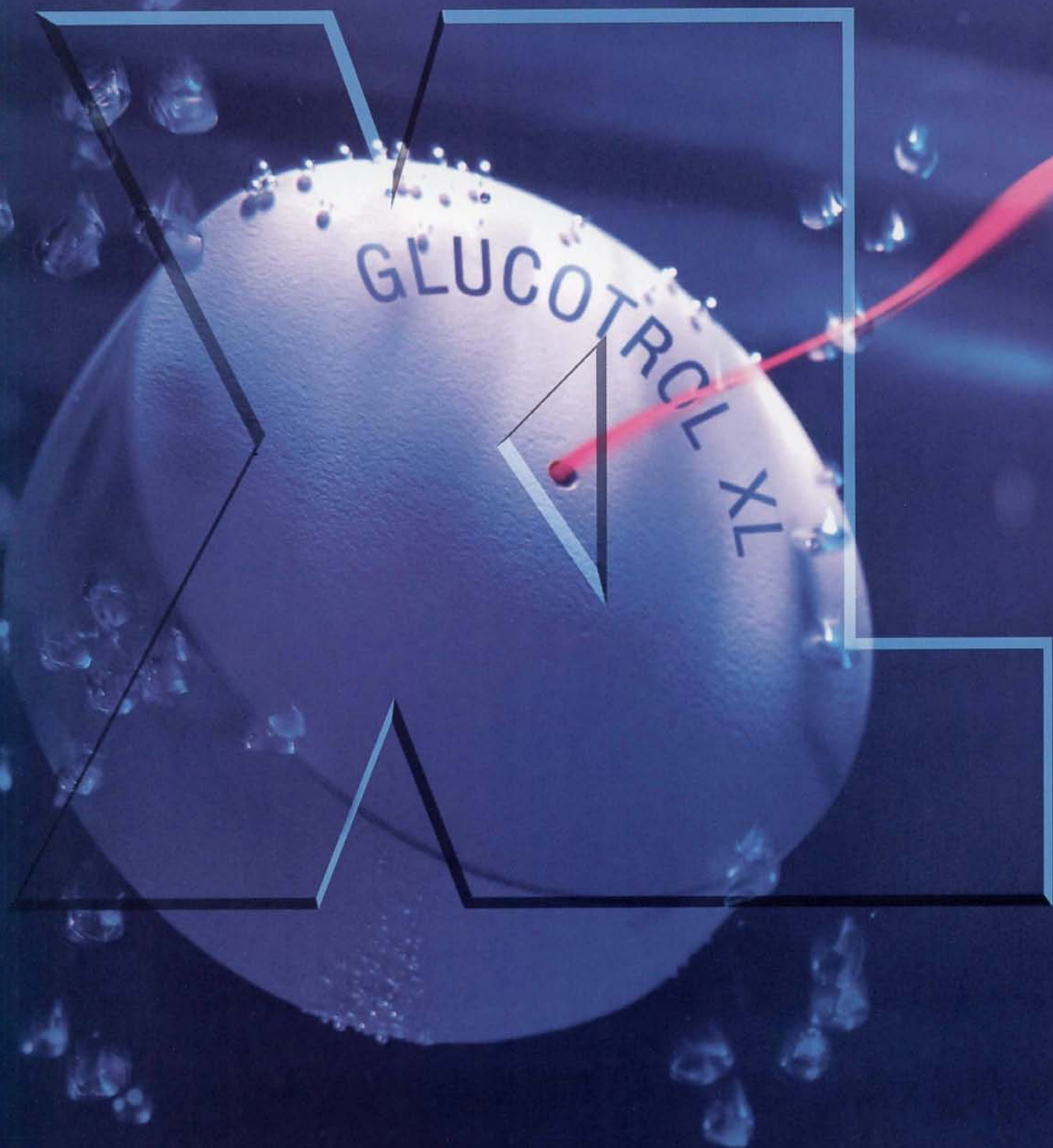
- 923** High incidence of childhood-onset IDDM in Kuwait A.A. Shaltout, M.A. Qabazard, N.A. Abdella, R.E. LaPorte, M.A. Arouj, A.B. Nekhi, M.A. Moussa, M.A. Al Khawari, Kuwait Study Group of Diabetes in Childhood
- 928** A double-blind placebo-controlled trial evaluating the safety and efficacy of acarbose for the treatment of patients with insulin-requiring type II diabetes R.F. Coniff, J.A. Shapiro, T.B. Seaton, B.J. Hoogwerf, J.A. Hunt
- 933** Association between lipoprotein(a) and insulin-like growth factor I during puberty and the relationship to microalbuminuria in children and adolescents with IDDM S. Rudberg, B. Persson
- 940** Feasibility and acceptability of a proposed infant feeding intervention trial for the prevention of type I diabetes H.C. Gerstein, J.R. Simpson, S. Atkinson, D.W. Taylor, J. VanderMeulen
- 943** Patient empowerment: Results of a randomized controlled trial R.M. Anderson, M.M. Funnell, P.M. Butler, M.S. Arnold, J.T. Fitzgerald, C.C. Feste
- 950** The influence of pregnancy on IDDM complications A. Hemachandra, D. Ellis, C.E. Lloyd, T.J. Orchard
- 955** Diabetes in urban African-Americans. II. High prevalence of microalbuminuria and nephropathy in African-Americans with diabetes M.G. Goldschmid, W.S. Domin, D. C. Ziemer, D.L. Gallina, L.S. Phillips
- 962** Physiological modulation of plasma free fatty acid concentrations by diet: metabolic implications in nondiabetic subjects T.M.S. Wolever, A. Bentum-Williams, D.J.A. Jenkins
- 971** The prevalence and severity of microvascular complications in pancreatic diabetes and IDDM N.S. Levitt, G. Adams, J. Salmon, I.N. Solly Marks, G. Musson, C. Swanepoel, M. Levy, M.J. Byrne
- 975** Noninvasive detection of functional alterations of the arterial wall in IDDM patients with and without microalbuminuria B.M. Zenere, G. Arcaro, F. Saggiani, L. Rossi, M. Muggeo, A. Lechi
- 983** Angiotensin I-converting enzyme gene polymorphism is associated with myocardial infarction, but not with retinopathy or nephropathy, in NIDDM T. Fujisawa, H. Ikegami, G.-Q. Shen, E. Yamato, K. Takekawa, Y. Nakagawa, Y. Hamada, H. Ueda, H. Rakugi, J. Higaki, M. Ohishi, K. Fujii, M. Fukuda, T. Ogihara
- 986** Absorption of rapid-acting insulin in obese and nonobese NIDDM patients P.G. Clauson, B. Linde
- 992** Apolipoprotein E polymorphism and insulin levels in a biethnic population R. Valdez, B.V. Howard, M.P. Stern, S.M. Haffner
- 1001** Factors determining the blood pressure response to enalapril and nifedipine in hypertension associated with NIDDM J.C.N. Chan, M.G. Nicholls, C.-K. Cheung, L.-K. Law, R. Swaminathan, C.S. Cockram

Short Reports

- 1007** An assessment of the association between functional edentulism, obesity, and NIDDM T.J. Cleary, J.E. Hutton
- 1010** Positive methane-producing status associated with increased serum cholesterol in subjects with impaired glucose tolerance T.M.S. Wolever, J. Fernandes, V.A. Rao, J.-L. Chiasson, R.G. Josse, L.A. Leiter
- 1013** Abnormal albuminuria as a predictor of mortality and renal impairment in Chinese patients with NIDDM J.C.N. Chan, C.-K. Cheung, M.Y.F. Cheung, R. Swaminathan, J.A.J.H. Critchley, C.S. Cockram
- 1017** IDDM in the province of Pavia, Italy, from a population-based registry: a descriptive study M.T. Tenconi, G. Devoti, I. Albani, R. Lorini, M. Martinetti, P. Fratino, E. Ferrari, E. Ferrero, F. Severi
- 1020** Features of syndrome X in first-degree relatives of NIDDM patients M.W. Stewart, D.B. Humphriss, T.S. Berrish, L.A. Barriocanal, L.R. Trajano, K.G.M.M. Alberti, M. Walker
- 1023** Extra-pancreatic manifestations in diabetes secondary to mitochondrial DNA point mutation within the tRNA^{Leu(UUR)} gene B. Vialettes, V. Paquis-Fluckinger, P. Silvestre-Aillaud, D.B. Dahan, J.-F. Pelissier, F. Etchary-Bouyx, D. Raccach, H. Gin, P.J. Guillausseau, D. Vanuxen, F. Orsini, J. Pouget, P. Cozzone, C. Desnuelle

►Table of contents continued

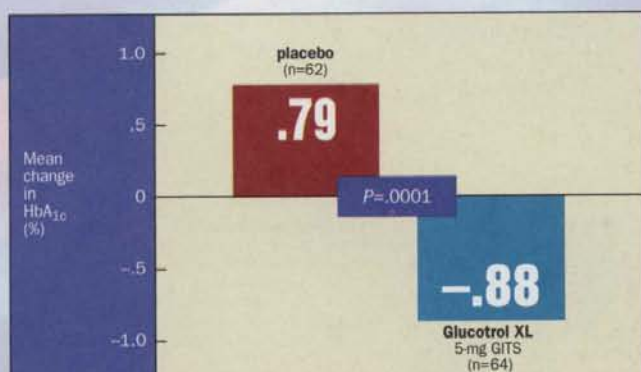
**When diet alone fails in NIDDM*—
Effective 24-hour glucose control
with once-daily dosing at all doses**



* Non-insulin-dependent diabetes mellitus.

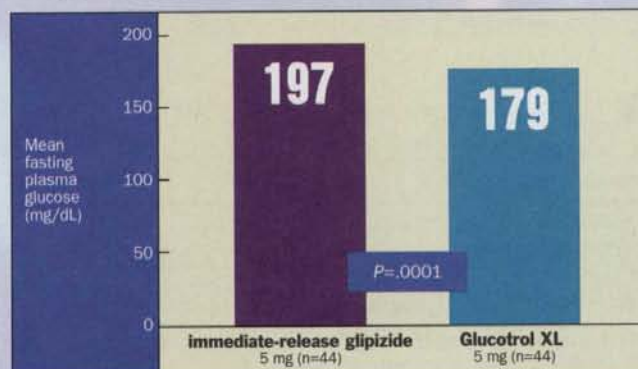
† Gastrointestinal therapeutic system.

Significant decrease in glycosylated hemoglobin (HbA_{1c}) vs placebo¹



A pooled analysis of two 16-week, multicenter, randomized, double-blind, placebo-controlled, fixed-dose studies. After a 1-week washout from current sulfonylurea therapy, or diet failures, patients received 3 weeks of placebo. Following a 4-week titration period in a fixed, double-blind regimen, patients were treated with the assigned dose for 8 weeks.¹

Significantly lower fasting plasma glucose (FPG) levels and equivalent HbA_{1c} concentrations compared with immediate-release glipizide¹



Glucotrol XLTM (glipizide) extended release tablets and immediate-release glipizide were compared in a 16-week, multicenter, open-label, crossover study. The data represent the final FPG levels after 8 weeks of each treatment.¹

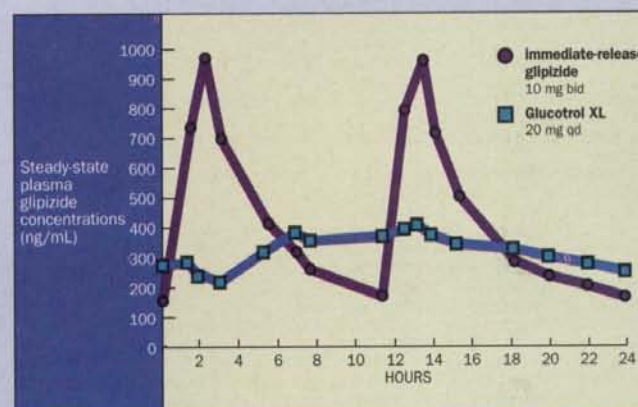
Glucotrol XL is well tolerated¹

	placebo (%) (n=69)	Glucotrol XL (%) (n=278)
Adverse experiences reported with an incidence of 3% or more ¹		
Asthenia	13.0	10.1
Headache	8.7	8.6
Dizziness	5.8	6.8
Diarrhea	0.0	5.4 [†]
Nervousness	2.9	3.6
Tremor	0.0	3.6
Flatulence	1.4	3.2

[†]Only diarrhea was statistically significant vs placebo.

Incidence of hypoglycemia in 580 patients, who received Glucotrol XL in doses ranging from 5 mg to 60 mg, was 3.4%; only 2.6% of patients discontinued due to hypoglycemia. None of the patients required hospitalization. In the controversial UGDP study, there have been reports of increased cardiovascular risk associated with hypoglycemic therapy.¹

Glucotrol XL maintains consistent drug levels throughout the day and night¹



Glucotrol XL 20 mg qd or immediate-release glipizide 10 mg bid were studied in a 5-day, open, randomized, multiple-dose, two-way, crossover study of 20 male patients with NIDDM. Mean glipizide concentration-time profiles on day 5 are shown.¹

When diet alone fails in NIDDM...

ONCE DAILY
Glucotrol XLTM
 (glipizide) extended release
 Tablets 5 mg and 10 mg GITS[†]

As with all sulfonylureas, hypoglycemia may occur.
 Please see brief summary of prescribing information on last page.

When diet alone fails in NIDDM...

ONCE DAILY Glucotrol XLTM (glipizide) extended release Tablets 5 mg and 10 mg GITS

- No need to dose 30 minutes before a meal
- Optimal patient care requires careful titration to the lowest effective dose when using all oral sulfonylureas
- Continued monitoring of HbA_{1c} or FPG levels is recommended throughout therapy

Reference: 1. Data on file.

Brief Summary of Prescribing Information

INDICATIONS AND USAGE: GLUCOTROL XL is indicated as an adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with non-insulin-dependent diabetes mellitus (NIDDM; type II), formerly known as maturity-onset diabetes, after an adequate trial of dietary therapy has proved unsatisfactory.

CONTRAINDICATIONS: Glipizide is contraindicated in patients with: 1. Known hypersensitivity to the drug and 2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.

As with any other non-deformable material, caution should be used when administering GLUCOTROL XL Extended Release Tablets in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of another drug in this non-deformable sustained release formulation.

PRECAUTIONS: Renal and Hepatic Disease: The pharmacokinetics and/or pharmacodynamics of glipizide may be affected in patients with impaired renal or hepatic function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management should be instituted.

GI Disease: Markedly reduced GI retention times of the GLUCOTROL XL Extended Release Tablets may influence the pharmacokinetic profile and hence the clinical efficacy of the drug.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Renal or hepatic insufficiency may affect the disposition of glipizide and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs.

Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of Control of Blood Glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue glipizide and administer insulin. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

Laboratory Tests: Blood and urine glucose should be monitored periodically. Measurement of hemoglobin A_{1c} may be useful.

Information for Patients: Patients should be informed that GLUCOTROL XL Extended Release Tablets should be swallowed whole. Patients should not chew, divide or crush tablets. Patients should not be concerned if they occasionally notice in their stool something that looks like a tablet. In the GLUCOTROL XL Extended Release Tablet, the medication is contained within a nonabsorbable shell that has been specially designed to slowly release the drug so the body can absorb it. When this process is completed, the empty tablet is eliminated from the body.

Patients should be informed of the potential risks and advantages of GLUCOTROL XL and of alternative modes of therapy. They should also be informed about the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure also should be explained.

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. In vitro binding studies with human serum proteins indicate that glipizide binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to the clinical situation and in the use of glipizide with these drugs.

Certain drugs tend to produce hyperglycemia and may lead to loss of 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.

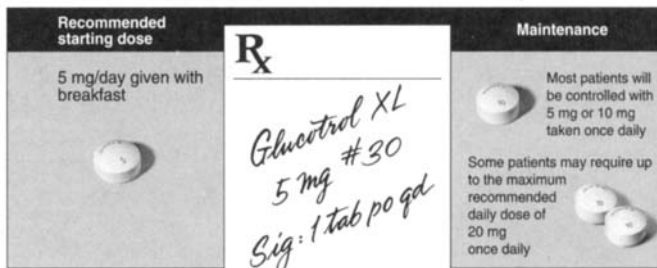
A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known. The effect of concomitant administration of Diflucan[®] (fluconazole) and Glucotrol[®] has been demonstrated in a placebo-controlled crossover study in normal volunteers. All subjects received Glucotrol alone and following treatment with 100 mg of Diflucan[®] as a single daily oral dose for 7 days. The mean percentage increase in the Glucotrol AUC after fluconazole administration was 56.9% (range: 35 to 81%).

Carcinogenesis, Mutagenesis, Impairment of Fertility: A twenty month study in rats and an eighteen month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and in vivo mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

Pregnancy: Pregnancy Category C: Glipizide was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of glipizide. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well controlled studies in pregnant women. Glipizide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Neonates: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. If glipizide is used during pregnancy, it should be discontinued at least one month before the expected delivery date.

Flexible dosing schedule



Nursing Mothers: Although it is not known whether glipizide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. A decision should be made whether to discontinue nursing or to discontinue the drug. If the drug is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use: Safety and effectiveness in children have not been established.

Geriatric Use: Of the total number of patients in clinical studies of GLUCOTROL XL, 33 percent were 65 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some individuals cannot be ruled out. Approximately 1-2 days longer were required to reach steady state in the elderly. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: In U.S. controlled studies the frequency of serious adverse experiences reported was very low and causal relationship has not been established. The 580 patients from 31 to 87 years of age who received GLUCOTROL XL Extended Release Tablets in doses from 5 mg to 60 mg in both controlled and open trials were included in the evaluation of adverse experiences. All adverse experiences reported were tabulated independently of their possible causal relation to medication.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

In double-blind, placebo-controlled studies the adverse experiences reported with an incidence of 3% or more in GLUCOTROL XL-treated patients (N=278) and placebo-treated patients (N=69), respectively, include: Asthenia - 10.1% and 13.0%; Headache - 8.6% and 8.7%; Dizziness - 6.8% and 5.8%; Nervousness - 3.6% and 2.9%; Tremor - 3.6% and 0.0%; Diarrhea - 5.4% and 0.0%; Flatulence - 3.2% and 1.4%.

The following adverse experiences occurred with an incidence of less than 3% in GLUCOTROL XL-treated patients:

Body as a whole - pain; Nervous system - insomnia, paresthesia, anxiety, depression and hypesthesia; Gastrointestinal - nausea, dyspepsia, constipation and vomiting; Metabolic - hypoglycemia; Musculoskeletal - arthralgia, leg cramps and myalgia; Cardiovascular - syncope; Skin - sweating and pruritus; Respiratory - rhinitis; Special senses - blurred vision; Urogenital - polyuria.

Other adverse experiences occurred with an incidence of less than 1% in GLUCOTROL XL-treated patients:

Body as a whole - chills; Nervous system - hyperreflexia, confusion, vertigo, somnolence, gait abnormality and decreased libido; Gastrointestinal - anorexia and trace blood in stool; Metabolic - thirst and edema; Cardiovascular - arrhythmia, migraine, flushing and hypertension; Skin - rash and urticaria; Respiratory - pharyngitis and dyspnea; Special senses - pain in the eye, conjunctivitis and retinal hemorrhage; Urogenital - dysuria.

There have been rare reports of gastrointestinal irritation and gastrointestinal bleeding with use of another drug in this non-deformable sustained release formulation, although causal relationship to the drug is uncertain.

The following are adverse experiences reported with immediate release glipizide and other sulfonylureas, but have not been observed with GLUCOTROL XL:

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic: Hepatic porphyria and disulfiram-like reactions have been reported with sulfonylureas. In the mouse, glipizide pretreatment did not cause an accumulation of acetaldehyde after ethanol administration. Clinical experience to date has shown that glipizide has an extremely low incidence of disulfiram-like alcohol reactions.

Endocrine Reactions: Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with glipizide and other sulfonylureas.

OVERDOSAGE: Overdosage can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours since hypoglycemia may recur after apparent clinical recovery. Clearance of glipizide from plasma may be prolonged in persons with liver disease. Because of the extensive protein binding of glipizide, dialysis is unlikely to be of benefit.

DOSEAGE AND ADMINISTRATION: There is no fixed dosage regimen for the management of diabetes mellitus with GLUCOTROL XL Extended Release Tablet or any other hypoglycemic agent. In general, GLUCOTROL XL should be given with breakfast.

Recommended Dosing: The recommended starting dose of GLUCOTROL XL is 5 mg per day, given with breakfast. The recommended dose for geriatric patients is also 5 mg per day.

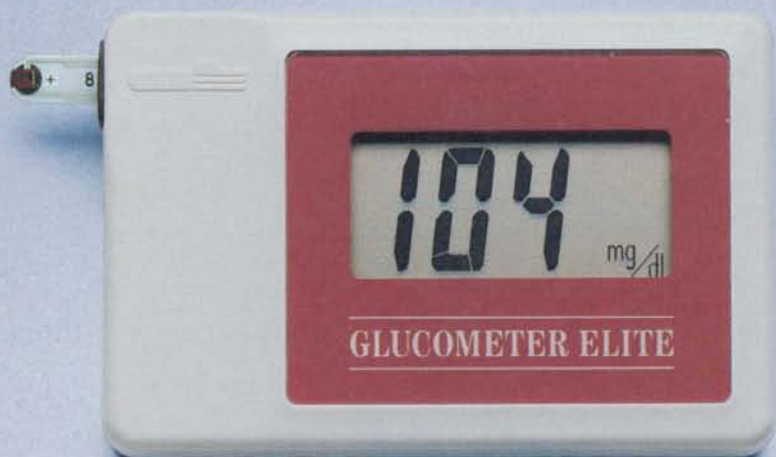
Dosage adjustment should be based on laboratory measures of glycemic control. While fasting blood glucose levels generally reach steady state following initiation or change in GLUCOTROL XL dosage, a single fasting glucose determination may not accurately reflect the response to therapy. In most cases, hemoglobin A_{1c} level measured at three month intervals is the preferred means of monitoring response to therapy.

Hemoglobin A_{1c} should be measured as GLUCOTROL XL therapy is initiated at the 5 mg dose and repeated approximately three months later. If the result of this test suggests that glycemic control over the preceding three months was inadequate, the GLUCOTROL XL dose may be increased to 10 mg. Subsequent dosage adjustments should be made on the basis of hemoglobin A_{1c} levels measured at three month intervals. If no improvement is seen after three months of therapy with a higher dose, the previous dose should be resumed. Decisions which utilize fasting blood glucose to adjust GLUCOTROL XL therapy should be based on at least two or more similar, consecutive values obtained seven days or more after the previous dose adjustment.

Most patients will be controlled with 5 mg or 10 mg taken once daily. However, some patients may require up to the maximum recommended daily dose of 20 mg. While the glycemic control of selected patients may improve with doses which exceed 10 mg, clinical studies conducted to date have not demonstrated an additional group average reduction of hemoglobin A_{1c} beyond what was achieved with the 10 mg dose.

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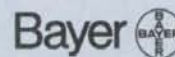
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Table of contents (continued)

- 1029** The epidemiology of diabetes and pregnancy in the U.S., 1988 M.M. Engelgau, W.H. Herman, P.J. Smith, R.P. German, R.E. Aubert

Commentaries

- 1034** Diabetes complications: the renal-retinal link: An epidemiological perspective C.E. Lloyd, T.J. Orchard
- 1037** Beyond glycemia A.I. Vinik, Z. Milicevic, G.L. Pittenger
- 1042** Which test for diagnosing diabetes? D.R. McCance, R.L. Hanson, M.-A. Charles, L.T.H. Jacobsson, D.J. Pettitt, P.H. Bennett, W.C. Knowler
- 1045** Why use the oral glucose tolerance test? R.P. Stolk, T.J. Orchard, D.E. Grobbee

Special Article

- 1050** The pathogenesis and prevention of diabetes in adults: genes, autoimmunity, and demography P.Z. Zimmet

Review Article

- 1065** An alternative approach to the diagnosis of diabetes with a review of the literature M.B. Davidson, A.L. Peters, D.L. Schriger

Editorial

- 1072** Is the oral glucose tolerance test obsolete? A.L. Drash

Letters

- 1074** Scuba diving and diabetes: practical guidelines D.F. Kruger, S.K. Owen, F.W. Whitehouse
- Measurement of D-chiro-inositol in clinical studies R.E. Ostlund, Jr., W.R. Sherman
- The effect of hyperglycemia on glipizide absorption in NIDDM patients E. Esmatjes, P. Vinuesa, P. Navarro, C. Rodriguez-Villar, R. Gomis, E. Vilardell
- Impaired glucose tolerance of pregnancy by WHO and NDDG criteria E.A. Ryan

Perspectives on the News

- 1078** Metformin Z.T. Bloomgarden
- 1081** Issues & Updates
- 1084** Instructions for Authors

JULY AUTHOR INDEX (VOLUME 18, NUMBER 7)

- Abdella, Nabila A., 923
Adams, Ganief, 971
Al Arouj, Mounira, 923
Al Khawari, Mona A., 923
Albani, Ileana, 1017
Alberti, K. George M. M., 1020
Anderson, Robert M., 943
Arcaro, Guido, 975
Arnold, Marilyn S., 943
Atkinson, Stephanie, 940
Aubert, Ronald E., 1029
Barriocanal, Luis A., 1020
Bennett, Peter H., 1066
Bentum-Williams, Anita, 962
Berrish, Taher S., 1020
Bloomgarden, Zachary T., 1078
Butler, Patricia M., 943
Byrne, Michael J., 971
Chan, Juliana C. N., 1001, 1013
Charles, Marie-Aline, 1066
Cheung, Chi-Keung, 1001, 1013
Cheung, Margaret Y. F., 1013
Chiasson, Jean-Louis, 1010
Clauson, Per G., 986
Cleary, Thomas J., 1007
Cockram, Clive S., 1001, 1013
Coniff, Robert F., 928
Cozzone, Patrick, 1023
Critchley, Julian A. J. H., 1013
Dahan, David Ben, 1023
Davidson, Mayer B., 1065
Desnuelle, Claude, 1023
Devoti, Gabriele, 1017
Domin, William S., 955
Drash, Allan L., 1072
Ellis, Demetrius, 950
Engelgau, Michael M., 1029
Esmatjes, Enric, 1076
Etchary-Bouyx, Frédérique, 1023
Fernandes, Judlyn, 1010
Ferrari, Ettore, 1017
Ferrero, Enrico, 1017
Feste, Catherine C., 943
Fitzgerald, James T., 943
Fratino, Pietro, 1017
Fujii, Kenshi, 983
Fujisawa, Tomomi, 983
Fukuda, Masakatsu, 983
Funnell, Martha M., 943
Gallina, Daniel L., 955
German, Robert R., 1029
Gerstein, Hertz C., 940
Gin, Henri, 1023
Goldschmid, Marilyn G., 955
Gomis, Ramon, 1076
Grobbee, Diederick, 1069
Guillausseau, Pierre Jean, 1023
Haffner, Steven M., 992
Hamada, Yoichi, 983
Hanson, Robert L., 1066
Hemachandra, Anusha, 950
Herman, William H., 1029
Higaki, Jitsuo, 983
Hoogwerf, Byron J., 928
Howard, Barbara V., 992
Humphriss, David B., 1020
Hunt, John A., 928
Hutton, John E., 1007
Ikegami, Hiroshi, 983
Jacobsson, Lennart T. H., 1066
Jenkins, David J. A., 962
Josse, Robert G., 1010
Knowler, William C., 1066
Kruger, Davida F., 1074
Kuwait Study Group of Diabetes in Childhood, 923
LaPorte, Ronald E., 923
Law, Lap-Kay, 1001
Lechi, Alessandro, 975
Leiter, Lawrence A., 1010
Levitt, Naomi S., 971
Levy, Margaret, 971
Linde, Birgitta, 986
Lloyd, Cathy E., 950, 1034
Lorini, Renata, 1017
Martinetti, Miryam, 1017
McCance, David R., 1066
Milicevic, Zvonko, 1061
Moussa, Mohamed A., 923
Muggeo, Michele, 975
Musson, Gregory, 971
Nakagawa, Yusuke, 983
Navarro, Pino, 1076
Nekhi, Abdulla Ben, 923
Nicholls, M. Gary, 1001
Ogihara, Toshio, 983
Ohishi, Mitsuru, 983
Orchard, Trevor J., 950, 1034, 1069
Orsini, Frederic, 1023
Ostlund, Jr, Richard E., 1075
Owen, Susan K., 1074
Paquis-Fluckinger, Véronique, 1023
Pelissier, Jean-François, 1023
Persson, Bengt, 933
Peters, Anne L., 1065
Pettitt, David J., 1066
Phillips, Lawrence S., 955
Pittenger, Gary L., 1061
Pouget, Jean, 1023
Qabazard, Mariam A., 923
Raccach, Denis, 1023
Rakugi, Hiromi, 983
Rao, Venketeshwer A., 1010
Rodriguez-Villar, Camino, 1076
Rossi, Luca, 975
Rudberg, Susanne, 933
Ryan, Edmond A., 1077
Saggiani, Francesca, 975
Salmon, John, 971
Schriger, David L., 1065
Seaton, Timothy B., 928
Severi, Francesca, 1017
Shaltout, Azza A., 923
Shapiro, Jo Ann, 928
Shen, Gong-Qing, 983
Sherman, William R., 1075
Silvestre-Aillaud, Pascale, 1023
Simpson, Janis Randall, 940
Smith, Philip J., 1029
Solly Marks, I. N., 971
Stern, Michael P., 992
Stewart, Murray W., 1020
Stolk, Ronald P., 1069
Swaminathan, Ramasmyiyer, 1001, 1013
Swanepoel, Charles, 971
Takekawa, Kiyoshi, 983
Taylor, D. Wayne, 940
Tenconi, Maria T., 1017
Trajano, Laura R., 1020
Ueda, Hironori, 983
Valdez, Rodolfo, 992
VanderMeulen, John, 940
Vanuxen, Danielle, 1023
Viale, Bernard, 1023
Vilardell, Enric, 1076
Vinik, Aaron I., 1061
Vinuesa, Paz, 1076
Walker, Mark, 1020
Whitehouse, Fred W., 1074
Wolever, Thomas M. S., 962, 1010
Yamato, Eiji, 983
Zenere, Beatrice M., 975
Ziemer, David C., 955
Zimmet, Paul Z., 1050



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Reference: 1. Korte JJ, Cooper Research, Inc, Cincinnati, Ohio. The National Preference Trial: A study of patient preferences among blood glucose monitors. August 1994. Data on file, Boehringer Mannheim Corporation. ©1994 Boehringer Mannheim Corporation. All rights reserved.

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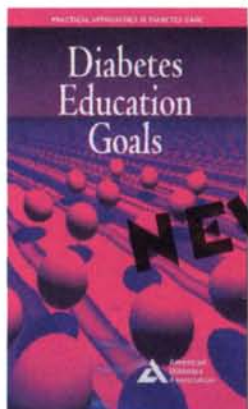
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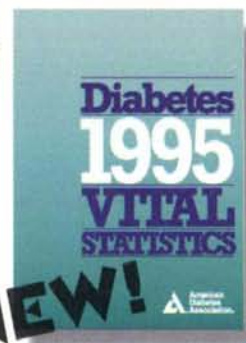
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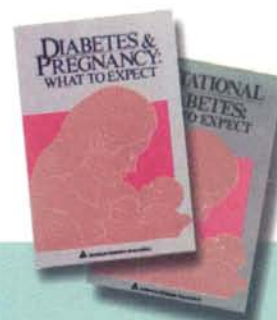
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GLUCOPHAGE®

(METFORMIN HYDROCHLORIDE TABLETS)_{500 mg}

THE NEW APPROACH TO NIDDM*



* Non-insulin-dependent diabetes mellitus (type II).

Please see brief summary of prescribing information, including the **boxed WARNING** regarding Lactic Acidosis, on the last page of this advertisement.

 Bristol-Myers Squibb Company

THE NEW **NON-SULFONYLUREA** APPROACH TO NIDDM

BYPASSES THE PANCREAS WITH

GLUCOPHAGE
lowers blood glucose
levels without
stimulating insulin
secretion.¹

No effect on pancreatic beta cells
or insulin secretion.¹

Does not produce hypoglycemia.¹

GLUCOPHAGE is
highly effective first-
line drug therapy.²

Significantly decreases fasting
plasma glucose (FPG) when used
as an adjunct to diet.²

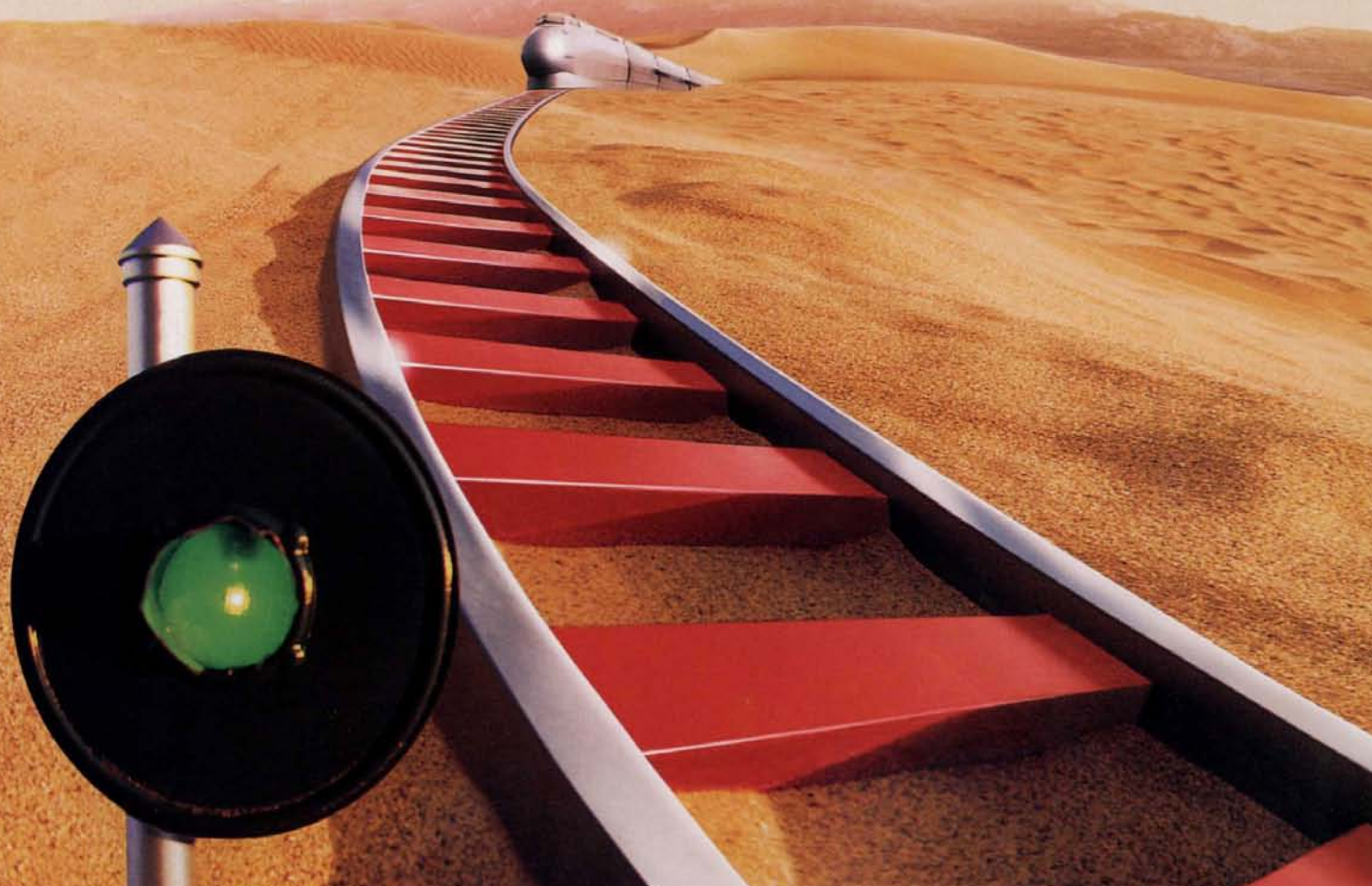
Mean difference in FPG compared
to placebo

GLUCOPHAGE
vs placebo

$P=0.001$

-59
mg/dL

Study 1: Results of a double-blind, placebo-controlled, multicenter trial over 29 weeks. 286 randomized NIDDM patients: GLUCOPHAGE, $n=141$; placebo, $n=145$. Average dosage of GLUCOPHAGE was 1,980 mg/day.²



DIRECT ANTIHYPERGLYCEMIC ACTION.

GLUCOPHAGE is synergistic in combination.²

Combining GLUCOPHAGE and a sulfonylurea with diet lowers FPG significantly more than monotherapy.²

Mean difference in FPG compared to monotherapy

GLUCOPHAGE plus glyburide vs glyburide alone

-77 mg/dL

P=0.001

Study 2: Results of a double-blind, placebo-controlled, parallel-group, multicenter trial comparing GLUCOPHAGE (n=210), glyburide (n=209), and the combination (n=213) over 29 weeks. 632 randomized NIDDM patients in whom glyburide monotherapy (20 mg/day) had failed to provide adequate control. Average dosage of GLUCOPHAGE was 2,050 mg/day as monotherapy and 1,894 mg/day in combination.²

GLUCOPHAGE produces modest improvements in key lipids.¹

Significantly reduces total cholesterol, LDL cholesterol, and triglycerides (P<0.05), and has a neutral effect on HDL cholesterol.^{1,2}

Improvement noted particularly when baseline lipid levels were elevated.¹

GLUCOPHAGE can help NIDDM patients keep their weight under control while lowering blood glucose.¹

In contrast to sulfonylureas, body weight of individuals on GLUCOPHAGE tends to remain stable or decrease.¹

NEW

WITH DIET—ALONE OR WITH A SULFONYLUREA

GLUCOPHAGE[®]

(METFORMIN HYDROCHLORIDE TABLETS)^{500 mg}

THE NEW APPROACH TO NIDDM

Please see brief summary of prescribing information, including the boxed **WARNING** regarding Lactic Acidosis, on the last page of this advertisement.

THE NEW **NON-SULFONYLUREA** APPROACH TO NIDDM

PROVIDES ESTABLISHED SAFETY AND OFFERS BID DOSING.

Safety established in over 3 million patient-years of experience.³

Mild and transient GI side effects are most common.¹

Diarrhea, nausea, vomiting, bloating, or flatulence may occur, especially during initiation of GLUCOPHAGE

- approximately 30% more frequent than with placebo¹
- approximately 4% of patients discontinue therapy due to GI reactions.¹

Rare occurrence of lactic acidosis, a serious condition.

Approximately 0.03 cases per 1,000 patient-years reported worldwide¹

- if cases occur, up to half may be fatal
- seen primarily in patients with renal insufficiency
- Patient Package Insert lists symptoms to be discussed with patients.

The UGDP study suggested increased cardiovascular risk with oral antidiabetics.

Appropriate patient selection is key.¹

Contraindicated in patients with renal disease or renal dysfunction and in patients with metabolic acidosis.

Temporarily withhold in patients receiving iodinated contrast materials for radiologic studies.

Avoid in patients with impaired hepatic function or excessive alcohol intake (acute or chronic).

Not recommended for children or pregnant women.

Recommended starting dosage: 500 mg bid with meals.¹

Increase dosage by one 500 mg tablet each week.

Minimize GI reactions by slow titration and administration with food

- occasionally, temporary dose reduction may be useful.

Individualize dosage based on effectiveness and tolerance, up to a maximum of 2500 mg administered on a tid schedule.

NEW

WITH DIET—ALONE OR WITH A SULFONYLUREA


GLUCOPHAGE[®]

(METFORMIN HYDROCHLORIDE TABLETS)_{500 mg}

THE NEW APPROACH TO NIDDM

References: 1. GLUCOPHAGE Package Insert. 2. Data on file, Bristol-Myers Squibb Company. 3. Sirtori CR, Pasik C: Re-evaluation of a biguanide, metformin: mechanism of action and tolerability. *Pharmacol Res* 30(3):187-228, 1994.

Please see brief summary of prescribing information, including the boxed **WARNING** regarding **Lactic Acidosis**, on the last page of this advertisement.

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GLUCOPHAGE® (METFORMIN HYDROCHLORIDE TABLETS) 500 mg

CONTRAINDICATIONS: GLUCOPHAGE is contraindicated in patients with: 1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see WARNINGS and PRECAUTIONS). 2. GLUCOPHAGE should be temporarily withheld in patients undergoing radiologic studies involving parenteral administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. (See also PRECAUTIONS). 3. Known hypersensitivity to metformin hydrochloride. 4. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

WARNINGS: Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with GLUCOPHAGE; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 μ g/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1,000 patient-years, with approximately 0.015 fatal cases/1,000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking GLUCOPHAGE and by use of the minimum effective dose of GLUCOPHAGE. In addition, GLUCOPHAGE should be promptly withheld in the presence of any condition associated with hypoxemia or dehydration. Because impaired hepatic function may significantly limit the ability to clear lactate, GLUCOPHAGE should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking GLUCOPHAGE, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, GLUCOPHAGE should be temporarily discontinued prior to any intravascular radiocast study and for any surgical procedure (see also PRECAUTIONS). The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence and nonspecific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). GLUCOPHAGE should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of GLUCOPHAGE, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking GLUCOPHAGE do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity or technical problems in sample handling. (See also PRECAUTIONS.) Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia). Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking GLUCOPHAGE, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See also CONTRAINDICATIONS and PRECAUTIONS).

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral antidiabetic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.

PRECAUTIONS: General: **Monitoring of renal function** — GLUCOPHAGE is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive GLUCOPHAGE. In patients with advanced age, GLUCOPHAGE should be carefully titrated to establish the minimum dose for adequate glycemetic effect, because aging is associated with reduced renal function. In elderly patients, renal function should be monitored regularly and, generally, GLUCOPHAGE should not be titrated to the maximum dose (see DOSAGE AND ADMINISTRATION). Before initiation of GLUCOPHAGE therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and GLUCOPHAGE discontinued if evidence of renal impairment is present. — **Use of concomitant medications that may affect renal function or metformin disposition** — Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of GLUCOPHAGE, such as cationic drugs that are eliminated by renal tubular secretion (see Drug Interactions), should be used with caution. — **Radiologic studies involving the use of iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and scans with contrast materials)** — Parenteral contrast studies with iodinated materials can lead to acute renal failure and have been associated with lactic acidosis in patients receiving GLUCOPHAGE (see CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned, GLUCOPHAGE should be withheld for at least 48 hours prior to, and 48 hours subsequent to, the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

— **Hypoxic states** — Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on GLUCOPHAGE therapy, the drug should be promptly discontinued. — **Surgical procedures** — GLUCOPHAGE therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal. — **Alcohol intake** — Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving GLUCOPHAGE. — **Impaired hepatic function** — Since impaired hepatic function has been associated with some cases of lactic acidosis, GLUCOPHAGE should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. — **Vitamin B₁₂ levels** — A decrease to subnormal levels of previously normal serum vitamin B₁₂ levels, without clinical manifestations, is observed in approximately 7% of patients receiving GLUCOPHAGE in controlled clinical trials of 29 weeks duration. Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of GLUCOPHAGE or vitamin B₁₂ supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on GLUCOPHAGE and any apparent abnormalities should be appropriately investigated and managed (see Laboratory Tests). Certain individuals (those with inadequate vitamin B₁₂ or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B₁₂ levels. In these patients, routine serum vitamin B₁₂ measurements at two- to three-year intervals may be useful. — **Change in clinical status of previously controlled diabetic** — A diabetic patient previously well controlled on GLUCOPHAGE who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate and metformin levels. If acidosis of either form occurs, GLUCOPHAGE must be stopped immediately and other appropriate corrective measures initiated (see also WARNINGS). — **Hypoglycemia** — Hypoglycemia does not occur in patients receiving GLUCOPHAGE alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas) or ethanol. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs. — **Loss of control of blood glucose** — When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold GLUCOPHAGE and temporarily administer insulin. GLUCOPHAGE may be reinstituted after the acute episode is resolved. The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with GLUCOPHAGE or sulfonylurea monotherapy, combined therapy with GLUCOPHAGE and sulfonylurea may result in a response. Should secondary failure occur with combined GLUCOPHAGE/sulfonylurea therapy, it may be necessary to initiate insulin therapy.

— **Information for Patients:** Patients should be informed of the potential risks and advantages of GLUCOPHAGE and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function and hematologic parameters. The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the WARNINGS and PRECAUTIONS sections should be explained to patients. Patients should be advised to discontinue GLUCOPHAGE® (metformin hydrochloride tablets) immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of GLUCOPHAGE, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Patients should be counseled against excessive alcohol intake, either acute or chronic, while receiving GLUCOPHAGE. GLUCOPHAGE alone does not usually cause hypoglycemia, although it may occur when GLUCOPHAGE is used in conjunction with oral sulfonylureas. When initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients. (See Patient Package Insert.) — **Laboratory Tests:** Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control (see also DOSAGE AND ADMINISTRATION). Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with GLUCOPHAGE therapy, if this is suspected, vitamin B₁₂ deficiency should be excluded. — **Drug Interactions:** **Glyburide** — In a single-dose interaction study in NIDDM subjects, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain (see DOSAGE AND ADMINISTRATION, Concomitant Glucophage and Oral Sulfonylurea Therapy). — **Furosemide** — A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically. — **Nifedipine** — A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine. — **Cationic drugs** — Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of GLUCOPHAGE and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system. — **Other** — Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazide 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 GLUCOPHAGE, the patient should be closely observed to maintain adequate glycemic control. In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies. Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins. — **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately three times the maximum recommended human daily dose on a body surface area basis. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. However, an increased incidence of benign stromal uterine polyps was seen in female rats treated with 900 mg/kg/day. No evidence of a mutagenic potential of metformin was found in the Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes), or *in-vivo* micronuclei formation test (mouse bone marrow). Fertility of male or female rats was unaffected by metformin administration at doses as high as 600 mg/kg/day, or approximately two times the maximum recommended human daily dose on a body surface area basis. — **Pregnancy:** **Teratogenic effects** — **Pregnancy Category B.** Safety in pregnant women has not been established. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, or about two times the maximum recommended human daily dose on a body surface area basis. Determination of fetal concentrations demonstrated a partial placental barrier to metformin. Because animal reproduction studies are not always predictive of human response, any decision to use this drug should be balanced against the benefits and risks. Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, there is a consensus among experts that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. — **Nursing Mothers:** Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers, but caution should be exercised in such patients, and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. — **Pediatric Use:** Safety and effectiveness in children have not been established. Studies in maturity-onset diabetes of the young (MODY) have not been conducted. — **Geriatric Use:** Controlled clinical studies of GLUCOPHAGE did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. GLUCOPHAGE is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, it should only be used in patients with normal renal function (see CONTRAINDICATIONS, CLINICAL PHARMACOLOGY, Pharmacokinetics). Because aging is associated with reduced renal function, GLUCOPHAGE should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of GLUCOPHAGE (see also DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: **Lactic Acidosis:** See WARNINGS, PRECAUTIONS and OVERDOSAGE Sections. — **Gastrointestinal Reactions:** Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to GLUCOPHAGE and are approximately 30% more frequent in patients on GLUCOPHAGE monotherapy than in placebo-treated patients, particularly during initiation of GLUCOPHAGE therapy. These symptoms are generally transient and resolve spontaneously during continued treatment. Occasionally, temporary dose reduction may be useful. In controlled trials, GLUCOPHAGE was discontinued due to gastrointestinal reactions in approximately 4% of patients. Because gastrointestinal symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take GLUCOPHAGE with meals (see DOSAGE AND ADMINISTRATION). Because significant diarrhea and/or vomiting may cause dehydration and prerenal azotemia, under such circumstances, GLUCOPHAGE should be temporarily discontinued. For patients who have been stabilized on GLUCOPHAGE, nonspecific gastrointestinal symptoms should not be attributed to therapy unless intercurrent illness or lactic acidosis have been excluded. — **Special Senses:** During initiation of GLUCOPHAGE therapy, approximately 3% of patients may complain of an unpleasant or metallic taste, which usually resolves spontaneously. — **Dermatologic Reactions:** The incidence of rash/dermatitis in controlled clinical trials was comparable to placebo for GLUCOPHAGE monotherapy and to sulfonylurea for GLUCOPHAGE/sulfonylurea therapy. — **Hematologic:** (See also PRECAUTIONS). During controlled clinical trials of 29 weeks duration, approximately 9% of patients on GLUCOPHAGE monotherapy and 6% of patients on GLUCOPHAGE/sulfonylurea therapy developed asymptomatic subnormal serum vitamin B₁₂ levels; serum folic acid levels did not decrease significantly. However, only five cases of megaloblastic anemia have been reported with metformin administration (none during U.S. clinical studies) and no increased incidence of neuropathy has been observed. Therefore, serum B₁₂ levels should be appropriately monitored or periodic parenteral B₁₂ supplementation considered.

OVERDOSAGE: Hypoglycemia has not been seen even with ingestion of up to 85 grams of GLUCOPHAGE, although lactic acidosis has occurred in such circumstances (see WARNINGS). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

Consult package insert before prescribing GLUCOPHAGE (metformin hydrochloride tablets). F5-8001A 1/95

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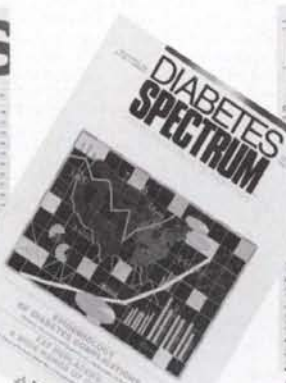
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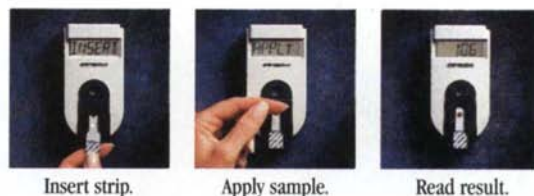
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