notropin" [Mojsov et al. *J Clin Invest*, 79:616]) are cited.

3. GLP-1 7–37 is suggested as a potential therapeutic agent for the treatment of type II diabetes. The true natural peptide GLP-1 (7–36 amide) stimulates insulin secretion with at least equal potency and, in addition, inhibits glucagon secretion, as reported by Kreymann et al. (*Lancet* 2:1300, 1987), Ørskov et al. (*Endocrinology* 123:2009, 1988), and Komatsu et al. (*Diabetes* 38:902, 1989), whereas GLP-1 7–37, at least in rats, has no effect on glucagon secretion (Weir et al. *Diabetes* 38:338, 1989). Thus, GLP-1 7–36 amide, the naturally occurring peptide, is a better candidate as a therapeutic agent for the treatment of type II diabetes.

JENS JUUL HOLST, MD
CATHRINE ØRSKOV, MD

FROM THE UNIVERSITY OF COPENHAGEN, DEPARTMENT OF MEDICAL PHYSIOLOGY C, COPENHAGEN, DENMARK.

ADDRESS CORRESPONDENCE TO JENS JUUL HOLST, MD, UNIVERSITY OF COPENHAGEN, DEPARTMENT OF MEDICAL PHYSIOLOGY C, DK-2200, COPENHAGEN, DENMARK.

Reply

The comments by Holst and Ørskov on our report of the insulinotropic actions of glucagonlike peptide-I (7–37) in diabetic and nondiabetic subjects raise some interesting and important points (1). Because of the preliminary stage of our studies, the editors requested that our report be condensed. This necessitated an abbreviation of the reference list, which is quite extensive considering the many publications from United States, European, and Japanese investigators (reviewed in Fehmann and Habener 2). In our view, whether or not one or the other of the isoforms of glucagonlike peptide-I (7–37) or (7–36) amide is the predominant form of the peptide, or whether either one has unique biological actions, remains to be proven. In the rat intestine, both isoforms are expressed, and all-or-none expression of one or the other of the isoforms in the human intestine is not yet established (3). Regardless of the levels of expression of the two isopeptides, both appear to have equivalent potencies of insulinotropic actions.

The issue of whether or not glucagonlike peptide-I suppresses glucagon secretion by a direct action on α-cells or indirectly by stimulating insulin release, which in turn exerts a paracrine suppression of glucagon is unsettled (4). There is no a priori reason to believe that the two isoforms of glucagonlike peptide-I would differ in their actions, either direct or indirect, on glucagon-producing α-cells.

We are in complete agreement with Drs. Holst and Ørskov that glucagonlike peptide-I appears to be a potentially novel therapeutic agent for the treatment of NIDDM, a devastating disease for which minimal progress in treatment has been made over the last decade. Our studies, and those reported later in the year by Gutniak et al. (5), provide an impetus to pursue further the potential of glucagonlike peptide-I in the treatment of NIDDM.

Finally, in our report we had no intention of laying claim to priority of the discovery of the insulinotropic actions of glucagon-like peptide-1. Our goals are to extend understanding of the actions of the peptide and its role in the causation and treatment of NIDDM.

DAVID M. NATHAN, MD
JOEL F. HABENER, MD

FROM THE DIABETES UNIT, MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASSACHUSETTS.

ADDRESS CORRESPONDENCE TO DAVID NATHAN, MD, MASSACHUSETTS GENERAL HOSPITAL, DIABETES UNIT, BOSTON, MA 02114.

References

1. Nathan DM, Schreiber E, Fogel H, Mojsov S, Habener JF. Insulinotropic action of glucagon-like peptide-I (7–37) administered to diabetic and non-diabetic subjects. *Diabetes Care* 15:270–76, 1992
2. Fehmann HC, Habener JF. Insulinotropic glucagon-like peptide-I (7–37)/(7–36) amide: a new incretion hormone. *Trends Endocrinol Metab* 3:158–63, 1992
3. Mojsov S, Kopczynski M, Habener JF. Insulinotropic glucagon-like peptides I (7–37) and (7–36) amide are both produced in the rat intestine. *J Biol Chem* 265:8001–8008, 1990
4. Marugama H, Hisatomi A, Orci L, Grodsky GM, Unger RH. Insulin within islets is a physiologic glucagon release inhibitor. *J Clin Invest* 74:2296–99, 1984
5. Gutniak M, Orskov C, Holst JJ, Ahren B, Efendic S. Antidiabetogenic effect of glucagon-like peptide-1 (7–36) amide in normal subjects and patients with diabetes mellitus. *N Eng J Med* 326:1316–22, 1992

Lp(a) Serum Concentrations and Metabolic Control

Epidemiological studies have identified Lp(a) as a major risk factor for coronary heart disease (1). Elevated concentrations in diabetic patients could contribute to their increased risk. Despite this possibly important link, little information is available concerning the dependence of Lp(a) on metabolic control.

Eighteen patients (9 with NIDDM, 9 with IDDM; 9 women, 9 men; mean age 45 yr, range 16–76 yr) were studied prospectively for 21 days after hospitalization for improvement of diabetic control. All of these patients suffered from long-term poor metabolic control without recent deterioration (e.g., because of infection). Lp(a) deter-

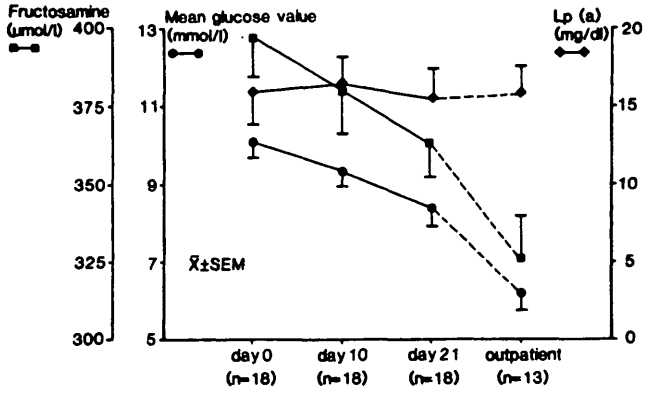


Figure 1—*Lp(a) during metabolic improvement. Values are means ± SE.*

minations (by a two-site anti-apoLp(a) immunoradiometric assay, (Pharmacia, Uppsala, Sweden) were done at day 1, day 10, and day 21 during the hospital stay (intra- and interassay variances <5 and <9%, respectively). Thirteen of these patients were followed on an outpatient basis for another determination 1–4 wk after the hospital stay. Blood glucose determinations were performed seven times daily. From 49 values, a mean glucose value of the week was calculated (Fig. 1).

All patients exhibited improved diabetic control. Glucose values fell from 10.2 ± 0.4 to 8.9 ± 0.7 mM ($P < 0.001$, Wilcoxon's nonparametric ranking test). The fructosamine concentration dropped from 399 (16) to 369 µM (16) ($P < 0.05$). Despite the improvement of diabetic control, there was no relevant change of Lp(a) (from 16.0 ± 3.0 to 15.5 ± 3.1 mg/dl). In the 13 patients studied as outpatients, the improvement in metabolic control continued (fructosamine fell to 325 µM, mean glucose value fell to 6.2 mM), whereas the Lp(a) values for the subgroup remained unchanged (15.8 mg/dl). The constancy of Lp(a) also was present when patients with NIDDM and IDDM were studied separately (NIDDM mean day 1, 12.4 mg/dl; day 21, 14.1 mg/dl).

Two studies with 10 (2) and 12 (3) IDDM patients concluded that hyperglycemia is associated with an increased Lp(a) concentration, which declines with improvement in metabolic control. A cross-sectional study demonstrated a correlation between glycosylated hemoglobin and Lp(a) in white (but not in black) diabetic children (4).

As far as we know, our observations are the first longitudinal data available for patients with NIDDM. A cross-sectional study found a trend to lower levels in patients with NIDDM compared with control subjects (5). Our discrepant results, compared with the two former studies in patients with IDDM, are not easy to explain. One study involved a different ethnic group (mainly Mexican Americans; 3). The strong decrease of 36% (from 46 to 29 mg/dl) reported by Bruckert et al. (2) is unique. Although unlike other risk factors Lp(a) is very resistant to diet and drug manipulation (1), some preliminary data suggests that Lp(a) might behave as an acute phase protein (6). We suggest that our exclusion of patients with an associated disease as the cause of metabolic deterioration prevented an observation of the decline of Lp(a) reported before.

There are many good reasons to treat hyperglycemia, but our results do not support the idea that high concentrations of Lp(a) are lowered to a great extent during metabolic improvement in otherwise healthy diabetic patients.

M.M. RITTER, MD
W.O. RICHTER, MD
K. LYKO, MD
P. SCHWANDT, MD

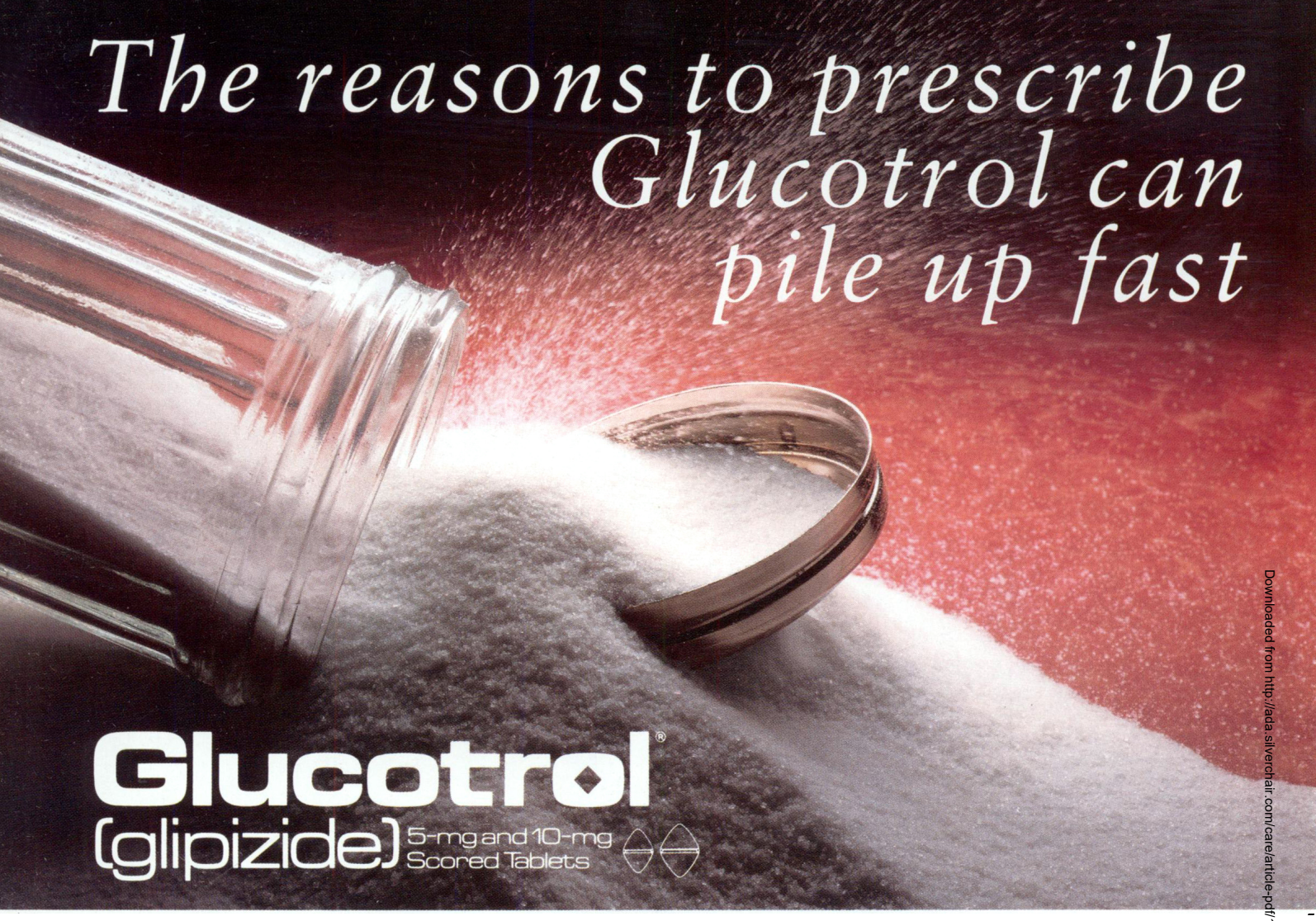
FROM THE MEDIZINISCHE KLINIK II, KLINIKUM GROßHADERN, UNIVERSITY OF MUNICH, MUNICH, GERMANY.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO M.M. RITTER, MD, MEDIZINISCHE KLINIK II, KLINIKUM GROßHADERN, UNIVERSITY OF MUNICH, 8000 MUNICH 70, GERMANY.

LP(A), LIPOPROTEIN A; IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS.

References

1. Scanu AM, Lawn RM, Berg K: Lipoprotein(a) and atherosclerosis. *Ann Intern Med* 115:209–18, 1991
2. Bruckert E, Davidoff P, Grimaldi A, Truffert J, Giral P, Doumith R, Thervet F, DeGennes JL: Increased serum levels of lipoprotein(a) in diabetes mellitus and their reduction with glycemic control. *JAMA* 263:35–36, 1990
3. Haffner SM, Tuttle KR, Rainwater DL: Decrease of lipoprotein(a) with improved glycemic control in IDDM subjects. *Diabetes Care* 14:302–307, 1991
4. Levitsky LL, Scanu AM, Gould SH: Lipoprotein(a) levels in black and white children and adolescents with IDDM. *Diabetes Care* 14:283–87, 1991
5. Joven J, Vilella E: Serum levels of lipoprotein(a) in patients with well-controlled non-insulin-dependent diabetes mellitus. *JAMA* 265:1113–14, 1991
6. Maeda S, Abe A, Seishima M, Makino K, Noma A, Kawade M: Transient changes of serum lipoprotein(a) as an acute phase protein. *Atherosclerosis* 78:145–50, 1989



Brief Summary of Prescribing Information

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

CONTRAINDICATIONS: GLUCOTROL is contraindicated in patients with known hypersensitivity to the drug or with diabetic ketoacidosis, with or without coma, which 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. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes*, 19, supp. 2:747-830, 1970). UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of GLUCOTROL and of alternative modes of therapy. Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS: Renal and Hepatic Disease: The metabolism and excretion of GLUCOTROL may be slowed in patients with impaired renal and/or hepatic function. Hypoglycemia may be prolonged in such patients should it occur.

Hypoglycemia: All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemia. Renal or hepatic insufficiency may increase the risk of 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 may be difficult to recognize in the elderly or people taking beta-adrenergic blocking 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: A loss of control may occur in diabetic patients exposed to stress such as fever, trauma, infection, or surgery. It may then be necessary to discontinue GLUCOTROL and administer insulin.

Laboratory Tests: Blood and urine glucose should be monitored periodically. Measurement of glycosylated hemoglobin may be useful.

Information for Patients: Patients should be informed of the potential risks and advantages of GLUCOTROL, of alternative modes of therapy, as well as 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 should also 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* studies indicate that GLUCOTROL 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. Certain drugs tend to produce hyperglycemia and may lead to loss of control including 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A 20-month study in rats and an 18-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: GLUCOTROL (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 GLUCOTROL. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well-controlled studies in pregnant women. GLUCOTROL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia 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. GLUCOTROL should be discontinued at least one month before the expected delivery date.

Nursing Mothers: Since some sulfonylurea drugs are known to be excreted in human milk, insulin therapy should be considered if nursing is to be continued.

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

ADVERSE REACTIONS: In controlled studies, the frequency of serious adverse reactions reported was very low. Of 702 patients, 11.8% reported adverse reactions and in only 1.5% was GLUCOTROL discontinued.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

Gastrointestinal: Gastrointestinal disturbances, the most common, were reported with the following approximate incidence: nausea and diarrhea, one in 70; constipation and gastralgia, one in 100. They appear to be dose-related and may disappear on division or reduction of dosage. Cholestatic jaundice may occur rarely with sulfonylureas. GLUCOTROL should be discontinued if this occurs.

Dermatologic: Allergic skin reactions including erythema, morbilliform or maculopapular eruptions, urticaria, pruritus, and eczema have been reported in about one in 70 patients. These may be transient and may disappear despite continued use of GLUCOTROL; if skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

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

Metabolic: Hepatic porphyria and disulfiram-like alcohol reactions have been reported with sulfonylureas. Clinical experience to date has shown that GLUCOTROL has an extremely low incidence of disulfiram-like reactions.

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

Miscellaneous: Dizziness, drowsiness, and headache have each been reported in about one in fifty patients treated with GLUCOTROL. They are usually transient and seldom require discontinuance of therapy.

OVERDOSAGE: Overdosage of sulfonylureas including GLUCOTROL can produce hypoglycemia. If hypoglycemic coma is diagnosed or suspected, the patient should be given a 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 GLUCOTROL from plasma would be prolonged in persons with liver disease. Because of the extensive protein binding of GLUCOTROL, dialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION: There is no fixed dosage regimen for the management of diabetes mellitus with GLUCOTROL; in general, it should be given approximately 30 minutes before a meal to achieve the greatest reduction in postprandial hyperglycemia.

Initial Dose: The recommended starting dose is 5 mg before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg. Dosage adjustments should ordinarily be in increments of 2.5–5 mg, as determined by blood glucose response. At least several days should elapse between titration steps.

Maximum Dose: The maximum recommended total daily dose is 40 mg.

Maintenance: Some patients may be effectively controlled on a once-a-day regimen, while others show better response with divided dosing. Total daily doses above 15 mg should ordinarily be divided.

HOW SUPPLIED: GLUCOTROL tablets are white, dye-free, scored, diamond-shaped, and imprinted as follows:

5 mg—Pfizer 411; 10 mg—Pfizer 412.

5 mg Bottles: 100's (NDC 0049-4110-66); 500's (NDC 0049-4110-73); Unit Dose 100's (NDC 0049-4110-41)

10 mg Bottles: 100's (NDC 0049-4120-66); 500's (NDC 0049-4120-73); Unit Dose 100's (NDC 0049-4120-41)

CAUTION: Federal law prohibits dispensing without prescription.

More detailed professional information available on request.

Pfizer Roerig

Revised August 1990