PRODUCT MONOGRAPH

[Pr] NOVO-GLIMEPIRIDE

(glimepiride)

Tablets 1 mg, 2 mg and 4 mg

Oral Hypoglycemic (Sulfonylurea)

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 1 mg, 2 mg and 4 mg	Lactose monohydrate *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

NOVO-GLIMEPIRIDE (glimepiride) is indicated for:

- NOVO-GLIMEPIRIDE (glimepiride) is indicated as an adjunct to proper dietary management, exercise and weight reduction to lower the blood glucose in patients with Type 2 Diabetes whose hyperglycemia cannot be controlled by diet and exercise alone.

- NOVO-GLIMEPIRIDE is also indicated for use in combination with insulin to lower blood glucose in patients with Type 2 Diabetes whose hyperglycemia cannot be controlled by diet and exercise in conjunction with an oral hypoglycemic agent alone.

CONTRAINDICATIONS

NOVO-GLIMEPIRIDE (glimepiride) is contraindicated in patients with:

- Type 1 Diabetes (formerly known as insulin-dependent diabetes mellitus or IDDM)
- Known hypersensitivity or allergy to any sulfonylurea, sulfonamides or any other component of the formulation. For a complete listing, see Dosage Forms, Composition and Packaging section of the product monograph.
- Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
- Pregnant or breast-feeding women.

No experience has been gained concerning the use of glimepiride in patients with severe impairment of liver function and in dialysis patients. In patients with severe impairment of renal or hepatic function, change-over to insulin is indicated, to achieve optimal metabolic control.

WARNINGS AND PRECAUTIONS

General

Use of NOVO-GLIMEPIRIDE (glimepiride) must be considered as treatment in addition to a proper dietary regimen and not as a substitute for diet.

Over a period of time, patients may become progressively less responsive to therapy with oral hypoglycemic agents because of deterioration of their diabetic state. Patients should therefore be monitored with regular clinical and laboratory evaluations, including blood glucose and glycosylated hemoglobin (HbA_{1C}) determinations, to determine the minimum effective dosage and to detect primary failure (inadequate lowering of blood glucose concentrations at the maximum recommended dosage) or secondary failure (progressive deterioration in blood sugar control following an initial period of effectiveness). The rate of primary failure will vary greatly depending upon patient selection and adherence to diet and exercise. The etiology of secondary failure is multifactorial and may involve progressive β-cell failure as well as exogenous diabetogenic factors such as obesity, illness, drugs, or tachyphylaxis to the sulfonylurea. If a loss of adequate blood glucose lowering response to a sulfonylurea is detected, the addition of a different type of oral antidiabetic may be considered, although insulin is often required. Certain patients who demonstrate an inadequate response or true primary or secondary failure to one sulfonylurea may benefit from a switch to another sulfonylurea.

In initiating treatment for Type 2 Diabetes, non-pharmacologic therapy (proper dietary management, exercise and weight reduction) should be emphasized as the initial form of treatment. Caloric restriction, weight loss and exercise are essential in the obese diabetic patient. Proper dietary management and exercise alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. In addition to regular physical activity, cardiovascular risk factors should be identified and corrective measures taken when possible.

Patient Selection and Follow-up: Careful selection of patients is important. Patients most likely to respond to sulfonylurea therapy are: obese or normal body weight; duration of diabetes less than 5 to 10 years before initiation of therapy; and, absence of ketoacidosis. It is imperative that there be careful attention to diet, careful adjustment of dosage, instruction of the patient on hypoglycemic reactions and their treatment, as well as regular, thorough follow-up examinations. If non-pharmacologic therapy fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea should be considered. Use of NOVO-GLIMEPIRIDE (glimepiride) must be viewed by both the physician and patient as a treatment in addition to diet and exercise and not as a substitute for proper dietary management, exercise and weight reduction or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet and exercise alone may be transient, thus requiring only short-term administration of NOVO-GLIMEPIRIDE.

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as illness during therapy, fever, trauma, infection, or surgery, a loss of glycemic control may occur. At such times, it may be necessary to adjust the dosage of NOVO-GLIMEPIRIDE, add insulin in combination with NOVO-GLIMEPIRIDE or even use insulin monotherapy. The effectiveness of any oral hypoglycemic drug, including glimepiride, in

lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon, known as secondary failure, is distinctive of primary failure in which the drug is ineffective in an individual patient when given for the first time.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Signs of severe hypoglycemia can include disorientation, loss of consciousness, and seizures. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Elderly, debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Patients with impaired renal function may be more sensitive to the glucose-lowering effect of NOVO-GLIMEPIRIDE. A starting dose of 1 mg once daily followed by appropriate dose titration is also recommended in those patients. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when other drugs with blood-glucose lowering potential are used. (see **Drug-Drug Interactions** section below). In clinical trials, patients receiving glimepiride in combination with insulin reported more incidence of hypoglycemia than patients on monotherapy.

Cardiovascular

It has been suggested, based on a study conducted by the University Group Diabetes Program (UDGP), that certain sulfonylurea antidiabetic agents increase cardiovascular mortality in diabetic patients, a population at greater risk of cardiovascular disease. This finding was not confirmed by a more recent trial, the United Kingdom Prospective Diabetes Study (UKPDS) which showed that intensive glycemic control with either sulfonylureas or insulin did not have an adverse effect on cardiovascular outcomes. Despite questions regarding the design of these studies and interpretation of the results, the results of these studies provide a basis for caution, especially high risk patients with cardiovascular disease.

In clinical trials more patients receiving glimepiride and insulin reported an increase in peripheral edema compared to patients receiving insulin alone. Patients receiving this combination therapy should be asked to report any edema or weight gain.

Renal

In patients with renal insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. On the basis of results from animal studies, NOVO-GLIMEPIRIDE (glimepiride tablets) should not be used during pregnancy. Recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Experts, including the Canadian Diabetes Association and the Canadian Medical Association recommend that insulin be used during pregnancy to maintain glucose levels as close to normal as possible.

Teratogenic Effects: Glimepiride did not produce teratogenic effects in rats exposed orally up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately 60 times the maximum recommended human dose based on surface area). Glimepiride has been shown to be associated with intrauterine fetal death in rats when given in doses as low as 50 times the human dose based on surface area and in rabbits when given in doses as low as 0.1 times the human dose based on surface area. This fetotoxicity, observed only at doses inducing maternal hypoglycemia, has been similarly noted with other sulfonylureas, and is believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride.

Nonteratogenic Effects: In some studies in rats, offspring of dams exposed to high levels of glimepiride during pregnancy and lactation developed skeletal deformations consisting of shortening, thickening, and bending of the humerus during the postnatal period. Significant concentrations of glimepiride were observed in the serum and breast milk of the dams as well as in the serum of the pups. These skeletal deformations were determined to be the result of nursing from mothers exposed to glimepiride.

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. Patients who are planning a pregnancy should consult their physician, and it is recommended that they change over to insulin for the entire course of pregnancy and lactation.

Nursing Women: In rat reproduction studies, significant concentrations of glimepiride were observed in the serum and breast milk of the dams, as well as in the serum of the pups. Although it is not known whether glimepiride is excreted in human milk, other sulfonylureas are excreted in human milk. Since the potential for hypoglycemia in nursing infants may exist, and because of the effects on nursing animals, NOVO-GLIMEPIRIDE should be discontinued in nursing mothers. If NOVO-GLIMEPIRIDE is discontinued, and if diet and exercise alone are inadequate for controlling blood glucose, insulin therapy should be considered (See above **Pregnant Woman**, Nonteratogenic Effects).

Pediatrics: Safety and efficacy in pediatric Type 2 patients have not been established.

Monitoring and Laboratory Tests

Fasting blood glucose should be monitored periodically to determine therapeutic response. Glycosylated hemoglobin (HbA_{1C}) should also be monitored, usually every 3 to 6 months, to more precisely assess long-term glycemic control.

Occupational Hazards

Driving a vehicle or operating machinery: Hypo- or hyperglycemia may impair alertness and reactions, especially when beginning or after altering treatment or when NOVO-GLIMEPIRIDE is not taken regularly. This may, for example, affect the ability to drive or to operate machinery.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety profile of glimepiride has been evaluated in clinical trials. A total of 2,013 patients were exposed to glimepiride in US controlled trials, 1,489 patients in European trials and 783 patients in Japanese trials. More than 1,800 of these patients were treated for at least 1 year.

The overall incidence of hypoglycemia with glimepiride was approximately 14% in placebo controlled trials, the incidence of hypoglycemia ranged from 2.1 to 3.1% in two long-term, well-controlled studies, and hypoglycemic episodes occurred in 51% in clinical trials involving patients treated with glimepiride in combination with insulin. The most frequent adverse events occurring in US placebo-controlled trials were: dizziness (1.7%); asthenia (1.6%); headache (1.5%); nausea (1.1%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The overall incidence of hypoglycemia with glimepiride in placebo controlled trials was approximately 14% versus 2% for placebo. In two long-term (2 - 2.5 years) and well-controlled studies, the incidence of hypoglycemic reaction ranged from 2.1 to 3.1%. In clinical trials involving patients treated with glimepiride in combination with insulin, hypoglycemic episodes occurred in 51% of the patients, respectively.

Adverse events, other than hypoglycemia, considered to be possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with glimepiride are shown below.

Adverse Events Occurring in > 1% Glimepiride Patients

	Glimepiride		Placebo	
	No. patients (n = 746)	%	No. patients (n = 294)	%
Dizziness	13	1.7	1	0.3
Asthenia	12	1.6	3	1.0
Headache	11	1.5	4	1.4
Nausea	8	1.1	0	0.0

Endocrine and Metabolism:
Hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas; however, no cases have yet been reported with glimepiride tablets. Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormones. Although there have been no reports for glimepiride, the syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

Gastrointestinal:
Gastrointestinal (GI) disturbances e.g. nausea, GI fullness, occur occasionally. Vomiting, gastrointestinal pain, and diarrhea have been reported, but the incidence in placebo-controlled trials was similar to that of placebo. In rare cases, there may be elevation of liver enzyme levels. Sulfonylureas, including glimepiride, may also - in isolated instances - cause impairment of liver function (e.g. with cholestasis and jaundice), as well as hepatitis which may also lead to liver failure.

Other Adverse Reactions:
Changes in accommodation and/or blurred vision may occur with the use of NOVO-GLIMEPIRIDE. This is thought to be due to changes in blood glucose, and may be more pronounced when treatment is initiated. This condition is also seen in untreated diabetic patients, and may actually be reduced by treatment. In placebo-controlled trials of glimepiride, the incidence of blurred vision was placebo, 3.4%, and glimepiride, 1.7%.

Skin:
Allergic skin reactions, e.g., pruritus, erythema, urticaria, vasculitis, and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients. Such mild reactions may develop into serious reactions sometimes progressing to shock. These may be transient and may disappear despite continued use of glimepiride, if skin reactions persist, the drug should be discontinued. Although there have been no reports for glimepiride, porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

Less Common Clinical Trial Adverse Drug Reactions (<1%)
Clinical adverse events occurring in less than 1% of patients treated with glimepiride in all US clinical trials are listed below by body system:

Body as a whole: abdominal pain, laboratory test abnormal, and pain in extremity

Cardiovascular: palpitation and vasodilation

Digestive: diarrhea, increased appetite, dyspepsia, anorexia and gastrointestinal pain

Metabolic and Nutritional Disorders: hypoglycemic reaction and hyperglycemia

Nervous System: tremor, insomnia, sweating increased, nervousness, dry mouth, hot flashes and parasthesia

Skin and Appendages: pruritus and urticaria

Special Senses: blurred vision

Urogenital System: increased urinary frequency and nocturia

Post-Market Adverse Drug Reactions:
The following adverse events, not seen in clinical trials, have been reported during post-marketing surveillance:

Hematologic: Changes in the blood picture may occur. Rarely (≥1/10,000 and <1/1000), thrombopenia and, in isolated cases (<1/10,000), leucopenia, hemolytic anemia. erythrocytopenia, granulocytopenia, agranulocytosis or pancytopenia may develop.

Skin: In isolated cases (<1/10,000), allergic vasculitis or hypersensitivity of the skin to light may occur.

Other: In isolated cases (<1/10,000), a decrease in serum sodium concentration may occur.

DRUG INTERACTIONS

Overview
Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). This should be taken into account when glimepiride is coadministered with inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole) of CYP 2C9. Both acute and chronic alcohol intake may potentiate or weaken the blood-glucose-lowering action of glimepiride in an unpredictable fashion.

Drug-Drug Interactions
The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e. those identified as contraindicated).

Table 1 - Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Acetylsalicyclic acid (ASA)	CT	↓ 34% mean glimepiride AUC ↑ 34% mean glimepiride C1/F ↓ 4% mean glimepiride C_{max}	Blood glucose and serum C-peptide concentrations were unaffected and no hypoglycemic symptoms were reported. Pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of acetylsalicylic acid and other salicylates.
Cimetidine or Ranitidine	CT	No clinically significant effect	Coadministration of either cimetidine (800 mg once daily) or ranitidine (150 mg bid) with a single 4 mg oral dose of glimepiride did not significantly alter the absorption and disposition of glimepiride, and no differences were seen in hypoglycemic symptomatology. Pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of H_2-receptor antagonists.
Propranolol	CT	↑ glimepiride C_{max} by 23% ↑ glimepiride AUC by 22% ↑ glimepiride $T_{1/2}$ by 15% ↓ glimepiride C1/F by 18%	The recovery of M1 and M2 from urine, however, did not change. The pharmacodynamic responses to glimepiride were nearly identical in normal subjects receiving propranolol and placebo. Pooled data from clinical trials in patients with Type 2 Diabetes showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of beta-blockers. However, if beta-blockers are used, caution should be exercised and patients should be warned about the potential for hypoglycemia.

Proper name	Ref	Effect	Clinical comment
Warfarin	CT	No clinically significant effect	Concomitant administration of glimepiride (glimepiride tablets) (4 mg once daily) did not alter the pharmacokinetic characteristics of R- and S-warfarin enantiomers following administration of a single dose (25 mg) of racemic warfarin to healthy subjects. No changes were observed in warfarin plasma protein binding. Glimepiride treatment did result in a slight, but statistically significant, decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the prothrombin time (PT) curve and maximum PT values during glimepiride treatment were very small (3.3% and 9.9%, respectively) and are unlikely to be clinically important.
Ramipril	CT	No clinically significant effect	The responses of serum glucose, insulin, C-peptide, and plasma glucagon to 2 mg glimepiride were unaffected by coadministration of ramipril 5 mg once daily in normal subjects. No hypoglycemic symptoms were reported. Pooled data from clinical trials in patients with Type 2 Diabetes showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of ACE inhibitors.
Drugs metabolized by cytochrome P450 2C9	T	Potential interactions	Potential interactions of glimepiride with other drugs metabolized by cytochrome P450 2C9 also include phenytoin, diclofenac, ibuprofen, naproxen, and mefenamic acid.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Although no specific interaction studies were performed, pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of calcium-channel blockers, estrogens, fibrates, NSAIDS, HMG CoA reductase inhibitors, sulfonamides, or thyroid hormone.

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including ACE inhibitors, anabolic steroids and male sex hormones, nonsteroidal anti-inflammatory drugs and other drugs that are highly protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, cyclophosphosphamine, disopyramide, fibrates, fluconazole, fluoxetine, guanethidine, ifosfamide, monoamine oxidase inhibitors, para-aminosalicylic acid, pentoxifylline (high dose parenteral), phenylbutazone, probenecid, quinolones, salicylates, sulfonamide antibiotics and tetracyclines. When these drugs are administered to a patient receiving NOVO-

GLIMEPIRIDE, the patient should be observed closely for hypoglycemia. When these drugs are withdrawn from a patient receiving NOVO-GLIMEPIRIDE, the patient should be observed closely for loss of glycemic control.

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, acetazolamide, barbiturates, corticosteroids, diazoxide, epinephrine and other sympathomimetic agents, glucagon, isoniazid, laxatives (after protracted use), nicotinic acid (in high dose), estrogens and progestogens, phenothiazines, phenytoin, rifampicin and thyroid products. When these drugs are administered to a patient receiving NOVO-GLIMEPIRIDE, the patient should be closely observed for loss of glycemic control. When these drugs are withdrawn from a patient receiving NOVO-GLIMEPIRIDE, the patient should be observed closely for hypoglycemia.

H_2 receptor antagonists, beta-blockers, clonidine and reserpine may lead to either potentiation or weakening of the blood-glucose-lowering effect.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The patient's fasting blood glucose and HbA_{1C} must be measured periodically to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of adequate blood glucose lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels (HbA_{1C}) should be performed to monitor the patient's response to therapy.

Short-term administration of NOVO-GLIMEPIRIDE (glimepiride) may be sufficient during periods of transient loss of glycemic control in patients usually controlled well on diet and exercise.

Recommended Dose and Dosage Adjustment

Usual Starting Dose

The usual starting dose of NOVO-GLIMEPIRIDE as initial therapy is 1 mg once daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be titrated carefully. (See **WARNINGS AND PRECAUTIONS** Section).

Failure to follow an appropriate dosage regimen may precipitate hypoglycemia. Patients who do not adhere to their prescribed dietary, exercise, weight loss and drug regimen are more prone to exhibit unsatisfactory response to therapy.

Adjustment of dosage must also be considered, whenever:

- The patient's weight changes,
- The patient's life-style changes, other factors arise which cause an increased susceptibility to hypoglycemia or hyperglycemia (see **WARNINGS AND PRECAUTIONS** Section)

Usual Maintenance Dose

The usual maintenance dose is 1 to 4 mg once daily. The maximum recommended dose is 8 mg once daily. After reaching a dose of 2 mg, dosage increases should be made in increments of no more than 1 mg at 1 - 2 week intervals based upon the patient's blood glucose response. Long-term efficacy should be monitored by measurement of HbA_{1C} levels, for example every 3 to 6 months.

NOVO-GLIMEPIRIDE -Insulin Combination Therapy

Combination therapy with NOVO-GLIMEPIRIDE and insulin may be used in secondary failure patients. The recommended NOVO-GLIMEPIRIDE dose is 8 mg once daily administered with the first main meal. After starting with low-dose insulin, upward adjustments of insulin can be done approximately weekly as guided by frequent measurements of fasting blood glucose. Once stable, combination-therapy patients should monitor their capillary blood glucose on an ongoing basis, preferably daily. Periodic adjustments of insulin may also be necessary during maintenance as guided by glucose and HbA_{1C} levels.

Specific Patient Populations

NOVO-GLIMEPIRIDE is not recommended for use in pregnancy, nursing mothers, or children. In elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions (See **CLINICAL PHARMACOLOGY, Special Populations and Conditions** and **WARNINGS AND PRECAUTIONS**, **General).**

Changeover from Other Oral Hypoglycemic Agents

No exact dosage relationship exists between NOVO-GLIMEPIRIDE and the other oral hypoglycemic agents. When substituting NOVO-GLIMEPIRIDE for other oral hypoglycemic agents, it is recommeded that the procedure be the same as for initial dosage starting with daily doses of 1 mg. Consideration must be given to the potency and duration of the previous antidiabetic agent. Patients should be observed carefully (1 -2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (e.g., chlorpropamide) to NOVO-GLIMEPIRIDE due to potential overlapping of drug effect.

A break from medication may be required to avoid any summation of effects entailing a risk of hypoglycemia.

Missed Dose

Take the miss dose as soon as possible, unless it is almost time for the next dose. Do not take two doses at the same time.

OVERDOSAGE

Overdosage of sulfonylureas, including NOVO-GLIMEPIRIDE (glimepiride), can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated 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. In case of overdosage, current medical intervention for the treatment of hypoglycemia should be followed according to the condition of the patient. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extra-pancreatic effects may also play a role in the activity of glimepiride. This is supported by both preclinical and clinical studies demonstrating that glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin. These findings are consistent with the results of a long-term, randomized, placebo-controlled trial in which glimepiride therapy improved postprandial insulin/C-peptide responses and overall glycemic control without producing clinically meaningful increases in fasting insulin/C-peptide levels. However, the mechanism by which glimepiride lowers blood glucose during long-term administration has not been clearly established.

Pharmacodynamics

A mild glucose-lowering effect first appeared following single oral doses as low as 0.5 - 0.6 mg in healthy subjects. The time required to reach the maximum effect (i.e., minimum blood glucose level [T_{min}]) was about 2 to 3 hours. In Type 2 Diabetes (formerly known as non-insulin-dependent diabetes mellitus or NIDDM) patients, both fasting and 2-hour postprandial glucose levels were significantly lower with glimepiride (1, 2, 4, and 8 mg once daily) than with placebo after 14 days of oral dosing. The glucose-lowering effect in all active treatment groups was maintained over 24 hours.

In larger dose-ranging studies, blood glucose and glycosylated hemoglobin (HbA_{1C}) were found to respond in a dose-dependent manner over the range of 1 to 4 mg of glimepiride once daily. Some patients, particularly those with higher fasting plasma glucose (FPG) levels, may benefit from doses of NOVO-GLIMEPIRIDE up to 8 mg once daily. No difference in the decrease in blood glucose and HbA_{1C} concentrations were found when glimepiride was administered once or twice daily.

In two 14-week, placebo-controlled studies in 720 subjects, the average net reduction in HbA_{1C} for glimepiride patients treated with 8 mg once daily was 2.0% (0.02) in absolute units compared with placebo-treated patients. Efficacy results were not affected by age, gender, weight, or race.

In a 22-week, randomized, placebo-controlled study of Type 2 Diabetic patients unresponsive to dietary management, glimepiride therapy improved postprandial insulin/C-peptide responses, and 75% of patients achieved and maintained control of blood glucose and HbA_{1C}. The results of three long-term studies demonstrated that glimepiride, when administered over a prolonged treatment period of one-year (N = 986), was effective in maintaining metabolic control in Type 2 Diabetic patients who were responders to sulfonylurea therapy. In an extension of long-term trials with patients previously treated with glimepiride, no meaningful deterioration in mean fasting blood glucose (FBG) or HbA_{1C} levels was seen after up to 2.5 years of glimepiride therapy (N=445).

Combination therapy with glimepiride and insulin (70% NPH/30% regular) was compared to placebo/insulin in secondary failure patients whose body weight was > 130% of their ideal body weight. Initially, 5-10 units of insulin were administered with the main evening meal and titrated upward weekly to achieve predefined FPG values. Both groups in this double-blind study achieved similar reductions in FPG levels but the glimepiride/insulin therapy group showed an insulin sparing effect with a use of 38% less insulin.

Glimepiride therapy is effective in controlling blood glucose without deleterious changes in the plasma lipoprotein profiles of patients treated for Type 2 Diabetes.

Pharmacokinetics

Absorption: After oral administration, glimepiride is completely (100%) absorbed from the GI tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with Type 2 Diabetes have shown significant absorption of glimepiride within 1 hour after administration and peak drug levels (C_{max}) at 2 to 3 hours. When glimepiride was given with meals, the mean T_{max} (time to reach C_{max}) was slightly increased (12%) and the mean C_{max} and AUC (area under the curve) were slightly decreased (8% and 9%, respectively). In normal healthy volunteers, the intra-individual variabilities of C_{max}, AUC, and total body clearance after oral dosing (Cl/F) for glimepiride were 23%, 17%, and 15%, respectively, and the inter-individual variabilities were 25%, 29%, and 24%, respectively.

The pharmacokinetics of glimepiride obtained from a single-dose, crossover, dose-proportionality (1, 2, 4, and 8 mg) study in normal subjects and from a single- and multiple-dose, parallel, dose-proportionality (4 and 8 mg) study in patients with Type 2 Diabetes are summarized below:

	Volunteers	Patients with Type 2 Diabetes	
	Single Dose Mean ± SD (n)	Single Dose (Day 1) Mean ± SD (n)	Multiple Dose (Day 10) Mean ± SD (n)
C_{max} (ng/mL), 1 mg	103 ± 34 (12)	-	-
2 mg	177 ± 44 (12)	-	-
4 mg	308 ± 69 (12)	352 ± 222 (12)	309 ± 134 (12)
8 mg	551 ± 152 (12)	591 ± 232 (14)	578 ± 265 (11)
T_{max} (h), 1 mg	2.3 ± 0.5 (12)	-	-
2 mg	2.4 ± 0.5 (12)	-	-

		Volunteers	Patients with Type 2 Diabetes	
	4 mg	2.1 ± 0.6 (12)	2.08 ± 0.51 (12)	2.22 ± 1.21 (12)
	8 mg	2.8 ± 1.2 (12)	2.80 ± 1.46 (14)	3.46 ± 2.82 (11)
Cl/F(mL/min),	1 mg	55.3 ± 16.3 (12)	-	-
	2 mg	53.5 ± 15.5 (12)	-	-
	4 mg	53.6 ± 10.6 (12)	54.2 ± 41.1 (12)	63.4 ± 53.5 (12)
	8 mg	56.5 ± 21.1 (12)	43.6 ± 13.0 (14)	41.0 ± 11.2 (11)
Vd/f (L),	1 mg	10.6 ± 1.8 (12)	-	-
	2 mg	12.6 ± 2.9 (12)	-	-
	4 mg	15.7 ± 5.4 (12)	20.8 ± 11.3 (12)	40.2 ± 22.3 (12)
	8 mg	20.9 ± 6.9 (12)	18.9 ± 14.1 (14)	33.8 ± 12.6 (11)
$t_{1/2}$ (h),	1 mg	1.2 ± 0.5 (12)	-	-
	2 mg	1.3 ± 0.4 (12)	-	-
	4 mg	1.5 ± 0.5 (12)	5.30 ± 2.54 (12)	8.82 ± 4.36 (12)
	8 mg	1.5 ± 0.4 (12)	4.69 ± 2.61 (14)	9.63 ± 2.63 (11)

(n) = number of subjects
Vd/f = Volume of distribution calculated after oral dosing

These data indicate that glimepiride did not accumulate in serum, and the pharmacokinetics of glimepiride were not different in healthy volunteers and in Type 2 Diabetic patients. Oral clearance of glimepiride did not change over the 1 - 8 mg dose range, indicating linear pharmacokinetics.

Distribution: After intravenous dosing in normal subjects, the volume of distribution (Vd) was 8.8 L (113 mL/kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%.

Metabolism: Glimepiride is completely metabolized by oxidative biotransformation after either IV or oral administration. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about 1/3 of the pharmacological activity as compared to its parent in an animal model; however, whether the glucose-lowering effect of M1 is clinically meaningful in humans is not clear.

Excretion: When ^{14}C-glimepiride was given as a single dose orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80-90% of that recovered in the urine. Approximately 40% of the total radioactivity was recovered in feces and M1 and M2 (predominant) accounted for about 70% of that recovered in feces. After IV dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite has been observed.

Special Populations and Conditions

Pediatrics: No studies were performed in pediatric patients.

Geriatrics: Comparison of glimepiride pharmacokinetics in Type 2 Diabetic patients ≤ 65 years and those > 65 years was performed in a study using a dosing regimen of 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the two age groups. The mean AUC at steady state for the older patients was about 13% lower than that for the younger patients; the mean weight-adjusted clearance for the older patients was about 11% higher than that for the younger patients. (See **WARNING AND PRECAUTIONS, General**).

Gender: There were no differences between males and females in the pharmacokinetics of glimepiride when adjusting for differences in body weight.

Race: No pharmacokinetic studies to assess the effects of race have been performed, but in placebo-controlled studies of glimepiride (glimepiride tablets) in patients with Type 2 Diabetes, the hypoglycemic effect was comparable in whites (n = 536), blacks (n = 63), and Hispanics (n = 63).

Hepatic Insufficiency: No studies were performed in patients with hepatic insufficiency.

Renal Insufficiency: A single-dose, open-label study was conducted in 15 patients with renal impairment. Glimepiride (3 mg) was administered to 3 groups of patients with different levels of mean creatinine clearance (CLcr): Group I, CLcr = 77.7 mL/min (1.30 mL/sec), n = 5; Group II, CLcr = 27.7 mL/min (0.462 mL/sec), n = 3; and Group III, CLcr = 9.4 mL/min (0.16 mL/sec), n = 7. Glimepiride was found to be well tolerated in all 3 groups. The results showed that M1 and M2 serum levels (mean AUC values) increased 2.2 and 6.1 times from Group I to Group III as renal function decreased. The apparent terminal half-life ($T_{1/2}$) for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as percent of dose, however, decreased (44.4%, 21.9%, and 9.3% for Groups I to III).

A multiple-dose titration study was also conducted in 16 Type 2 Diabetic patients with renal impairment using doses ranging from 1 - 8 mg daily for 3 months. The results were consistent with those observed after single doses. All patients with a CLcr less than 22 mL/min (0.37 mL/sec) had adequate control of their glucose levels with a dosage regimen of only 1 mg daily. The results from this study suggested that a starting dose of 1 mg glimepiride may be given to Type 2 Diabetic patients with kidney disease, and the dose may be titrated based on fasting blood glucose levels. (See **WARNING AND PRECAUTIONS, Renal** section).

Other Populations: There were no important differences in glimepiride metabolism in subjects identified as phenotypically different drug-metabolizers by their metabolism of sparteine.

The pharmacokinetics of glimepiride in morbidly obese patients were similar to those in the normal weight group, except for a lower C_{max} and AUC. However, since neither C_{max} nor AUC values were normalized for body surface area, the lower values of C_{max} and AUC for the obese patients were likely the result of their excess weight and not due to a difference in the kinetics of glimepiride.

STORAGE AND STABILITY

Protect from heat, moisture and direct light. Store between 15 and 30˚C.
Dispense in well-closed container.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms and Packaging:
NOVO-GLIMEPIRIDE (glimepiride) tablets are available in the following strengths and package sizes:

1 mg: Mottled pink, round tablet, bisected on both sides. One side of the tablet debossed with "9" on one side of score and "3" on the other. The other side of the table debossed with "72" on one side of score and "54" on the other. Supplied in bottles of 30 and 100 tablets, and unit dose of 10.

2 mg: Mottled green, round tablet, bisected on both sides. One side of the tablet debossed with "9" on one side of score and "3" on the other. The other side of the table debossed with "72" on one side of score and "55" on the other. Supplied in bottles of 30 and 100 tablets, and unit dose of 10.

4 mg: Mottled light blue, round tablet, bisected on both sides. One side of the tablet debossed with "9" on one side of score and "3" on the other. The other side of the table debossed with "72" on one side of score and "56" on the other. Supplied in bottles of 30 and 100 tablets, and unit dose of 10.

Composition:
NOVO-GLIMEPIRIDE (glimepiride) is formulated into tablets of 1 mg, 2 mg, and 4 mg strengths for oral administration. NOVO-GLIMEPIRIDE tablets contain the active ingredient glimepiride and the following non medicinal ingredients: lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. In addition: NOVO-GLIMEPIRIDE 1 mg tablets contain Ferric Oxide, NOVO-GLIMEPIRIDE 2 mg tablets contain FD&C Blue #2 Aluminum Lake and Ferric Oxide, and NOVO-GLIMEPIRIDE 4 mg tablets contain FD&C Blue #2 Aluminum Lake.

PART II: SCIENTIFIC INFORMATION

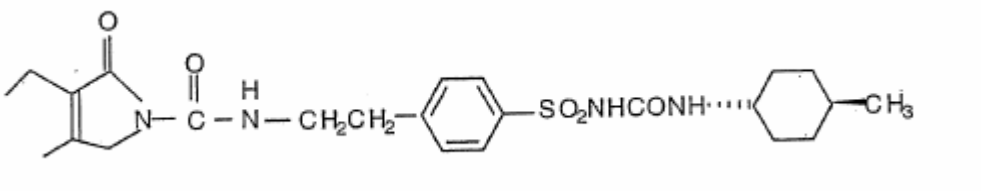
PHARMACEUTICAL INFORMATION

Drug Substance

Common name: Glimepiride

Chemical name: 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea

Structural formula:



Empirical formula: $C_{24}H_{34}N_4O_5S$

Molecular weight: 490.62

Physical form: Glimepiride is a white crystalline powder

Solubility: Glimepiride is practically insoluble in water.
Soluble in N,N dimethylformamide, very slightly soluble in methanol, acetonitrile and acetone.

pKa values: 6.2 ± 0.1 at 37 ^{o}C

Melting point: 205 ^{o}C to 208 ^{o}C

CLINICAL TRIALS

Efficacy: Indication I

The primary indication (Indication I) for glimepiride is for use as an adjunct to diet and exercise in patients with non-insulin-dependent Type 2 Diabetes Mellitus whose hyperglycemia cannot be controlled by diet and exercise alone. This indication is supported by the results of three pivotal placebo-controlled trials. In addition, four non-pivotal trials provide complementary information to support the primary indication.

Trials Supporting the Efficacy of Glimepiride for Indication I.

Study	Design	Doses	Treatment Duration	No. of Subjects			
				Glimepiride	Glyburide	Placebo	Study Totals
1	Fixed-dose, MC, DB, R, PC (Pivotal)	Pbo Glim: 1, 4, 8 mg qd	14 weeks	230	-	74	304
2	Dose-titration, MC, DB, R, PC (Pivotal)	Pbo Glim: 1, 2, 3, 4, 6, 8 mg qd	22 weeks	123	-	126	249
3	Fixed-dose, MC, DB, R, PC (Pivotal)	Pbo Glim: 8 mg qd; 4 mg bid; 16 mg qd; 8 mg bid	14 weeks	337	-	79	416
4	Fixed-dose, MC, DB, R, CO (Non-Pivotal)	Glim: 3 mg bid; 6 mg qd	2 x 4 weeks	106	-	-	106
5	Dose-titration, MC, DB, R, dose stratification (Non-pivotal)	Glim: 1, 2, 4, 8 mg qd; 8 mg AM and 4 mg PM; 8 mg bid Gly: 1.25, 2.5, 5, 10 mg qd; 10 mg AM and 5 mg PM; 10 mg bid	12 months	289	288	-	577
6	Dose-titration (301)/ Long term (302) MC, DB, R, AC (Non-Pivotal)	Glim: 1 - 4, 6, 8 mg qd Gly: 2.5, 5, 7.5, 10 mg qd; 10 mg AM and 5 mg PM; 10 mg bid	1 - 2 years	524	520	-	1044
7	Dose-titration (311)/ Long term (302) MC, DB, R, AC (Non-Pivotal)	Glim: 1 - 4, 6, 8 mg qd Gly: 1.75, 3.5, 5.25, 7 mg qd; 7 mg AM and 3.5 mg PM; 7 mg bid	1 - 2.5 years	425	427	-	852

MC = Multicentre; DB = Double Blinded; R = Randomised; PC = Placebo controlled,
AC = Active Controlled, CO = Glim = Glimepiride; Gly = Glyburide; Pbo = Placebo

The key efficacy variables measured in each of the three pivotal studies were:

- Primary: Fasting Plasma Glucose, HbA_{1C}, 2-hour Postprandial Plasma Glucose;
- Secondary: C-peptide, Insulin

Clinically meaningful differences, based on general clinical experience were defined as 1.4 mmol/L for FPG levels and 0.6% (0.006) for HbA_{1C} levels.

Primary Efficacy Results

All glimepiride treatment regimens (1-16 mg qd; 4 and 8 mg bid) produced significant and clinically meaningful reductions from Baseline in Fasting Plasma Glucose (FPG) and Postprandial Glucose (PPG) levels and HbA_{1C} with one exception (HbA_{1C} at 1 mg/day).

All dosages of glimepiride produced significant and clinically meaningful reductions in the primary efficacy variables, when compared to placebo.

Variable	Study No.	Placebo	Median Difference from Placebo at end point[a]					
			1 qd	4 qd	8 qd	4 bid	16 qd	8 bid
FPG (mmol/L)	1 3 2	0.92 1.33 -0.50	-2.39	-3.92	-4.11 -4.72	-5.14	-4.72	-5.28
HbA_{1C} (%) (ratio)	1 3 2	1.4 (0.014) 1.4 (0.014) -0.7 (-0.007)	-1.2 (-0.012)	-1.8 (-0.018)	-1.9 (-0.019) -2.0 (-0.020)	-2 (-0.020)	-1.9 (-0.019)	-2.2 (-0.022)
PPG (mmol/L)	1 3 2	0.72 1.72 -0.94	-3.50	-5.06	-5.17 -6.61	-5.94	-5.72	-6.28

[a] All differences from placebo were significant ($p<0.001$) and clinically meaningful.

When stratified by baseline FPG levels, glimepiride subjects in the high glucose stratum (13.4 – 16.7 mmol/L) achieved greater reduction in median FPG levels (-4.72 mmol/L) than subjects in the lower stratum (10 - 13.3mmol/L; -2.5 mmol/L). Likewise, in the longer term placebo controlled trial, when stratified by baselineHbA_{1C}, glimepiride subjects in the high HbA_{1C} percentile group ($\geq$75; HbA_{1C}> 10.5% (0.105)) had a greater reduction of the HbA_{1C} (-3.7% (0.037)) then those in the low percentile (< 75; $HbA_{1C}\leq$ 10.5% (0.105)) (-1.6%). These two findings suggest patients with more severe Type 2 Diabetes can also benefit from glimepiride treatment.

Dose regimen

No significant differences were detected between the qd and bid dose regimens for FPG or PPG levels at any of the 6, 8 or 16 mg total daily dosages as shown in the table below. These results were obtained from one pivotal and one non-pivotal trial.

Variable	Dose[b]	Change from Baseline at Endpoint[a]					
		qd	bid	Difference	95%	Cl	p-value
FPG (mmol/L)	6 mg	-3.81	-3.3	-0.46	-1.43	0.51	0.358
	8 mg	-3.2	-3.81	0.44	-	-	0.117
	8/16 mg	-3.33	-4.00	0.56	0.0	1.17	0.047*
	16 mg	-3.33	-4.11	0.61	-	-	0.152
24-hr Glucose (mmol/L)	6 mg	-4.37	-4.95	0.58	0.11	1.12	0.018*
HbA_{1C} (%)(ratio)	8 mg	-0.5 (-0.005)	-0.5 (-0.005)	-0.1 (-0.001)	-0.3	0.2	0.694
	16 mg	-0.5 (-0.005)	-0.7 (-0.007)	0.3 (-0.003)	0.0	0.5	0.024*

Variable	Dose[b]	Change from Baseline at Endpoint[a]					
		qd	bid	Difference	95%	Cl	p-value
PPG[c] (mmol/L)	6 mg	-4.39	-3.79	-0.60	-1.67	0.49	0.283
	8 mg	-5.22	-4.33	-0.67	-	-	0.326
	8/16 mg	-4.83	-4.33	-0.11	-0.83	0.67	0.809
	16 mg	-4.28	-4.36	0.50	-	-	0.410

[a] Change from baseline is the median for study 3 and the mean for study 4.
[b] Data for the 8/16-mg daily dosage is the combined data for both dosage levels.
[c] PPG is the 2-hour level after breakfast for study 3 and the 4-hour average after breakfast for study 4. Significance indicated at *$p \leq 0.05$.

Long-Term Efficacy
The benefits of glimepiride were maintained over long treatment periods and the treatment was as efficacious as higher and often divided dosages of glyburide or gliclazide.

Subjects in study 2 showed significant and clinically meaningful improvements in FPG and HbA_{1C} levels after 22 weeks of treatment with glimepiride in comparison with placebo. Subjects in the studies 5, 6 and 7 showed no clinically meaningful differences in FPG/FBG and $HbA1_C$ levels between glimepiride and glyburide treatment after up to 30 months of therapy.

C-Peptide and Insulin Results
The C-peptide and insulin response to glimepiride administration was evaluated in the three pivotal studies. Results showed that glimepiride increased fasting C-peptide and insulin levels by statistically significant but not clinically meaningful amounts when compared with placebo. Glimepiride increased postprandial C-peptide and insulin levels by statistically significant and clinically meaningful amounts over placebo levels. These results suggest that in Type 2 patients, the effects of glimepiride mimic the physiologic response to food intake with insulin levels comparable to placebo during fasting conditions.

Efficacy: Indication II
The second indication for glimepiride is for use in combination therapy with insulin to lower blood glucose levels in patients who are secondary failures to sulfonylurea therapy, that is, in patients whose hyperglycemia can no longer be effectively controlled by diet and oral hypoglycemic agents alone. Support for this indication was obtained through the results of a double-blind study that compared the efficacy of combination therapy with glimepiride plus insulin *vs.* that obtained with placebo plus insulin. A total of 145 Type 2 patients participated in the 24-week randomised, double-blind phase of this study; 72 received glimepiride plus insulin and 73 received placebo plus insulin. Each subject took fixed, oral dosages of glimepiride (8 mg bid) or placebo before breakfast and dinner, plus injections of insulin (qd, titrated to an optimised dose) before dinner.
The two primary efficacy variables were the 4-week average insulin dose at Endpoint and the change from baseline in HbA_{1C} levels at Endpoint.

The mean daily insulin dose in the glimepiride group was approximately 30 U lower than in the placebo group, and this difference was clinically meaningful as well as statistically significant. Fewer subjects in the glimepiride group (6%) than in the placebo group (14%) required more than 100 U per day of insulin. Similarly, a greater percent of patients in the glimepiride group

(64%) than in the placebo group (28%) required ≤ 50 unit of insulin. This suggests that fewer patients would require multiple daily insulin injections if treated with combination therapy rather than insulin monotherapy. The results of this study also demonstrated that variability in the insulin-titration procedure did not affect the overall outcome of combination therapy. In smaller studies, success has previously been obtained with titration procedures that were either more aggressive[1] or generally less aggressive[2] than those used in the present study. Taken together, these results suggest that glimepiride plus insulin therapy would be efficacious using a variety of insulin titration procedures.

Glycemic variability (as measured by the mean within-subject variance) was lower in the glimepiride group (433 mg^2/dl^2) than in the placebo group (627 mg^2/dl^2), indicating a trend to more stable glycemic control in the glimepiride-treated group. This may become more important with very aggressive insulin titration procedures, during which the risk of serious hypoglycemia is greater.

[1]Riddle M, Hart J, Bingham P, Garrison C, and McDaniel P (1992) Combined therapy for obese Type 2 diabetes: suppertime mixed insulin with daytime sulfonylurea. American Journal of Medical Sciences 303, 151-156.

[2]Riddle M, Hart J, Bouma D, Phillipson B, and Youker G (1989) Efficacy of bedtime NPH insulin with daytime sulfonylurea for subpopulation of type II diabetic subjects. Diabetes Care 12, 623-629.

Safety

Overall, glimepiride demonstrated a very safe adverse event profile, differing little from that of placebo. In both US and European trials, there was no drug-related pattern of deaths.

No laboratory abnormalities could be attributed to the use of the drug. The most commonly reported adverse events possibly or probably related to the use of glimepiride occurring in at least 1% of subjects in placebo-controlled studies were hypoglycemia, dizziness, asthenia, headache, rash and nausea.

No medically important interactions were seen between glimepiride and any of the demographic, disease or drug groups reviewed.

Human Ophthalmology Data

Ophthalmic examinations were carried out in over 500 subjects during long-term studies using the methodology of Taylor and West and Laties et al. No significant differences were seen between glimepiride and glyburide in the number of subjects with clinically important changes in visual acuity, intra-ocular tension, or in any of the five lens-related variables examined.

Ophthalmic examinations were carried out during long-term studies using the method of Chylack et al. No significant or clinically meaningful differences were seen between glimepiride and glipizide with respect to cataract progression by subjective LOCS II grading and objective image analysis systems, visual acuity, intraocular pressure, and general ophthalmic examination.

COMPARATIVE BIOAVAILABILITY

A single-dose, randomized crossover comparative bioavailability study of two Glimepiride tablet products, NOVO-GLIMEPIRIDE 4 mg Tablets and AMARYL™ 4 mg tablets in healthy subjects, under fasting conditions.

The pharmacokinetic data calculated for the NOVO-GLIMEPIRIDE and AMARYL™ tablet formulation, under fasting conditions, is tabulated below: Module 4, Volume 1, pages 1-006

Table of the Comparative Bioavailability Data
Glimepiride
(1 x 4 mg tablet)
From measured data
Geometric Mean
Arithmetic Mean (CV%)

Parameter	Test Novo-Glimepiride Tablets	Reference Amaryl®**	Ratio of Geometric Means (%)	90% Confidence Interval
AUC_{0-t} (ng.h/mL)	1267.56 (46) 1152.72	1250.90 (51) 1115.67	103.32	97.95 - 108.98
AUC_{0-inf} (ng.h/mL)	1292.88 (45) 1178.05	1282.25 (51) 1146.67	102.74	97.71 - 108.03
Cmax (ng/mL)	203.33 (38) 188.78	204.15 (34) 192.36	98.14	89.70 - 107.38
Tmax (h)*	3.38 (47)	3.73 (48)	-	-
Kel (1/h)	0.1561 (32)	0.1503 (54	-	-
T½ (h)*	4.77 (25)	5.52 (34)	-	-

* Expressed as the arithmetic mean (C.V.%) only.
**Amaryl® manufactured by Aventis Pharm Inc., and purchased in Canada.

DETAILED PHARMACOLOGY

Animal Pharmacology

Blood glucose decreasing activity
Compared to other conventional sulfonylureas, glimepiride had more pronounced blood glucose decreasing activity in animals. In normal fasted rats and rabbits, single oral (5 - 400 μg/kg) and intravenous (5 - 500 μg/kg) doses of glimepiride were more acutely and chronically potent than glyburide. Following oral administration to dogs (60 and 120 μg/kg), glimepiride produced faster glucose decrease and longer lasting blood glucose reduction than did glyburide.

When orally administered to rabbits and rats, the metabolites of glimepiride, M1 and M2, were found to be 3 to 2000 times less active then the parent drug.

Insulin releasing activity
In perfused islets of Langerhans and pancreas of rats, glimepiride had a more pronounced insulin secretion activity when compared to glyburide at normal and high glucose concentrations. This effect on insulin secretion is thought to be due to a different molecular interaction with ATP-sensitive potassium channel in the beta cell membrane. Unlike other sulfonylureas, glimepiride binds specifically to a 65 kDa protein located in the membrane of the beta cell. This interaction of glimepiride with its binding protein determines the probability of the ATP-sensitive potassium channel being open or closed.

In the whole-cell patch clamp, glimepiride had a higher (EC_{50} of 3.1 nM) depolarization activity of the beta cell membrane of the mouse than glyburide (EC_{50} of 4.0 nM). Glimepiride had a higher exchange rate with the binding protein resulting from a more rapid association and dissociation kinetics and a higher *in vitro* insulin releasing activity of glimepiride compared to that of glyburide.

The *in vitro* higher insulin releasing activity of glimepiride compared to that of glyburide with and in islets and pancreas of rats is only partially reflected *in vivo*, probably due to species specificity in dogs. In dogs, after 60 µg/kg intravenous and 90 µg/kg oral doses, at neither phase did glimepiride induce a higher plasma insulin release than glyburide, indicating species specificity.

The relation between plasma insulin releasing and blood glucose decreasing activity of glimepiride and other sulfonylureas *in vivo* suggested that the insulin-independent glucose lowering effects are more pronounced with glimepiride. In rabbits and dogs, treated intravenously (10 - 60 µg/kg) and/or orally (90 µg/kg) with glimepiride the lower early phase plasma insulin levels to that after glyburide was reflected in a lower blood glucose decreasing activity. In dogs, blood glucose levels remained relatively constant or decreased for up to 48 to 52 hours after dose administration although the plasma insulin values did not differ markedly from those of the control animals.

The longer-lasting blood glucose decreasing activity of glimepiride, compared to glyburide, after oral and intravenous administration, despite low insulin release in dogs, can be explained in terms of a higher extrapancreatic activity**.**

<u>Extrapancreatic effects</u>
Extrapancreatic effects may be defined as a direct stimulation or enhancement of insulin stimulation of the peripheral and/or hepatic glucose disposal. *In vitro* studies with diaphragm, fat cells and hepatocytes showed a direct insulin-mimetic activity of glimepiride:

- concentration-dependently inhibited gluconeogenesis and ketogenesis from alanine;
- concentration-dependently stimulated the TCA cycle;
- stimulated glucose transport, the rate limiting step of lipogenesis and glycogenesis, time- and concentration-dependently more effectively than glyburide.

In addition to the activation of glucose transport *via* Glut4 dephosphorylation, glimepiride also stimulated subsequent steps of glucose metabolism, the key enzymes of lipid and glycogen synthesis, which may be mediated by activation of the glycosyl-phosphatidylinositol-specific phospholipase C (GPI-PLC). *In vitro* studies showed that glimepiride regulated the following activities slightly more efficiently than glyburide:

- cellular cAMP-specific phosphodiesterase activity;
- reduction of protein kinase A activity;
- stimulation of glycogen synthase activity;
- stimulation of glycerol-3-P-acyltransferase activity.

In isolated rat hepatocytes, glimepiride inhibited hepatic glucose output by increasing the concentration of fructose-2,6-biphosphate.

However, direct insulin-mimetic effects (in the absence of insulin), observed *in vitro*, were not observed in animal's models of insulin deficiency. In streptozotocin-diabetic rats (20 mg/kg twice daily for 5 days) and pancreatectomized and alloxan-diabetic dogs (100 mg/kg once daily for 8 days) treated orally with glimepiride and glyburide, neither compound had any effect on blood glucose. This suggested that the direct insulin-mimetic activity of sulfonylureas may depend on the presence of insulin which may control positively the expression of genes coding for certain components of the signal transduction cascade which mediates the direct insulin-mimetic effects of glimepiride in fat and muscle cells. *In vitro* study in 3T3 adipocytes, suggested that glimepiride increases the sensitivity of peripheral tissues for glucose transport stimulation by insulin slightly more efficiently than glyburide, which may explain the extrapancreatic effects of sulfonylureas and especially of glimepiride.

Effect on glucagon secretion

In perfused islets of Langerhans and pancreas of rats, glimepiride when compared to glyburide had no effect on glucagon release. In vivo, in normal fasted dog, a plasma glucagon increase was observed during intravenous infusion of glyburide but was not observed with glimepiride.

Safety Pharmacology

CNS-related effects

After oral administration to mice, glimepiride had no CNS-stimulating or depressant effects. Oral doses of up to 1.0 mg/kg did not affect pentobarbital anesthesia, amphetamine group toxicity, motor coordination or pentetrazole-induced ptosis and had neither an anti-convulsive nor an analgesic effect.

Cardiovascular effects

In vivo and *in vitro* studies showed that glimepiride has an approximately 3 - 4 fold lower cardiovascular activity than glyburide, gliclazide or glipizide. Under physiological conditions, cardiovascular effects with glyburide and glimepiride (ECG rat studies and intracoronary infusion dog study) were observed at concentrations calculated to be 200 - 300 times higher than C_{max} observed in clinical trials after oral administration of therapeutic doses. Under ischemic

conditions, vascular and cardiomyocytic effects were observed with glyburide at a dose of 0.15 mg/kg, i.v., but no or only slight effects with glimepiride at a dose of 0.45 - 0.5 mg/kg, i.v. The maximal plasma concentrations in the ischemic studies were probably one order of magnitude higher than the therapeutic C_{max} concentrations.

As shown in various in vitro and in vivo studies, glimepiride had less influence than glyburide on the cardiomyocyte.

Glimepiride had no effect on systemic blood pressure, arterial blood flow and left ventricular contractility in anesthetized normal cats at intraduodenal doses up to 1 mg/kg.

Anti-atherogenic effect
Glimepiride had been shown to have an anti-atherogenic effect. Rabbits treated for 10 weeks with pellet diet containing 1% cholesterol and 3 ppm glimepiride, showed significantly fewer fatty streaks were seen on the intimal surface of the thoracic aorta than the control animals (20% vs 60%). In animals treated with cholesterol diet with 7 ppm glyburide or 120 ppm gliclazide no significant inhibition of fatty streak deposition was seen.

Glimepiride affected key steps of the thrombin-induced platelet activation and aggregation such as:

- Inhibiting dose-dependently, the decrease in the number of blood platelets after ADP infusion in rabbits treated with single i.v. doses up to 0.1 mg/kg or oral doses of 0.1 mg/kg once daily for 1 week. In contrast, single oral doses of up to 0.3 mg/kg were without effect.
- inhibiting the thrombin-stimulated increase of intracellular Ca^{2+} in platelets of human volunteers to a similar degree as glyburide at concentrations of 20 - 40 μM
- inhibiting selectively the cyclooxygenase pathway at concentrations up to 40 μM, whereas glyburide inhibited both the cyclooxygenase and 12-lipoxygenase pathways
- having no effect on thrombin-induced aggregation of human platelets. This missing inhibitory effect of glimepiride on thrombin aggregation of human platelets *in vitro* is not contradictory (even 1 mM acetylsalicylic acid had no effect) since at the thrombin concentration used (0.2 IU/mL) platelet aggregation is independent of thromboxane A_2 formation.

Gastrointestinal effects
There was no effect on gastric emptying after oral doses of up to 1 mg/kg in rats. At doses of up to 1 mg/kg i.p. in rats, glimepiride had no effect on exocrine pancreatic secretion, bile secretion or histamine-induced gastric secretion.

Anti-inflammatory effects
After oral doses of up to 1 mg/kg once daily for 4 days, glimepiride had no antiexudative effect in the ganuloma pouch in rats.

In yeast-induced fevered rats body temperature was not affected by an oral dose of glimepiride of 0.1 mg/kg; however, 1.0 mg/kg induced a slight but significant drop in temperature. The

antifebrile effect seems to be related to the hypoglycemic effect since it was also observed after an oral dose of 1 mg/kg glyburide and after 5 IU/kg regular insulin s.c.

A single oral dose of 0.1 mg/kg glimepiride did not affect, but 1 mg/kg inhibited carrageen paw edema in rats. The anti-inflammatory effect seems to be related to the hypoglycemic activity since it was also observed after an oral dose of 1 mg/kg glyburide and after 5 IU/kg insulin s.c.

Diuretic effects
Oral doses of up to 1.0 mg/kg glimepiride to rats had no diuretic effect.

Animal Pharmacokinetics
Glimepiride was slowly but completely absorbed after single oral administration of 0.5 mg/kg to male and female rats, male dogs and male rabbits compared with an intravenous dose. The serum protein binding was generally greater than 99% in all species studied. Following administration of ^{14}C-glimepiride, peak blood levels were reached earlier in rats and dogs than in rabbits. Mean half-life was 1.7 h in rats, 12.5 h in the dog and 7 h in rabbits. In lactating rats, absorption was moderate and led to similar maximum blood levels of radioactivity (0.079 µg equiv./mL) as in male animals and non-lactating females. On the basis of the radioactivity measured in milk and daily milk production, the amount excreted *via* this route was estimated to be less than 0.1% of the total administered dose.

After single or multiple oral dosing, the major organ of localisation in the rat was the liver. At 2, 4 and 8 hours after oral dosing of ^{14}C-glimepiride, the concentration of radioactivity in the liver was approximately 16 fold higher than the blood. Other than the kidneys, all other organs including the pancreas contained concentrations similar to or less than those found in the blood. Similar distribution profiles were observed after intravenous administration. In rabbits, the major site of localisation was the kidneys. Pregnancy (Day 14 or Day 18) did not affect the distribution of radioactivity following oral administration of [^{14}C]-glimepiride to rats. The concentration of radioactivity in fetal tissues was always lower than in the placenta, which in turn was lower than in maternal blood. There was no evidence of recirculation of radioactivity from the amniotic fluid to the fetus nor of accumulation of the drug or its metabolites in the fetus.

The primary route of excretion in the rat, mouse and dog was through the feces while in the rabbit the majority of radioactivity was eliminated *via* the kidneys. Two major metabolites could be identified, the hydroxy derivative (M1) and the carboxylic acid derivative (M2). A study in biliary cannulated rats indicated that a substantial part of the radioactivity (predominantly metabolites M1 [41%] and M2 [21%] is subject to enterohepatic recirculation. Overall, the comparison between species revealed no major qualitative pharmacologic differences with respect to metabolism among animals and man, except for the observation that the metabolite M2 could not be found in dog.

TOXICOLOGY

Acute Toxicity Studies

Species/ Strain	Route*	Dose (mg/kg)	Test compound	No. Deaths/ No. per Group (M, F)	Earliest Deaths (Days)	Observations
Mouse HOE:NMRKf (SPF71)	PO	10,000	glimepiride	0/5, 0/5	-	A dose of 10,000 mg/kg was tolerated without signs of intoxication
	PO	10,000	D85 1704 (by product)	0/5, 0/5	-	A dose of 10,000 mg/kg was tolerated without signs of intoxication
	IP	4,000	glimepiride	0/3, 0/3	-	A dose of 4,000 mg/kg was tolerated without deaths. Reduced motility and retracted flanks were observed.
Mouse Jcl:ICR (SPF71)	IP	2,000	glimepiride M1 M2	1/5, 0/5 0/5, 0/5 0/5, 0/5	2 - -	Acute Lethal Dose >2,000 mg/kg IP for glimepiride, M1, and M2.
	PO	2,000 500 1,000 2,000 2,000	glimepiride HOE 490D HOE 490D HOE 490D HOE 490I	0/5, -/- 0/5, -/- 0/5, -/- 6/7, -/- 0/5, -/-	- - - 1 -	Acute Lethal Doses: glimepiride: >2,000 mg/kg HOE 490D (decomposition product): 1,000 - 2,000 mg/kg HOE 490I (impurity): >2,000 mg/kg
Rat HOE:WISKf (SPF71)	PO	10,000	glimepiride	0/5, 0/5	-	A dose of 10,000 mg/kg was tolerated without signs of intoxication
	PO	5,000	glimepiride Urethane**	0/2, 0/2	-	Transient, increased salivation was seen in the females only.
	PO	5,000	glimepiride Ethyl-urethane**	0/2, 0/2	-	Transient, increased salivation was seen in the females only.
	PO	2,000	glimepiride-sulfonamide**	0/5, 0/5	-	Sunken flanks, squatting posture, stilted gait, and irregular respiration were observed in both sexes.
	IP	3,950	glimepiride	0/3, 0/3	-	A dose of 3,950 mg/kg was tolerated without deaths. Reduced motility, squatting position and retracted flanks were observed.
Dog Beagle	PO	2,000	glimepiride	0/2, -/-	-	Acute Lethal Dose >2,000 mg/kg

* PO = orally IP = intraperitoneally IV = intravenously
** glimepiride production intermediates

Multidose Toxicity Studies

Species/ Strain	No. of Animals per Group (M, F)	Route*	Dose Levels	Test Compound	Duration	Key Observations
Rat Wistar HOE:WISkf (SPF71)	15, 15	PO	0; 1.0; 50; 2,500 mg/kg/day	glimepiride	4 weeks	Clinical, hematological and clinico-chemical investigations revealed no pathological changes. Histological examination revealed that none of the doses of glimepiride administered led to any morphological changes.
	10, 10	PO	0; 1,000; 2,500 mg/kg/day	glimepiride	one month	The "No Observed Effect Level" was at 1,000 mg/kg body weight per day. However, there were no signs of clear toxicity detectable at the dose of 2,500 mg/kg body weight per day.
	5, 5	PO	0; 40; 200; 1,000 mg/kg/day	glimepiride-sulfonamide (production intermediate)	28 days	No compound-related macroscopically visible changes were observed at necropsy. Histopathological examination revealed focal cell necroses of the liver in three females of the high dose group. The "no observed effect level" was 40 mg/kg body weight per day.
	50, 50	PO	0; 20; 1,000; 50,000 ppm	glimepiride	12 months	Body weight development of male rats was slightly impaired at 1000 ppm and 50,000 ppm and in the females at 50,000 ppm, but feed consumption was not affected. Clinical examinations, hematological and clinico-chemical analysis, urinalysis and macroscopic inspection did not yield any compound related pathological findings. In females, heart weights were significantly decreased (all doses), liver weights decreased (1,000 ppm) and spleen weights increased (50,000 ppm). Histological examination did not reveal any compound-related morphological organ changes among treatment groups.
	20, 20	Feed	0; 1.0; 50; 2,500 mg/kg/day	glimepiride	6 months	The clinical, hematological and clinico-chemical investigation revealed no pathological changes due to study drug. The death of three animals in the 2500 mg/kg group was deemed independent of the compound. Histological examination revealed marked degranulation of the beta cells after 50 or 2,500 mg/kg. This finding was reversible within the four-week recovery period.
	5, 5	IV	0; 0.1; 1.0; 10.0 mg/kg	S 88 0610 (M1)	14 days	All doses tested were tolerated symptom-free. The clinical, haematological, clinico-chemistry or histological examinations revealed no further compound-induced changes.
	5, 5	IV	0; 0.1; 1.0; 10.0 mg/kg	S 88 0611 (M2)	14 days	The clinical examinations gave no indication of compound-induced changes. The macroscopic and microscopic examination did not reveal compound-induced organ changes.

Species/ Strain	No. of Animals per Group (M, F)	Route*	Dose Levels	Test Compound	Duration	Key Observations
	15, 15	IV	0; 0.1; 1.0; 10.0 mg/kg day	glimepiride	4 weeks	The 0.1 and 1.0 mg/kg doses were tolerated without the occurrence of any pathological changes. After 10 mg/kg there were no clinical, hematological, or clinico-chemistry changes. Histological examination revealed dose-dependent degranulation of the beta cells in the Islets of Langerhans at all doses. This finding was still present at the end of the four-week recovery period and is connected to the pharmacodynamic effect of the compound.
Dog Beagle Hoe:BEAK	3, 3	PO	0; 0.8; 16.0; 320 mg/kg/day	glimepiride	4 weeks	There were no relevant toxicological impairments in any of the dosage groups. A female from the highest dosage group showed a slight alteration in feed uptake.
	5, 5	PO	0; 0.8; 16.0; 320 mg/kg/day	glimepiride	26 weeks	The administration of HOE-490 in doses of 0.8 mg/kg and 16.0 mg/kg in dogs did not lead to any relevant toxicological changes. In the highest dosage group, only a slight loss in body weight for two animals was observed. In addition, on histological examination, a degranulation of the beta cells was revealed in all dosage groups (reversible within recovery period).
	6, 6	PO	0; 0.8; 16.0; 320 mg/kg/day	glimepiride	12 months	In the highest dosage group, bilateral posterior subcapsular cataracts were observed in one male and one female at the end of the study. Very marked aggravation of the lens opacity was observed in the female whose recovery was prolonged to12 weeks after the study. Microscopic examination revealed no histological correlate to the ophthalmological changes observed in the male and unilateral ocular degeneration of a few lens fibres in the female. In addition, on histological examination, a degranulation of the beta cells was revealed in all dosage groups.
	3, 3	IV	0; 0.08; 0.4; 2.0 mg/kg	either M1 or M2	2 weeks	No compound-induced toxic changes were detected in any of the dosage groups. The only pharmacological effect observed was a slight dose-dependent reduction in serum glucose at 0.40 and 2.0 mg/kg M1.
	3, 3	IV	0; 0.08; 0.4; 2.0 mg/kg/day	glimepiride	4 weeks	No compound-related toxicological effects in any of the study groups were observed. As the pharmacological effect, all dosage groups revealed a reduction in serum glucose and on histological examination, degranulation of the beta cells in the Islets of Langerhans was observed. Both of these effects were reversible within the four-week recovery period.

* PO = orally IP = intraperitoneally IV = intravenously

Carcinogenicity Studies and Associated Dose-Finding Studies

Species/ Strain	No. animals/ Group (M, F)	Dosage/Delivery Route	Duration	Observations
Mouse HOE:NMRKf (SPF71)	48, 48	320; 1,265 ppm in feed	2 weeks (toxicokinetics)	validated exposure to drug in carcinogenicity study
	10, 10	0; 200; 1,000; 5,000; 25,000; 50,000 ppm in feed	3 months (dose-finding)	5,000 ppm chosen as top dose for carcinogenicity study due to saturated absorption
	50, 50	0; 320; 1,265; 5,000 ppm in feed	24 months (carcinogenicity)	no demonstrated carcinogenicity
Rat Wistar HOE:WISkf (SPF71)	3, 3	0; 320; 1,000; 5,000; 10,000; 50,000 ppm in feed	3 months (dose-finding)	320 ppm chosen as top dose for carcinogenicity study (008166) as it caused maximum degranulation of β cells
	10, 10	0; 320; 1,000; 5,000; 10,000; 25,000; 50,000 ppm in feed	3 months (dose-finding)	5,000 ppm chosen as top dose for carcinogenicity study (009620) due to saturated absorption
	50, 50	0; 32; 100; 320 ppm in feed	30 months (carcinogenicity)	no demonstrated carcinogenicity
	50, 50	0; 320; 1,265; 5,000 ppm in feed	30 months (carcinogenicity)	no demonstrated carcinogenicity

Mutagenicity Studies

Study Type	Doses	Observations
In vitro Non-mammalian Ames	4 - 10,000 µg/plate	negative
	4 - 5,000 µg/plate	negative
	4 - 5,000 µg/plate (glimepiride-sulfonamide)	negative
	4 - 5,000 µg/plate (glimepiride-*cis*-isomer)	negative
	4 - 5,000 µg/plate (glimepiride-urethane)	negative
	4 - 5,000 µg/plate (glimepiride-ethylurethane)	negative
In vitro Mammalian HGPRT in V79 Chinese Hamster Cells	50 - 600 µg/mL	negative
In vitro Mammalian Unscheduled DNA Synthesis	1 - 1,000 µg/mL	negative
In vitro Mammalian Chromosome Aberrations in V79 Chinese Hamster Cells	10 - 1,250 µg/mL (glimepiride-urethane)	negative
	10 - 1,060 µg/mL (glimepiride-ethylurethane)	negative
	10 - 100 µg/mL (glimepiride-sulfonamide)	negative
In vivo Mammalian Chromosome Analysis of Chinese Hamster	0 - 5,000 mg/kg PO	negative
In vivo Mammalian Mouse - Micronucleus	400 mg/kg PO	negative
	2,500 mg/kg PO (glimepiride-sulfonamide)	negative
	2,000 mg/kg PO (glimepiride-*cis*-isomer)	negative

Reproduction Toxicity Studies

Species/ Strain	Route	Dosage	No. of animals/ group	Observations
Segment I: Fertility Studies				
Mouse, Jcl:ICR	PO	0; 250; 2,500 mg/kg	7 M	No effects on male fertility
Rat Hoe:WISKf (SPF71)	feed	0; 20; 1,000; 50,000 ppm	32 F	No effects on fertility. Postnatal effects on humerus in 1 adult offspring at 1,000 ppm and in 11 adult offspring from 7 litters at 50,000 ppm.
Segment II - Teratology Studies				
Rat Hoe:WISKf (SPF71)	PO	0; 1; 50; 2,500 mg/kg	35 F	No effect on pregnancy, parturition or intrauterine development of foetuses, other than uni- or bilateral microphthalmia seen in 2 and 4 fetuses in 1 and 50 mg/kg groups, which was due to pharmacologically induced hypoglycaemia.
Rabbit Himalayan	PO	0.0067; 0.0212; 0.0670; 0.32; 3.2; 32 mg/kg From the 6th-18th day of pregnancy	15 F	Hypoglycemia during pregnancy and in fetuses with doses of 0.0067 and 0.0212 mg/kg. Higher doses induced persistent hypo-glycemia, intolerance, modified feed consumption and body weight, abortion, ↑ no. of uterine death. Some surviving fetuses experienced eye malformation, sternal and abdominal fissures, and/or bends of the ulna, tibia, and fibula, and shortening or bends of the femur. All findings were attributed to hypoglycemia.
Rabbit Himalayan White	PO	0; 0.32 mg/kg/day HOE 490 or 0.96 mg/kg/day glibenclamide	15 F	Both compounds produced marked, persistent hypoglycemia. Normal pregnancies were observed in 14/15 in the control group, 5/15 in HOE 490 group, and 2/15 in glibenclamide group
	PO	0; 0.32 mg/kg/day HOE 490 or 0.96 mg/kg/day glibenclamide	15 F	Abortion/foetal loss in 5/15 dams treated with HOE 490, 9/15 with glibenclamide, and 1/15 controls. Hypoglycemia was considered to be cause of foetal deaths.
Rabbit Japanese White	PO	0; 3; 15 mg/kg/day HOE 490 or 50 mg/kg/day (b.i.d.) gliclazide	4-12 F	Both drugs produced hypoglycemia and increased incidences of abortions.
Rabbit:: Himalayan and New Zealand White	PO	0.32 mg/kg/day	15 F 19 F	Himalayan rabbits showed more hypoglycemia and higher abortion rate (11/15) than New Zealand White rabbits (2/19)
Segment III: Perinatal and Postnatal Studies				
Rat Hoe:WISKf (SPF71)	PO	0; 1; 50; 2,500 mg/kg	20-22 F	Dose-dependent increase in intrauterine foetal death in 50 and 2,500 mg/kg groups. Shortening and bending of right humerus of 1 pup from 2,500 mg/kg group.

Reproduction Toxicity Studies

Species/ Strain	Route	Dosage	No. of animals/ group	Observations
	Feed	0; 50,000 ppm	15 F	Pups exposed to HOE 490 in breast milk attained serum levels about twice that of the mothers. Dosage regimen increased number of stillbirths and retarded body weight development of pups.
	Feed PO	0; 20; 1,000; 5,000 ppm 0; 2,500 mg/kg	10-30 F 10 F	Effects on humerus and femorus detected by day 4 post-partum. Intrauterine exposure affected bones only slightly. Exposure during lactation produced severe bone deformities.
	Feed	50,000 ppm	40 F	Slight increase in retarded fetuses in offspring delivered by caesarean section. The rearing group exhibited a slight increase in the number of death births and reduced body weight development in second and third week of lactation.

Other Toxicity Studies

Species/ Strain	Route	Dosage	No. of animals per group	Observations
Cataractogenic Potential				
In vitro Bovine	bovine lens in culture	10^{-4}M	N/A	HOE 490 had no effect on lens metabolism.
Rat Brown-Norway Pigmented	PO	0; 1; 50; 250 mg/kg/day	14	HOE 490 has no demonstrated cocataractogenic potential.
Immunogenicity				
Mouse, A/J and Rat, Sprague-Dawley	SC (sensitizing) ID (challenge)	200 µg/mouse (HOE 490 and MI)	5 - 10 M 2 - 3 M	Neither HOE 490 nor its metabolite MI was antigenic.
Guinea Pig Hartley	PO (sensitizing) IV (challenge)	2 mg/kg (sensitizing) 2 mg/kg (challenge)	10 M	Neither HOE 490 nor its metabolite MI was antigenic.
Guinea Pig Pirbright White	ID	0.1 mL of 1% solution	10 F	Glimepiride-sulfonamide was not a sensitizer in the guinea pig maximisation test.

Toxicokinetics Studies

Species/ Strain	Dosage/ Route	Duration	No. of animals per group	Observations
Mouse Crl:NMRI BR	320; 1,265 ppm in food	2 weeks	48 M/48 F	Four-fold increase in quantity of drug in feed resulted in two-fold increase in C_{max}, C_{ave}, and AUD_{24}
Rat Wiskf (SPF71)	1,265; 5,000 ppm in food	2 weeks	24 M/48 F	Four-fold increase in quantity of drug in feed resulted in 1.5- and 1.2-fold increase in C_{max} and AUD_{24} respectively. C_{max} and AUD_{24} were 2.1- and 1.6-fold higher in females than in males.
Rat Wiskf (SPF71)	2,500 mg/kg stomach tube	2 weeks	24 M/24 F	AUD_{24} was 1.9-fold higher in females than in males (19.7 and 37.8 µg/h/mL for males and females respectively).
Rat Wiskf (SPF71)	5,000 ppm in food (Group 2) 2,500 mg/kg stomach tube (Group 3)	2 weeks	10 F 10F	In Group 2, treatment did not affect the endocrinological parameters investigated. In Group 3, a decrease in pituitary LHRH receptors and slight decrease in ovary and uterus weights was observed. No change in serum LH response and oestradiol in LHRH test and pituitary LH and FSH and ovarian oestradiol content.

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PART III: CONSUMER INFORMATION

Pr NOVO-GLIMEPIRIDE
(glimepiride tablets)

This leaflet is part III of a three-part "Product Monograph" published when **NOVO-GLIMEPIRIDE** was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **NOVO-GLIMEPIRIDE**. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
NOVO-GLIMEPIRIDE (glimepiride) is a medication that is used to treat Type 2 Diabetes. The chemical name for NOVO-GLIMEPIRIDE is "glimepiride"; it belongs to a class of drugs called sulfonylureas.

To properly control your diabetes, it is essential that you follow the diet, exercise and weight loss program recommended by your doctor. It is also important that you test your blood for sugar according to your doctor's recommendations.

What it does:
NOVO-GLIMEPIRIDE (glimepiride) is indicated as an addition to proper dietary management, exercise and weight reduction to lower the blood glucose in patients with Type 2 Diabetes whose high blood sugar levels cannot be controlled by diet and exercise alone.

NOVO-GLIMEPIRIDE is also indicated for use in combination with insulin to lower blood glucose in patients with Type 2 Diabetes whose high blood sugar levels cannot be controlled by diet and exercise in conjunction with an oral hypoglycemic agent (a drug used to lower blood sugar levels) alone.

When it should not be used:
NOVO-GLIMEPIRIDE should not be used:

- If you have Type 1 Diabetes.
- If you have known hypersensitivity or allergy to any sulfonylurea or any other component of the formulation. See "What the important nonmedicinal ingredients are".
- If you have diabetic ketoacidosis (an emergency condition with high blood glucose levels, a lack of insulin and an accumulation of ketones (chemicals) in the blood and urine), with or without coma. This condition should be treated with insulin.
- If you are pregnant or breast-feeding.

What the medicinal ingredient is:
The medicinal ingredient for NOVO-GLIMEPIRIDE is "glimepiride".

What the nonmedicinal ingredients are:
NOVO-GLIMEPIRIDE tablets contain the following non medicinal ingredients: lactose monohydrate, microcrystalline cellulose, magnesium stearate, povidone, and sodium starch glycolate. In addition: NOVO-GLIMEPIRIDE 1 mg tablets contain Ferric Oxide, NOVO-GLIMEPIRIDE 2 mg tablets contain FD&C Blue #2 Aluminum Lake and Ferric Oxide, and NOVO-GLIMEPIRIDE 4 mg tablets contain FD&C Blue #2 Aluminum Lake.

What dosage forms it comes in:
NOVO-GLIMEPIRIDE (glimepiride) is formulated into tablets of 1 mg, 2 mg, and 4 mg strengths for oral administration.

WARNINGS AND PRECAUTIONS

BEFORE you use NOVO-GLIMEPIRIDE talk to your doctor or pharmacist if you have kidney, liver, or heart disease.

- Do not take this medicine if you have had an allergic reaction to NOVO-GLIMEPIRIDE or other sulfonylurea drugs.
- This medicine has been prescribed for you alone because of your medical condition. This or any other prescription medicine should be used only by the person for whom it was prescribed. It should not be shared.
- Wear a medical identification (I.D.) bracelet or neck chain at all times. Also, carry an I.D. card in your wallet or purse that says that you have diabetes and a list of your medicines.

Low blood sugar (hypoglycemia):

- If your blood sugar gets too low, you may feel shaky, weak, drowsy, confused, or very hungry. You may sweat or have blurred vision, a fast heartbeat, trouble concentrating, or a headache that doesn't go away. Signs of severe hypoglycemia include disorientation, loss of consciousness and seizures.
- You may have low blood sugar while you are taking NOVO-GLIMEPIRIDE, especially if you miss a meal, exercise for a long time, drink alcohol or use

another antidiabetic medication with NOVO-GLIMEPIRIDE. Make sure you know what to do if your blood sugar gets too low (ask your doctor, pharmacist or diabetes educator). Teach your friends, co-workers, or family members what they can do to help you if you have low blood sugar.

Pregnancy and breastfeeding:
NOVO-GLIMEPIRIDE should not be used during pregnancy or if you are breast feeding. Make sure your doctor knows if you are breast feeding, pregnant, or think you might be pregnant. Your doctor may want you to use insulin during this time.

Driving a vehicle or operating machinery:
Low or high blood sugar levels may impair alertness and reactions, especially when beginning or after altering treatment or when NOVO-GLIMEPIRIDE is not taken regularly. This may affect the ability to drive or to operate machinery.

INTERACTIONS WITH THIS MEDICATION

Drugs and foods to avoid:
Ask your doctor or pharmacist before taking any other medicine, including over-the-counter products.

- Avoid drinking alcohol while you are taking this medicine.
- There are various drugs that can interact with NOVO-GLIMEPIRIDE and change the way the medicine works. Some of these drugs are acetylsalicylic acid such as Aspirin, "sulfa" drugs, warfarin and beta-blockers.
- Some medicines can make it harder for you to control your diabetes. These include ACE inhibitors (i.e. drugs used to treat high blood pressure – hypertension), diuretics (water pills), corticosteroids (such as prednisone), birth control pills, and some kinds of cold and allergy drugs.
- Make sure your doctor and pharmacist knows if you are taking these or any other medicines.

PROPER USE OF THIS MEDICATION

Usual dose:
NOVO-GLIMEPIRIDE is usually taken once daily, with breakfast or the first main meal of the day. NOVO-GLIMEPIRIDE tablets must be swallowed without chewing. Your doctor will prescribe for you how much to take and how often. It is important that you follow your doctor's instructions carefully.

Missed Dose:
Take the missed dose as soon as possible, unless it is almost time for your next dose.

Do not take two doses at the same time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with any type of medication, NOVO-GLIMEPIRIDE is associated with some side effects. It may, however, affect different people in different ways. Just because side effects have occurred in other people does not mean you will get them.
If you have problems with these side effects, talk with your doctor or pharmacist:

- Mild nausea or vomiting
- Dizziness
- Low blood sugar (hypoglycemia), see above.
- This medicine may make your skin sensitive to sunlight and could cause a rash or sunburn. Use a sunscreen when outdoors. Avoid using sunlamps or tanning beds.

Call your doctor right away if you have any of these side effects:

- Unexplained fever, chills or sore throat
- Unusual bleeding or bruising
- Yellowing of skin or eyes, dark-colored urine or light- coloured bowel movements
- Skin rash or hives
- Oedema, swelling of the legs or unexpected weight gain.

This is not a complete list of side effects. For any unexpected effects while taking NOVO-GLIMEPIRIDE, tell your doctor or pharmacist.

HOW TO STORE IT

- Store the tablets at room temperature (15 - 30^{0}C), away from heat, moisture, and direct light.
- As with all medicines, keep this product out of the reach of children.
- Do not keep outdated medicine or medicine no longer needed.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Novopharm Limited. at:
at: 1-800-268-4127 ext. 5005
or druginfo@novopharm.com

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