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Gliclazide Modified Release

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Contents

Abstract

- Gliclazide modified release (MR) is a new formulation of the drug gliclazide and is given once daily. The hydrophilic matrix of hypromellose-based polymer in the new formulation effects a progressive release of the drug which parallels the 24-hour glycaemic profile in untreated patients with type 2 diabetes mellitus.
- The formulation shows high bioavailability and its absorption profile is unaffected by coadministration with food. Mean plasma glucose levels are significantly reduced over a 24-hour period in patients with type 2 diabetes mellitus treated with gliclazide MR once daily, in both fasting and postprandial states.
- No cardiovascular ATP-sensitive potassium channel interaction has been observed at therapeutic concentrations of gliclazide MR. Gliclazide MR has also demonstrated antioxidant properties that are independent of glycaemic control.
- In a randomised, double-blind, multicentre study, gliclazide MR 30 to 120mg once daily showed similar efficacy to gliclazide immediate release (IR) 80 to 320 mg/day (in divided doses for doses >80mg) in patients with type 2 diabetes mellitus over a 10-month period, reducing glycosylated haemoglobin (HbA_{1c}) and fasting plasma glucose (FPG) to a similar extent.
- The drug appeared most efficacious in patients who had previously been treated by diet alone, where significant reductions in HbA_{1c} from baseline of 0.9% and 0.95% were seen at 10 and 24 months. Similarly, a sustained effect of gliclazide MR was observed in a subgroup of elderly patients defined *a priori*; HbA_{1c} was decreased to a similar degree to that observed in the general study population.
- Gliclazide MR showed similar tolerability to gliclazide IR after 10 months' treatment in the randomised trial. The most commonly observed adverse events were arthralgia, arthritis, back pain and bronchitis (each <5%). Bodyweight remained stable.
- In this study no episodes of nocturnal hypoglycaemia or hypoglycaemia requiring third party assistance were observed during treatment with gliclazide MR. Episodes of symptomatic hypoglycaemia were infrequent, occurring in approximately 5% of patients.

Features and properties of once-daily gliclazide modified release (MR)	
Indications	
Type 2 diabetes mellitus	
Mechanism of action	
Insulin secretagogue	Pancreatic ATP-dependent potassium channel agonist
Dosage and administration	
Dosage	30 to 120mg once daily with breakfast
Route of administration	Oral
Pharmacokinetic properties after oral administration of gliclazide MR 30 to 120mg once daily	
Bioavailability	≈97%
Time to peak plasma concentrations	Approximately 6h
Clearance	0.9 L/h
Elimination half-life	16h
Adverse events	
Most frequent	Arthralgia, arthritis, back pain and bronchitis (incidence <5% for each)

Diabetes mellitus affects ≈8% of the US population aged >20 years[1] and is especially prevalent in the elderly, with approximately one-third of those aged between 65 and 74 years having either impaired glucose tolerance or type 2 diabetes mellitus.[2] In addition, overall cardiovascular morbidity and mortality rates in patients with diabetes mellitus are 2- to 4-fold higher than in those without the disease,[3] and poor plasma glucose control hastens diabetic complications such as neuropathy, nephropathy and retinopathy.[4,5]

Guidelines for the treatment and management of patients with type 2 diabetes mellitus advocate a multiple risk factor approach aimed at both treating the disease and minimising other cardiovascular risk factors such as hypertension and dyslipidaemia.[6,7] The initial step in such an approach involves dietary and lifestyle modifications, as regular exercise and even modest weight loss can improve insulin sensitivity and lower fasting plasma glucose (FPG) levels.[2,8]

Sulphonylureas are recommended as first-line monotherapy in insulin-deficient patients in whom lifestyle interventions have proved ineffective,[6] and have been available for the treatment of type 2 diabetes mellitus for nearly 40 years.[9] However, some show vasoconstrictor properties, potentially promoting atherogenesis and increasing the risk of cardiovascular events, and may also cause weight gain and hypoglycaemia.[8] Additionally, some sulphonylureas (e.g. glibenclamide and chlorpropamide) are contraindicated in the elderly or patients with renal impairment.[6]

Gliclazide modified release (MR) is a new formulation of the sulphonylurea gliclazide. It consists of a hydrophilic matrix of hypromellose-based polymer that expands to form a gel when exposed to gastrointestinal fluid, progressively releasing gliclazide. The formulation is given once daily. This article focuses on pharmacology, efficacy and tolerability data relevant to the new MR formulation.

1. Pharmacodynamic Profile

Sulphonylureas stimulate insulin secretion from pancreatic β-cells by inhibiting ATP-sensitive potassium (K_{ATP}) channels. These channels are each composed of four clustered pore-forming Kir6.2 subunits, each with an associated sulphonylurea receptor (SUR). Gliclazide has high affinity, and strong selectivity, for the β-cell K_{ATP} channel.[10]

Insulin Sensitivity and Glycaemic Control

• The secretagogue effect of gliclazide is rapid in onset and ceases upon withdrawal of the drug. Under normal conditions and those simulating a hypoglycaemic state (glucose concentration 2.2 mmol/L) in the isolated perfused rat pancreas, gliclazide at therapeutic concentrations stimulated β-cell activity. By restoring the first peak of insulin secretion this effect produced a rapid biphasic pattern of insulin release.[11] Gliclazide had minimal effects on insulin release in the absence of glucose.[12]

• Insulin sensitivity also increases with gliclazide treatment. Glucose uptake into perfused rat skeletal muscle obtained from streptozotocin-diabetic rats treated with gliclazide 5 mg/kg twice daily for 12 days increased 2-fold under insulin-stimulated conditions, compared with untreated controls.[13]

• Over a 24-hour period, significant decreases in plasma glucose levels were observed in the mean 24-hour (2.70 mmol/L), fasting (2.63 mmol/L) and postprandial states (3.03 mmol/L) and at all measured timepoints (all $p < 0.001$ *vs* baseline) in 21 patients with type 2 diabetes mellitus treated with gliclazide MR. The drug was given once daily for 10 weeks (30mg initially, increasing to 60mg daily after 2 weeks if fasting plasma glucose was not <7.8 mmol/L) [figure 1].[14] A 27% reduction in area under the curve of plasma glucose levels was also seen over the 24-hour period ($p < 0.001$ *vs* baseline).[14]

Cell Selectivity

Sulphonylureas stimulate insulin secretion from pancreatic β-cells by closing K_{ATP} channels. K_{ATP} channels are also found in high density in cardiac, smooth and skeletal muscle, raising the question of

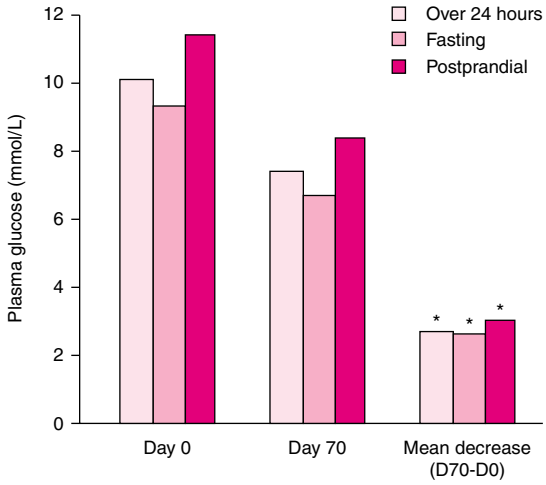

Fig. 1. Effect of 10 weeks' treatment with gliclazide modified release 30 to 60mg once daily on mean 24-hour fasting and postprandial plasma glucose levels (all measured during a 24-hour period at the end of the treatment period). Patients in this noncomparative study (n = 21) had type 2 diabetes mellitus and had been previously treated with diet alone or with an oral antidiabetic drug.[14] * $p < 0.001$ *vs* day 0.

whether sulphonylureas have the potential to increase cardiovascular risk. Recently, the cell selectivity of gliclazide and other sulphonylureas has been investigated in cloned β-cell (Kir6.2/SUR1), cardiac (Kir6.2/SUR2A) and smooth muscle (Kir6.2/SUR2B) K_{ATP} receptors expressed in *Xenopus* oocytes and in native cells from the same tissues.[10,11,15-17]

• *In vitro*, gliclazide 1 to 10 μmol/L (in native[15] and recombinant cells[10,16]) had a high affinity for inhibiting β-cell but not cardiac K_{ATP} channels. For example, in cloned cells the affinity constants (K_i) for gliclazide were 50 nmol/L and 3 mmol/L for high- and low-affinity β-cells sites and 0.8 mmol/L for cardiac sites.[10] Moreover, the β-cell interaction with gliclazide was rapidly reversible in cloned receptor models,[10] whole β-cells[15] and the isolated perfused pancreas.[11] Glibenclamide and glimepiride (both 100 μmol/L) impaired the ability of nicorandil (100 μmol/L), a K_{ATP} channel opener used in the treatment of ischaemic heart disease, to open cardiac SUR2A and smooth muscle SUR2B channels in cloned cells, whereas gliclazide (10 μmol/L) did not,[17] further indicating selectivity of gliclazide for SUR1 receptors.

• K_{ATP} channel vasodilation was not blocked *in vitro* by gliclazide in the guinea-pig and rat aorta, or *in vivo* in hamster cheek pouch microvessels, but was greatly inhibited by both glibenclamide and glimepiride; all drugs were used at therapeutic concentrations.[18]

Antioxidant Effects

• Gliclazide scavenges hydroxyl and superoxide radicals in a dose-dependent manner *in vitro*.[19,20] Over the clinically relevant concentration range of 0.5 to 5 mg/L the percent inhibition of control (photo-oxidation of dianisidine) ranged from 11 to 47%.[20]

• Patients with type 2 diabetes mellitus who had received gliclazide MR or immediate release (IR) [mean dosages 68.7 and 165 mg/day, respectively, at the end of a 4-month titration period; n = 44] for 10 months showed significant increases in total plasma antioxidant capacity (TPAC) [$p < 0.03$] and decreases in levels of 8-isoprostanes ($p < 0.001$), as well as significant increases in superoxide dismutase ($p < 0.01$) and thiols (which indicate an indirect effect of gliclazide) [$p < 0.001$], compared with baseline. Combined results were given for both gliclazide formulations.[21]

• These parameters improved between 4 and 10 months despite stable glycaemic control, suggesting a glycaemia-independent effect of the drug. The antioxidant effect of gliclazide appeared similar with both formulations, as evidenced by changes in 8-isoprostane levels, despite the lower dosage and once-daily regimen used with gliclazide MR.[21]

• Moreover, when low-density lipoprotein (LDL) isolated from patients with or without type 2 diabetes mellitus was supplemented *ex vivo* with gliclazide 1 μmol/L, lag time to LDL oxidation was increased by about 70 to 110%.[21,22] The increase was greater than with ascorbic acid 1 μmol/L ($p < 0.01$).[21,22]

• In an *in vitro* study gliclazide at therapeutic concentrations also enhanced TPAC by 13% ($p < 0.01$ *vs* control).[21] Glibenclamide, glimepiride, glipizide and tolbutamide did not show these effects.[21,22]

• Increasing concentrations of gliclazide (1 to 10 mg/L) *in vitro* resulted in dose-dependent decreases in human aortic smooth muscle cell (SMC)-mediated LDL oxidation. Additionally, there were decreases in oxidised LDL-induced human monocyte adhesion to SMCs, reduced proliferation of SMCs and decreases in oxidatively modified LDL-induced protein expression.[23]

Haemovascular Effects

• Gliclazide appears to reverse the endothelial dysfunction associated with diabetes mellitus. Impaired vasodilation induced by bradykinin in human mesenteric microvessels was prevented when coincubated with gliclazide 1 μmol/L, ascorbic acid 10 μmol/L or superoxide dismutase 100 U/ml, but not glibenclamide 10 μmol/L, when saturation of glycosylated oxyhaemoglobin was maintained at >10% to simulate the diabetic state.[24] Similarly, impaired nitric oxide-dependent vasorelaxation in rat aortic segments was reduced when coincubated with gliclazide 10 μmol/L, ascorbic acid 10 μmol/L or superoxide dismutase 100 U/ml, but not glibenclamide 10 μmol/L, when saturation of glycosylated oxyhaemoglobin was >14%.[25]

• Acetylcholine-induced endothelium-dependent vasodilation was maintained in isolated aortic segments and mesenteric microvessels from streptozotocin-induced diabetic rats which had been treated orally for 6 weeks with gliclazide 10 mg/kg or ascorbic acid 250 mg/kg. This was not evident with glibenclamide 1 and 10 mg/kg or pimagedine (aminoguanadine) 250 mg/kg.[26]

• Endothelial dysfunction associated with hyperglycaemia may also be prevented by gliclazide. Glycosylated albumin-stimulated human monocyte adhesion to human endothelial cells was significantly decreased when pretreated with gliclazide 10 mg/L *in vitro*.[27] In addition, a dose-dependent reduction in oxidised LDL-induced human monocyte adhesion to bovine aortic endothelial cells was observed when coincubated with gliclazide 1 to 10 mg/L.[28]

• Increased DNA binding activity of the transcription factor NF-κB (which regulates gene expression in endothelial cells), and the cell-associated expression of E-selectin, vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 (ICAM-1) were markedly inhibited when glycosylated albumin-stimulated monocyte-endothelial cells were pretreated with gliclazide 10 mg/L.[27] Glucose-mediated endothelial-neutrophil cell adhesion and increased expression of ICAM-1, P-selectin and E-selectin were significantly inhibited by coincubation with either gliclazide or epalrestat, but not glibenclamide, glimepiride, nateglinide or metformin [all between 1 to 10 μmol/L depending on maximum plasma concentrations (C_{max}) in humans].[29]

• A significant decrease in retinal leukostasis was observed in rats with diabetes mellitus who received 3 weeks' daily treatment with oral gliclazide 150 mg/kg, but not glibenclamide 8.6 mg/kg, compared with untreated diabetic controls ($p < 0.0008$).[30]

2. Pharmacokinetic Profile

The majority of pharmacokinetic data for gliclazide MR has been derived from a single-dose, randomised, nonblind crossover study in healthy volunteers[31] and from a population pharmacokinetic study in 1007 patients with type 2 diabetes mellitus; information for the latter study was obtained from an abstract[32] and from a full paper including 634 of these patients.[33] Some data from reviews are also included.[9,34]

• Upon contact of gliclazide MR with gastrointestinal fluid a hydrophilic matrix of hypromellose-based polymer expands to form a gel, which progressively releases gliclazide.[9] Gliclazide MR shows predictable and reproducible release of gliclazide over a 24-hour period which parallels the 24-hour glycaemic profile observed in untreated patients

with type 2 diabetes mellitus, as demonstrated in the population pharmacokinetic study.[32,33] Plasma gliclazide concentrations reach a plateau at 3 to 12 hours after a dose and decline thereafter.[32]

• Gliclazide MR shows linear pharmacokinetics over the 15 to 120mg dose range in patients with type 2 diabetes mellitus.[32] The intraindividual variability is low, at 16%.[32] C_{max} is reached at about 6 hours after administration (t_{max}).[31,32] Fasting C_{max} in 16 healthy volunteers given a single 30mg dose of gliclazide MR was 0.74 mg/L at a t_{max} of 7 hours, and the area under the plasma concentration-time curve (AUC) was 16.2 mg/L • h.[31]

•The mean absolute bioavailability of gliclazide was 97% (range 79 to 110%) after administration of a single oral dose of gliclazide MR 30mg to 16 healthy volunteers.[31]

• In patients with type 2 diabetes mellitus the apparent clearance of gliclazide MR was 0.9 L/h, with an apparent volume of distribution of 19L. Plasma concentrations declined exponentially, with an elimination half-life ($t_{1/2}$) of approximately 16 hours.[32] Gliclazide is highly bound to albumin (95%).[34] It is extensively metabolised to at least seven metabolites, with no circulating active metabolite.[9] Unchanged gliclazide accounts for <1% of compounds retrieved in the urine.[34]

• Age and mild to moderate renal impairment do not significantly influence the pharmacokinetic parameters of gliclazide MR.[32,34] Similarly, no significant effect of food on various pharmacokinetic parameters (t_{max}, $t_{1/2}$, C_{max} and AUC) was observed when gliclazide MR 30mg was given prior to, or 10 minutes after, starting breakfast.[31]

3. Therapeutic Trials

The clinical efficacy of gliclazide MR in patients with type 2 diabetes mellitus has been investigated in a long-term, randomised, double-blind, multicentre study[35] and a small short-term noncomparative trial,[14] both of which are available as fully published papers. In addition, a 12-month nonblind extension of the randomised study is available in abstract form.[36,37] Patients with glycosylated haemoglobin (HbA_{1c}) between 6 and 9% and an FPG level of between 7.8 and 13.9 mmol/L (15 mmol/L in Guillausseau et al.[14]) after a 2-week washout period were eligible for enrolment.[14,35] All of the percentage reductions in HbA_{1c} reported in this section are absolute, not relative, reductions.

• Briefly, in the randomised study patients were aged >35 years, had a body mass index (BMI) between 22 and 35 kg/m^2 and had been previously treated by diet alone or in combination with one or two other oral antidiabetic drugs. Treatment was initiated with either gliclazide MR 30mg once daily (n = 401) or gliclazide IR 80mg once daily (n = 399). The dosage could be titrated up at 4-week intervals over a 4-month titration period to a maximum of 120mg once daily or 320 mg/day (dosages greater than 80 mg/day were administered in two divided doses), respectively, if patients did not achieve satisfactory metabolic control (FPG between 4.4 and 6.6 mmol/L and 5.5 and 7.7 mmol/L for patients aged < and ≥65 years).[35]

• Patients then entered into a 6-month treatment period during which they received a fixed optimal dosage. In a further 2-month single-blind phase patients treated with gliclazide MR continued with this formulation, while those given gliclazide IR were invited to switch to gliclazide MR treatment on a tablet-for-tablet basis.[35]

• The primary endpoints in this trial were HbA_{1c} and FPG levels at the end of the 10-month double-blind treatment period. In each group, there were 378 evaluable patients and 55% were controlled on the lowest dosages.[35] Gliclazide MR showed similar efficacy to gliclazide IR with regard to these primary efficacy endpoints (treatment differences for HbA_{1c} and FPG were -0.08% and 0.14 mmol/L, respectively; both $p < 0.001$ for noninferiority). In patients who received gliclazide MR, mean decreases from baseline in HbA_{1c} and FPG of 0.22% and 0.83 mmol/L were achieved at 10 months ($p < 0.001$ *vs* baseline).[35]

• The efficacy of gliclazide MR was most clearly evidenced in the group of patients previously

treated by diet alone (n = 65) which was defined *a priori*. Reductions from baseline HbA_{1c} were 1.4% at 6 months and 0.9% at 10 months in these patients, and were sustained during the 10-month treatment period ($p < 0.001$ *vs* baseline for all timepoints).[35]

• Glycaemic control in a subgroup of elderly patients (aged ≥65 years; n = 310) defined *a priori* was similar to that observed in the entire study group; HbA_{1c} was reduced by 0.3% with both gliclazide formulations at 10 months. Forty-five percent of these elderly patients also had impaired renal function [creatinine clearance (CL_{CR}) between 1.2 and 4.8 L/h (20 and 80 ml/min)].[35]

• There were no clinically or statistically significant changes in the secondary endpoints of fasting serum insulin, triglyceride or total cholesterol levels over the 10-month double-blind treatment period with either formulation.[35]

• Preliminary results are available from a 12-month nonblind extension of this 1-year trial.[36,37] At the end of the study, treatment could be continued with either gliclazide MR alone (n = 290), or in combination with other oral antidiabetic drugs (n = 204; of whom 84.3% received metformin).[37]

• When assessed according to previous treatment, HbA_{1c} was significantly reduced 0.95 and 0.33% from baseline ($p < 0.05$) after 2 years of gliclazide MR therapy in patients previously treated with diet alone or in combination with one oral antidiabetic drug, respectively. HbA_{1c} was reduced over the 2-year period to a similar extent whether patients received gliclazide MR alone or with another oral antidiabetic drug [figure 2]. A sustained effect was also observed in 199 elderly patients treated with gliclazide MR over the 24-month period, in whom HbA_{1c} was significantly decreased by 0.49% from baseline ($p < 0.05$).[37]

• A nonblind 10-week study has investigated the short-term clinical efficacy of gliclazide MR 30 to 60mg once daily in 21 patients aged 35 to 75 years, with a BMI of 24 to 32 kg/m^2, who had previously received treatment with either diet alone, or diet with an α-glucosidase inhibitor and/or a sulphonylurea (at less than half the maximal dosage). The primary and secondary efficacy endpoints of mean 24-hour plasma glucose and fasting HbA_{1c} were assessed at 10 weeks.[14]

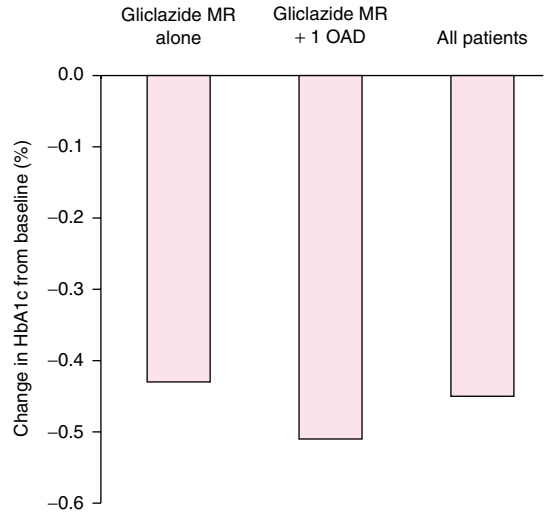

Fig. 2. Effect of treatment with gliclazide modified release (**MR**), either alone or in combination with other oral antidiabetic drugs (OAD), on glycosylated haemoglobin [HbA_{1c} (%)].[36,37] Patients initially received either gliclazide MR 30 to 120 mg/day with breakfast or gliclazide immediate release 80 to 320 mg/day (in divided doses for doses >80mg) for 12 months in a randomised, multicentre trial. The first 10 months were double-blind and the last 2 months were single-blind.[35] Patients then continued in a nonblind extension of this trial, and received gliclazide MR either alone (n = 290) or in combination with another OAD (n = 204) for a further 12 months (reported in abstract and poster form only).[36,37] Results are given for changes during the full 2 years; all are significant versus baseline ($p < 0.05$).

• Significant decreases in mean plasma glucose levels were observed in both the fasting and postprandial states after 10 weeks' treatment with gliclazide MR (by 2.63 and 3.03 mmol/L, respectively; both $p < 0.001$ *vs* baseline).[14] A significant decrease from baseline in HbA_{1c} (by 1.0%; $p = 0.022$) was observed in ten patients who had not been previously treated with antidiabetic drugs, although the small reduction in HbA_{1c} observed in the entire study population did not reach statistical significance. Compliance with gliclazide MR given once daily was high, at nearly 100%.[14]

4. Tolerability

The tolerability of gliclazide MR has been reported in the clinical trials described in section 3. The majority of adverse events observed during gliclazide MR treatment are mild to moderate in severity.[35]

• In the 10-month randomised, double-blind section of the 12-month study, adverse events were reported in 46.9 and 50.3% of patients who received gliclazide MR and gliclazide IR, respectively.[35] The most frequently reported events (in both groups) were arthralgia (3.4%), arthritis (2.8%), back pain (3.4%) and bronchitis (4.9%). Bodyweight remained stable over the 10-month treatment period both in the whole study population and in the subgroup of 131 obese patients (BMI >30 kg/m^2) who received gliclazide MR. Serious events were observed in 32 (8%) and 35 (9%) patients treated with gliclazide MR and gliclazide IR, respectively, of which one (malaise) was considered related to gliclazide MR treatment and four (one each with visual disturbance, gastrointestinal disorder, hyperglycaemia and hypertension) were considered related to gliclazide IR therapy.[35]

• Symptomatic hypoglycaemia occurred infrequently with gliclazide MR treatment, and there were no episodes of nocturnal hypoglycaemia or hypoglycaemia requiring third party assistance.[14,35,37] Mild to moderate hypoglycaemia was observed in approximately 5% of patients receiving either formulation, and in 1.4 and 1.2% of elderly patients treated with gliclazide MR or gliclazide IR over the 10-month treatment period.[35] Over the 2 years of this study, including the nonblind 12-month extension period, symptomatic hypoglycaemia was documented in 4.8 and 9.1% of patients aged ≥ or <65 years who received gliclazide MR.[36] No hypoglycaemic events were reported in the 10-week nonblind study.[14]

5. Dosage and Administration

The initial recommended dosage of gliclazide MR in patients with type 2 diabetes mellitus uncontrolled by diet, exercise and weight loss is 30mg once daily with breakfast. The dosage may be titrated by 30mg increments at intervals of 2 to 4 weeks, to a maximum of 120 mg/day. No dosage adjustments are needed for elderly patients or those with mild to moderate renal insufficiency [CrCL ≥1.2 L/h (20 ml/min)]. Gliclazide MR can be given in this dosage regimen as monotherapy or in combination with a biguanide (metformin), an α-glucosidase inhibitor, or insulin.[38]

6. Gliclazide Modified Release: Current Status

Gliclazide MR, administered once daily, has been approved for use in numerous countries worldwide, including in Europe and North America, for the treatment of adult patients with type 2 diabetes mellitus. Gliclazide MR reduces plasma glucose levels over a 24-hour period. It has shown similar efficacy to gliclazide IR in clinical trials, appears of particular benefit in patients previously untreated with oral antidiabetic drugs and is generally well tolerated.

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