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Tolerability Profile of Metformin/ Glibenclamide Combination Tablets (Glucovance®)

A New Treatment for the Management of Type 2 Diabetes Mellitus

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Abstract

It is important to manage blood glucose intensively in patients with type 2 diabetes mellitus in order to reduce the risk of long-term complications. Oral combination therapy that addresses insulin resistance and β-cell dysfunction is a proven means of improving glycaemic control when monotherapy becomes insufficiently effective. Metformin/glibenclamide (glyburide) combination tablets were developed to provide a means of applying this strategy while minimising polypharmacy. This review examines the tolerability profile of this treatment from four double-blind, randomised clinical trials in a total of 2342 type 2 diabetic patients with hyperglycaemia despite treatment with diet and exercise, a sulphonylurea or metformin. Treatment with combination tablets was associated with markedly superior blood glucose control, at lower doses of metformin and glibenclamide, compared with monotherapies. The incidence of symptoms of hypoglycaemia varied between dosages and trials, though the incidence of severe or biochemically confirmed hypoglycaemia or withdrawals from clinical trials for

this reason was consistently low and comparable with glibenclamide alone. No patient required third-party assistance for hypoglycaemia. Significantly fewer diet-failed patients receiving low-dose combination tablets reported gastrointestinal adverse effects compared with metformin alone, with a comparable incidence between metformin and combination tablets in post-monotherapy studies. The incidence of other adverse events, including serious adverse events, was similar for combination tablets and monotherapies. The lower doses of metformin and glibenclamide with the combination tablet approach, and the design of the combination tablets themselves, may underlie the beneficial tolerability profile of this treatment.

The landmark UKPDS (UK Prospective Diabetes Study) has proved beyond a doubt that intensive glycaemic control with oral antidiabetic therapy yields clinically significant improvements in microvascular outcomes during long-term treatment.[1] In addition, intensive glycaemic management with metformin in the UKPDS provided protection from macrovascular complications above and beyond that expected from blood glucose control alone.[2] An epidemiological analysis of the UKPDS database showed that the relationship between the level of glycosylated haemoglobin (HbA_{1c}, a marker of long-term hyperglycaemia) and an increased risk of diabetic complications is continuous and extends into the range of HbA_{1c} values considered normal (<6.5%).[3]

The results of the UKPDS and other studies have led to the introduction of challenging targets for the management of glycaemia in Europe[4] (HbA_{1c} levels ≤6.5%) and in the US (HbA_{1c} levels <7.0%[5] or <6.5%[6]). These targets are difficult to achieve during long-term treatment. The hyperglycaemia of type 2 diabetes mellitus worsens over time as β-cell function continues to decline. As a result, oral antidiabetic monotherapy with an oral agent or insulin will maintain glycaemia adequately for only a few years in the majority of patients.[7] Combinations of oral agents improve glycaemic control markedly in patients with glycaemia insufficiently responsive to monotherapy, especially where the combinations address the principal endocrine defects of insulin resistance and β-cell function that drive the progression of hyperglycaemia in almost all patients with type 2 diabetes.

However, polypharmacy is common among type 2 diabetic patients[8] and the added pill burden arising from the coadministration of oral antidiabetic agents may impair compliance with therapy. One solution to this problem is the combination of two treatments within a single tablet: an approach common in other fields of medicine (especially the management of hypertension) but relatively new in the management of type 2 diabetes.[9] The first such combination to become available for widespread clinical use contains metformin and glibenclamide (glyburide) [Glucovance®].[1] These components were chosen for inclusion within the combination tablet as they represent the most evidence-based oral antidiabetic combination available. For example, metformin addresses insulin resistance while glibenclamide addresses β-cell dysfunction, the two major endocrine defects of type 2 diabetes. Moreover, these agents are each supported by decades of clinical experience when used alone and in combination and each has been proven to reduce the risk of diabetic complications in the UKPDS.[1,2] Finally, their pharmacokinetics are sufficiently compatible to support administration as a combined formulation.[10]

Previous reviews have described in detail the design of the metformin/glibenclamide combination tablet[10] and its therapeutic efficacy in type 2 diabetic patients,[11] but its tolerability has been less well described. The principal tolerability issues associated with metformin and glibenclamide are gastrointestinal adverse effects and symptoms of hypoglycaemia, respectively.[12] Accordingly, this review focuses on these adverse events in a database com-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table I. Details of clinical trials reviewed in this paper

Study	No. of patients	Duration (weeks)	Previous therapy	Study therapy[a]	Mean HbA_{1c} levels at baseline (%)
Garber et al.[13]	806	20	Diet/exercise	Combination tablets 250/1.25mg; 500/2.5mg Metformin 500mg Glibenclamide (glyburide) 2.5mg Placebo	8.2
Garber et al.[14]	486	16	Diet/exercise	Combination tablets 250/1.25mg Metformin 500mg Glibenclamide 2.5mg	8.7
Blonde et al.[15]	639	16		Combination tablets 500/2.5mg; 500/5mg Metformin 500mg Glibenclamide 5mg	9.4
Marre et al.[16]	411	16	Metformin	Combination tablets 500/2.5mg; 500/5mg Metformin 500mg Glibenclamide 5mg	7.9

a Study treatments were based on the tablet strengths shown. Daily dosages were titrated for optimum efficacy and tolerability responses, except for Blonde et al.[15] where glibenclamide was given at a constant dosage of 20 mg/day throughout. All combination tablets are stated as metformin/glibenclamide doses.

HbA_{1c} = glycosylated haemoglobin.

prising four double-blind, multicentre, parallel-group clinical trials involving a total of 2342 patients with type 2 diabetes suboptimally controlled by diet and exercise, metformin or a sulphonylurea, who were randomised to receive the combination tablets or monotherapy with metformin or glibenclamide. The general tolerability of metformin/glibenclamide in these trials and, given the importance of avoiding exacerbation of the already elevated cardiovascular risk of type 2 diabetic patients, the effects of metformin/glibenclamide on lipid profiles, insulin levels and bodyweight are discussed.

1. Data Sources

Data reviewed here are from four double-blind, randomised, parallel-group, multicentre, active-controlled clinical trials of 16–20 weeks' duration (table I). Patients had glycaemia suboptimally controlled with a treatment based on diet and exercise,[13,14] at least half-maximal doses of a sulphonylurea[15] or metformin ≥1500 mg/day.[16] The only other double-blind, randomised evaluation of combination tablets in a substantial number of patients published in full at the time of writing was a placebo-controlled evaluation of additional rosiglitazone therapy in patients with glycaemia suboptimally controlled with metformin/glibenclamide.[17] This study sheds little additional light on the safety and tolerability of the metformin/glibenclamide combination and has not been included here. In addition, data are shown separately for individual studies and have not been pooled between studies. This was because of differences in trial populations and because differences in trial designs may have influenced the incidence of hypoglycaemic symptoms, especially in patients with glycaemia suboptimally controlled by diet.

Both of the trials in patients previously receiving diet and exercise therapy[13,14] and the post-sulphonylurea trial[15] were conducted in the US, whereas the post-metformin trial[16] enrolled patients from Europe (France, Belgium, The Netherlands, Denmark and Portugal). Data not provided in the original source publications have been supplemented by additional material from the original clinical study reports.

All trials compared one or two dose strengths of the combination tablets with metformin and glibenclamide monotherapies, and one of the post-diet trials[13] was also placebo controlled. The dose strengths of combination tablets used in individual trials reflect their intended clinical use. For example, the metformin/glibenclamide 250/1.25mg tablet strength is intended for initiation of therapy in drug-naive patients, with the 500/2.5mg tablet available for periodic intensification of therapy as hyperglycaemia progresses. Similarly, the 500/2.5mg tablet

is intended for initiation of therapy in patients previously receiving oral antidiabetic therapy, with the 500/5mg tablet available for further intensification of therapy. The doses of all the treatments in these trials were optimised for efficacy against *a priori* glycaemic targets, subject to tolerability, except that glibenclamide was given at a constant daily dose of 20mg in the post-sulphonylurea trial.[15] Combination tablets were always given with meals. Where patients received a single tablet each day, this was taken with breakfast. Combination tablet regimens involving two or more tablets daily were given as divided doses with breakfast and the evening meals. The maximum dosage allowed in all trials was four tablets/day, which is also the maximum allowed dosage during clinical use of this treatment.

Good compliance with therapy was encouraged by investigators and was monitored closely throughout the trials. Patients not achieving 80–120% of expected consumption of the study treatment were withdrawn from the studies carried out in the US. In the European study, failure to achieve this level of compliance was considered a minor protocol violation, with compliance outside 50–150% of expected consumption identified as a major protocol violation. Overall, only 15 randomised patients from all four studies discontinued from either a study lead-in phase or double-blind treatment for a specified reason of poor compliance with treatment.

2. Efficacy

A brief description of the blood glucose-lowering efficacy of the combination tablets is included to facilitate consideration of their overall benefit-risk profile. The combination tablets were significantly more effective in reducing HbA_{1c} levels than metformin or glibenclamide alone in all of the four trials (figure 1). Moreover, these efficacy benefits were achieved at lower average doses of metformin and glibenclamide delivered via combination tablets, compared with metformin and glibenclamide given alone (table II). The mean final HbA_{1c} values achieved in these studies in patients randomised to the correct dose strength for initiation of combination tablet therapy (metformin/glibenclamide 250/1.25mg or 500/2.5mg for patients that were hyperglycaemic despite diet and exercise or oral antidiabetic monotherapy, respectively) were 6.5%[13], 6.4%[14], 7.9%[15] and 6.7%.[16]

The proportions of patients achieving HbA_{1c} levels of <7% after treatment with the combination tablet strength recommended for initiation of treat-

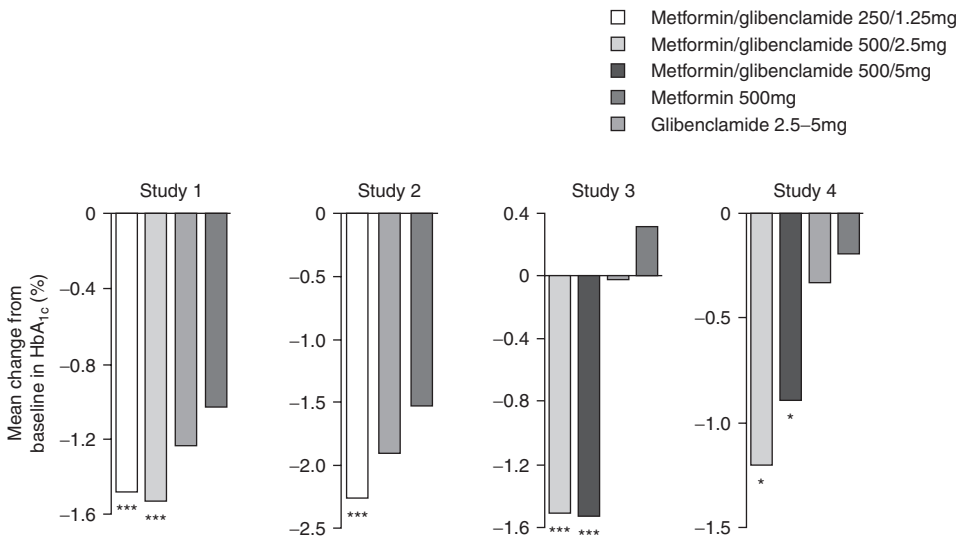

Fig. 1. Efficacy of metformin/glibenclamide (glyburide) combination tablets in four double-blind, randomised clinical trials: study 1,[13] study 2,[14] study 3[15] and study 4.[16] Reproduced from Dailey,[11] with permission. * $p < 0.05$, *** $p < 0.001$ vs baseline. **HbA_{1c}** = glycosylated haemoglobin.

Table II. Mean daily dosages of metformin and glibenclamide (glyburide) received by study participants

Study	Combination tablets[a]			Metformin (mg)	Glibenclamide (mg)
	250/1.25mg (mg)	500/2.5mg (mg)	500/5mg (mg)		
Garber et al.[13]	568/2.8	840/4.2		1324	5.4
Garber et al.[14]	735/3.7			1796	7.6
Blonde et al.[15]		1759/8.8	1744/7.4	1840	20[b]
Marre et al.[16]		1225/6.1	1170/11.7	1660	13.4

a All combination tablets are stated as metformin/glibenclamide doses.

b Glibenclamide not titrated but given as a constant dose.

ment in each patient population (see above), metformin or glibenclamide were 66%, 50% and 60%, respectively, for study 1[13] (diet-failed patients); 79%, 62% and 68% for study 2[14] (diet-failed patients); 25%, 3% and 3% for study 3[15] (post-sulphonylurea); and 75%, 38% and 42% for study 4[16] (post-metformin).[11,18] Corresponding figures for the higher strength combination tablet evaluated in studies 1, 3 and 4 were 72%, 25% and 64%, respectively. It should be noted that patients in study 3 were severely hyperglycaemic on average at baseline, compared with the other studies (table I), which accounts for the higher final mean HbA_{1c} level and lower proportion achieving HbA_{1c} levels <7.0% after treatment in this study, compared with the other trials.

Changes in fasting plasma glucose levels generally mirrored effects on HbA_{1c} levels, and 2-hour postprandial glucose levels also improved markedly in the combination tablet groups.[11]

3. Tolerability and Safety

3.1 Hypoglycaemia

3.1.1 Incidence of Hypoglycaemic Symptoms

Table III shows the incidences of symptoms commonly associated with hypoglycaemia (e.g. sweating, shaking, dizziness, faintness), biochemically confirmed hypoglycaemia (hypoglycaemic symptoms accompanied by a fingerstick blood glucose measurement of ≤2.8 mmol/L (≤50 mg/dL), hypoglycaemia classified by study investigators as severe and withdrawals of study treatment for hypoglycaemia. The incidence of hypoglycaemic symptoms with metformin was low in all trials, as expected from the known properties of this agent,[19] and data on metformin have been omitted from this discussion for clarity.

The incidence of hypoglycaemic symptoms with the metformin/glibenclamide 250/1.25mg combination tablet in patients who were hyperglycaemic despite previous diet and exercise interventions was significantly lower than that for glibenclamide alone in one study[13] but was higher than that for glibenclamide in the other.[14] In addition, the incidence of hypoglycaemic symptoms with the 500/2.5mg tablet (not intended for initiation of therapy in this population) was significantly higher than with glibenclamide alone.[13] Not all hypoglycaemic symptoms were accompanied by low blood glucose concentrations, and the proportion of patients with biochemically documented hypoglycaemia was almost identical between the 250/1.25mg combination tablets and glibenclamide monotherapy.[13,14]

Most hypoglycaemic symptoms were mild or moderate in severity, and the incidence of severe hypoglycaemia was low and similar between the treatment groups. Importantly, these hypoglycaemic symptoms were usually easily managed by the patients themselves, and none of the patients required third-party assistance for hypoglycaemia. Consistent with these observations, few of the patients receiving the appropriate starting dose of combination therapy withdrew prematurely from the four trials because of hypoglycaemia. Although the withdrawal rate of diet-failed patients receiving the 500/2.5mg combination tablet (not recommended for treatment initiation in diet-failed patients) was higher, it should be noted that half of these patients were taking one tablet/day at the time of withdrawal, so that there was no opportunity to reduce the dose.[13] Data are not available from these trials on the incidence of nocturnal hypoglycaemia. However, the generally low incidence of withdrawals for

Table III. Incidence of hypoglycaemic symptoms and hypoglycaemia (percentage of patients)

Study	Drug[a]	Symptoms of hypoglycaemia	Biochemically confirmed hypoglycaemia[b]	Withdrawals for hypoglycaemia	Severe hypoglycaemia[c]
Garber et al.[13]	Combination tablets 250/1.25mg	11[d]	5	2	2
	Combination tablets 500/2.5mg	38[d]	16	6	1
	Metformin 500mg	3	0	0	0
	Glibenclamide (glyburide) 2.5mg	21	6	1	3
Garber et al.[14]	Combination tablets 250/1.25mg	58	11	2	3
	Metformin 500mg	18	1	0	0
	Glibenclamide 2.5mg	39	11	1	2
Blonde et al.[15]	Combination tablets 500/2.5mg	9	NM	0	0
	Combination tablets 500/5mg	4	NM	0	0
	Metformin 500mg	1	NM	0	0
	Glibenclamide 5mg	2	NM	0	0
Marre et al.[16]	Combination tablets 500/2.5mg	11	NM	1	1
	Combination tablets 500/5mg	14	NM	1	2
	Metformin 500mg	1	NM	0	0
	Glibenclamide 5mg	8	NM	0	1

a All combination tablets are stated as metformin/glibenclamide doses.

b Plasma glucose ≤2.8 mmol/L (≤50 mg/dL) at the time of occurrence of symptoms of hypoglycaemia.

c Data for severe hypoglycaemia relate to adverse drug experiences (typically defined as adverse events with possible, probable, certain or unrecorded relationship to treatment).

d Significantly different from glibenclamide ($p < 0.05$ or lower).

NM = not measured.

hypoglycaemia and the absence of hypoglycaemia reported as a serious adverse event suggest that the incidence of this particularly serious form of hypoglycaemia was probably low in these trials.

3.1.2 Intensification of Therapy and Hypoglycaemia

Data from three of these trials[13,15,16] were used to determine whether patients reported hypoglycaemic symptoms more frequently during the dose-titration phase of the studies or during subsequent maintenance treatment (data from the second study by Garber et al.[14] were not available at the time of this analysis).[20] The appearance of symptoms of hypoglycaemia, whether or not they were confirmed biochemically, were used for this analysis. The majority of hypoglycaemic symptoms occurred during the titration phase of each trial, with a lower incidence once patients achieved maintenance treatment (figure 2).

3.2 Gastrointestinal Adverse Events

The incidence of gastrointestinal adverse effects was significantly lower with metformin/glibenclamide 250/1.25mg than with metformin alone in both studies in diet-failed patients (table IV).[13,14] The incidences of the three most common individual gastrointestinal adverse effects in the metformin/glibenclamide 250/1.25mg and metformin groups in the study in 806 diet-failed patients were 8% and 15%, respectively, for diarrhoea; 2% and 6% for nausea/vomiting; and 6% and 5% for abdominal pain.[13] Corresponding incidences in the study in 486 diet-failed patients were 8% and 18%, respectively, for diarrhoea; 5% and 10% for nausea/vomiting; and 4% and 6% for abdominal pain.[14] The incidences of gastrointestinal adverse effects for other combination tablet strengths and metformin were similar and markedly higher than the corresponding incidences for glibenclamide. As with hypoglycaemia, most adverse effects were of mild or moderate severity, and few patients withdrew from clinical trials because of gastrointestinal adverse effects.

3.3 Cardiovascular Risk Factors

Cardiovascular risk factors, including insulin resistance, dyslipidaemia and obesity, are common among the type 2 diabetic population, and most

patients with type 2 diabetes will ultimately die following a morbid cardiovascular event. It is therefore important that oral antidiabetic therapy does not adversely affect markers of cardiovascular risk.

3.3.1 Plasma Lipids

Treatment with the combination tablets did not generally affect lipid profiles to a clinically significant extent during the double-blind phase of any of the four studies.[13-16] However, significant changes from baseline in lipid profiles were observed during 52-week open-label extensions that followed one of the studies in patients with hyperglycaemia despite diet and exercise interventions[21,22] and the post-sulphonylurea study.[23]

The open-label extension study in diet-failed patients enrolled subjects from three sources: those who had completed the previous double-blind trial (n = 515), those who had discontinued double-blind treatment prematurely due to lack of glycaemic control (n = 138) and a population of 'direct enrolees' (n = 175) who were too hyperglycaemic for inclusion in the double-blind trial (fasting plasma glucose ≥13.3 mmol/L [≥240 mg/dL] with HbA_{1c} levels ≤12%, or HbA_{1c} levels between 11% and 12%).[21,22] Total cholesterol, low-density lipoprotein (LDL)-cholesterol and triglycerides improved in both the direct enrolees (by −0.6, −0.3 and −1.1 mmol/L, respectively) and in the general population (by −0.2, −0.1 and −0.3 mmol/L, respectively). The greater improvements observed in direct enrolees probably reflected their more severe dyslipidaemia, on average, at baseline.

The open-label extension to the post-sulphonylurea study did not include directly enrolled subjects, and all 477 patients had either completed the previous double-blind trial (n = 461) or had withdrawn prematurely due to lack of glycaemic control (n = 16).[23] Total cholesterol and LDL-cholesterol each improved by an average of 0.5 mmol/L from baseline values of 5.5 mmol/L and 3.5 mmol/L, respectively ($p < 0.05$ for each). A small increase in high-density lipoprotein (HDL)-cholesterol of 0.1 mmol/L from a baseline value of 1.0 mmol/L also achieved statistical significance ($p < 0.05$). Triglycerides were unaffected.

3.3.2 Bodyweight

Mean changes from baseline in bodyweight in diet-failed patients randomised to metformin/glibenclamide tablets ranged from 1.4 to 1.9kg, compared with 1.7–2.0kg with glibenclamide alone.[13,14] Corresponding values for post-monotherapy patients were 0.5–1.0kg for combination tablets and 0.4–0.9kg for glibenclamide alone.[15,16] In addition, there was little increase in weight in the long-term (1

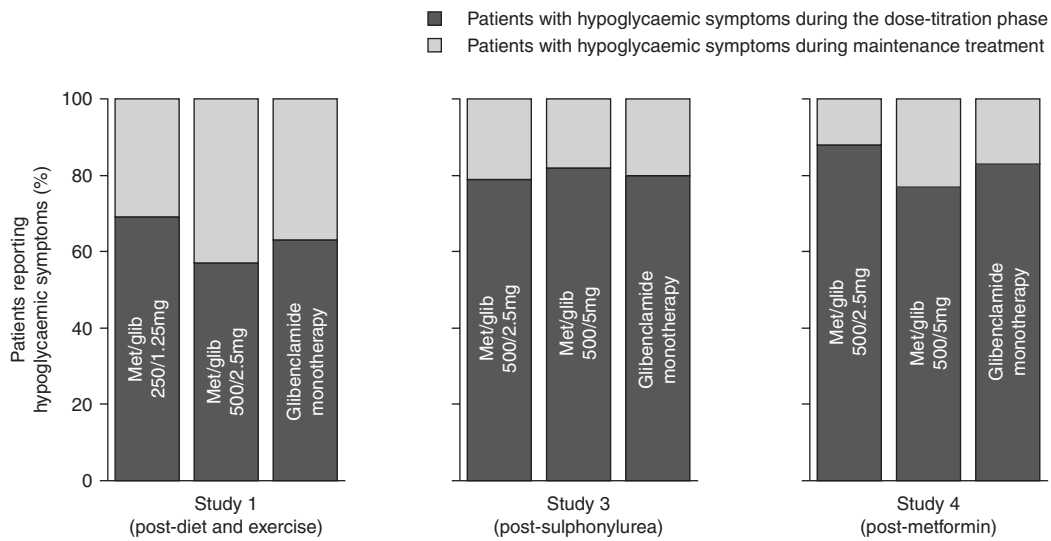

Fig. 2. Timing of appearance of hypoglycaemic symptoms in patients receiving metformin/glibenclamide (met/glib) combination tablets or glibenclamide (glyburide) monotherapy in three double-blind, randomised clinical trials: study 1,[13] study 3[15] and study 4.[16]

Table IV. Incidence of gastrointestinal (GI) adverse effects (percentage of patients)

Study	Drug[a]	GI adverse effects	Withdrawals for GI adverse effects	Severe GI adverse effects[b]
Garber et al.[13]	Combination tablets 250/1.25mg	32[c]	1	1
	Combination tablets 500/2.5mg	38	1	3
	Metformin 500mg	43	3	2
	Glibenclamide (glyburide) 2.5mg	24	1	0
Garber et al.[14]	Combination tablets 250/1.25mg	22[c]	2	3
	Metformin 500mg	32	4	1
	Glibenclamide 2.5mg	21	1	1
Blonde et al.[15]	Combination tablets 500/2.5mg	36	3	0
	Combination tablets 500/5mg	35	2	0
	Metformin 500mg	39	4	5
	Glibenclamide 5mg	20	1	1
Marre et al.[16]	Combination tablets 500/2.5mg	7	1	1
	Combination tablets 500/5mg	18	1	2
	Metformin 500mg	14	3	0
	Glibenclamide 5mg	12	0	1

a All combination tablets are stated as metformin/glibenclamide doses.

b Data for severe adverse events in the studies by Garber et al.[13,14] and Blonde et al.[15] relate to adverse drug experiences (adverse events with possible, probable, certain or unrecorded relationship to treatment); all-cause severe adverse events are shown for the study by Marre et al.[16]

c Significantly different from glibenclamide ($p < 0.05$ or lower).

year) open-label extension studies in patients hyperglycaemic despite treatment with diet and exercise[21,22] (mean change from baseline 2.3kg) or a sulphonylurea[23] (mean change from baseline −0.1kg). Overall, therefore, changes in bodyweight during double-blind treatment with the metformin/glibenclamide combination tablets were modest and similar to changes observed in patients receiving glibenclamide alone.

Bodyweight tended to decrease in the metformin groups (mean changes from baseline ranged from −0.6 kg to −2.8 kg in the four studies). This is consistent with previous clinical experience with metformin.[12]

3.3.3 Plasma Insulin

Fasting hyperinsulinaemia is a marker of insulin resistance and has been associated with an increased risk of adverse cardiovascular outcomes in patients with type 2 diabetes.[24] Plasma insulin was measured in the fasting state and 2 hours after a liquid meal challenge in the two studies in patients with hyperglycaemia despite diet and exercise interventions.[13,14] Glibenclamide monotherapy increased fasting insulin ($p < 0.05$), compared with metformin/glibenclamide 250/1.25mg combination tablets, in both studies at study end (mean changes from baseline were 7.2 μIU/mL vs 3.8 μIU/mL in one study and 4.5 μIU/mL vs 1.3 μIU/mL in the other study).

The postprandial insulin response was enhanced in the combination tablet groups, compared with glibenclamide alone (mean changes from baseline were 29.7 μIU/mL vs 15.1 μIU/mL, respectively, and 20.3 μIU/mL vs 16 μIU/mL, respectively), despite the lower average exposure to glibenclamide in these patients, compared with glibenclamide alone. This may be due to improved β-cell function associated with greater decreases in blood glucose in the combination tablet groups (reduced glucose toxicity) or may arise as a consequence of the design of the combination tablets themselves (see section 4).

3.4 Other Adverse Events

The incidence of commonly occurring adverse events with the metformin/glibenclamide combination tablets was similar to those observed in patients randomised to metformin or glibenclamide monotherapies. Incidences of all-cause adverse events, pooled between the two studies[13,14] in diet-failed patients were 79% for metformin/glibenclamide 250/1.25mg, 77% for metformin/glibenclamide 500/2.5mg, 78% for glibenclamide and 76% for metformin. Corresponding incidences of adverse

drug experiences[2] for these four treatments were 45%, 46%, 34% and 37%, respectively, while serious adverse events occurred in 6%, 4%, 5% and 5% of patients, respectively.

The incidences of all-cause adverse events pooled from studies[15,16] in prior monotherapy-treated patients were 59% (metformin/glibenclamide 500/2.5mg), 60% (metformin/glibenclamide 500/5mg), 55% (glibenclamide) and 57% (metformin). Corresponding incidences of adverse drug experiences were 33%, 34%, 25% and 33%, respectively, while serious adverse events were 4%, 3%, 4% and 3%, respectively. No individual adverse event other than hypoglycaemic symptoms or gastrointestinal adverse effects occurred with a greater frequency in patients randomised to combination tablets, compared with metformin or glibenclamide alone. No patient developed lactic acidosis.

4. Discussion

The combination tablets described in this report are a new treatment. The duration of exposure to this treatment is necessarily limited, and this report presents data on short-term double-blind studies and from open-label extensions to these trials of up to 1 year. An evaluation of long-term safety must await further clinical experience. Nevertheless, the four randomised, double-blind clinical trials discussed show that the metformin/glibenclamide combination tablets are well tolerated during the period in which maintenance treatment is achieved. Diet-failed patients randomised to the low-dose combination tablet were less likely to develop gastrointestinal adverse effects than with metformin alone, with a similar incidence between metformin alone and other tablet strengths in all studies. The incidence of hypoglycaemic symptoms was low, considering the large reductions in blood glucose achieved. Most hypoglycaemic symptoms were of mild or moderate severity, consistent with the observed low incidences of biochemically confirmed hypoglycaemia or withdrawal from trials for hypoglycaemia and the ability of all patients to manage hypoglycaemic episodes without third-party assistance.

The designs of the trials probably influenced the reporting of hypoglycaemia. Information on symptoms commonly associated with hypoglycaemia was actively solicited from patients during interviews with investigators in all four trials, which may partly explain the difference between the incidence of hypoglycaemic symptoms and biochemically documented hypoglycaemia. In addition, the relatively rapid intensification of oral hypoglycaemic therapy (driven by predetermined glycaemic targets) in the setting of a clinical trial may cause reductions in blood glucose levels that are sufficiently rapid to trigger symptoms of hypoglycaemia, even when blood glucose does not actually enter the hypoglycaemic range. The observation that most hypoglycaemic symptoms occurred during the titration phase of the trials, when blood glucose was changing most rapidly, supports this view. In a clinical trial, the rate of intensification of therapy is driven by the study protocol. In actual clinical practice, the dose of any oral hypoglycaemic agent should be intensified cautiously, with careful note of efficacy and tolerability responses in order to maximise the benefit-risk ratio associated with its use.

The doses of metformin and glibenclamide within the combination tablets were selected to represent commonly used doses of these agents when used in combination. For example, the maximum daily dose of the metformin/glibenclamide 500/2.5mg tablet (four tablets, equivalent to metformin/glibenclamide 2000/10mg) delivers the maximally effective daily dose of metformin for most patients[25] and covers the part of the dose-response curve for glibenclamide that provides dose-related efficacy.[26,27] The lower and higher strength tablets are intended for use in patients with glycaemia suboptimally controlled by diet and exercise, who require lower doses of drugs, or with glycaemia inadequately controlled by the maximum dose of 500/2.5mg combination tablets, respectively.

The lower doses of metformin and glibenclamide required to control glycaemia with the combination tablets compared with the doses used as monotherapy, and the formulation of the combination tablets themselves, probably helped to minimise the incidence of adverse events with the combination tablets. Each combination tablet contains slowly dissolving particles of glibenclamide in a carefully

2 Defined as an adverse event with possible, probable, certain, or unrecorded relationship to study treatment.

Table V. Benefit-risk ratios (average reduction from baseline in glycosylated haemoglobin [HbA_{1c}] levels vs incidence of hypoglycaemia) in published trials evaluating metformin and insulin secretagogue combinations

Study	Treatment	Previous treatment	Mean HbA_{1c} level at baseline (%)	Average change in HbA_{1c} levels vs baseline (%)	Hypoglycaemia (% of patients)
Goldstein et al.[28]	Metformin + glipizide	Sulphonylurea	8.7	−1.3	13[a]
DeFronzo and Goodman[29]	Metformin + glibenclamide (glyburide)	Sulphonylurea	8.7	−1.7	18
Gregorio et al.[30]	Metformin + sulphonylurea	Sulphonylurea	10.3	−1.6	2
Charpentier et al.[31]	Metformin + glimepiride	Metformin	6.5	−0.7	22
Moses et al.[32]	Metformin + repaglinide	Metformin	8.5	−1.4	33
Marre et al.[33]	Metformin + nateglinide	Metformin	8.1	−0.6	16[b]
Hermann et al.[34]	Metformin + glibenclamide	Various	6.8	−1.2[c]	33[c]
Horton et al.[35]	Metformin + nateglinide	Various	8.3	−1.4	26
Tosi et al.[36]	Metformin + glibenclamide	Various	8.0	−1.9	11

a Defined as blood glucose ≤2.8 mmol/L (≤50 mg/dL).

b ≤3.3 mmol/L (≤60 mg/dL) in patients receiving nateglinide 120mg + metformin.

c Applies to patients taking the low-dose combination (glibenclamide ≤10.5mg + metformin 1500mg).

controlled range of sizes, surrounded by freely soluble metformin.[10] Pharmacokinetic studies have shown that absorption of glibenclamide occurs earlier from the combination tablets than from standard glibenclamide tablets coadministered with metformin, although the maximal glibenclamide concentration achieved and overall exposure to glibenclamide are comparable.[10] The combination tablets are intended to be taken with meals, so that the earlier absorption of glibenclamide coincides with the postprandial glucose surge, thus supporting control of postprandial hyperglycaemia.

The data on hypoglycaemia discussed in section 3.1 reflects a comparison between the combination tablets and glibenclamide monotherapy. Direct, head-to-head comparisons of these tablets with coadministered metformin and an insulin secretagogue are not available. However, comparison of the data in table III with published evaluations (table V) suggests that the incidence of hypoglycaemia with the metformin/glibenclamide combination tablets is within the range of incidences reported with other combinations.

Increases in bodyweight have been observed following treatment with all insulin secretagogues[12] and also with the thiazolidinedione class of oral antidiabetic agents.[37] The changes in bodyweight seen with the combination tablets were modest and similar to those seen with glibenclamide alone in these studies. Other markers of cardiovascular risk (e.g. fasting insulin or lipid profiles) were not adversely affected.

The incidence of other adverse events or serious adverse events did not differ significantly between the combination treatments and the monotherapies. In particular, there were no cases of lactic acidosis, a rare, but life-threatening, condition that has raised concerns with metformin-based treatment in the past[12,38] and that delayed the approval for clinical use of metformin in the US until 1995. Most patients who develop this condition have other risk factors for metabolic acidosis and the actual contribution of metformin to its development is unclear.[39] It appears that the risk of lactic acidosis in patients receiving metformin-based regimens is very low where the contraindications and precautions relating to its use are respected, particularly with respect to renal or hepatic failure.[40,41] It should also be noted that the combination tablets provide superior glycaemic control at a lower dose of metformin, compared with metformin monotherapy.

5. Conclusions

The metformin/glibenclamide combination tablets were well tolerated. The incidence of biochemically confirmed or severe hypoglycaemia and the rate of withdrawal from trials for hypoglycaemia with the combination tablets were low and comparable with glibenclamide alone despite the much larger decreases in blood glucose that were achieved. In

addition, the gastrointestinal tolerability of low-dose combination tablets was superior to metformin alone in diet-failed patients, and there was no excess incidence of other adverse events or serious adverse events. The need for lower doses of metformin or glibenclamide to control glycaemia and/or the design of the combination tablet may underlie their beneficial tolerability profile. The combination treatment approach provides a potential solution for addressing the dual defects of insulin resistance and β-cell dysfunction in type 2 diabetes while minimising the burden of polypharmacy. Careful attention to efficacy and tolerability responses during intensification of therapy would maximise the benefit-risk ratio of this treatment during the routine day-to-day management of type 2 diabetes.

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