

A 4-6 Months Open Labelled, Multicentric, Non-comparative Study For Evaluation Of Efficacy, Safety And Tolerability Of Glizid-M In Type 2 Diabetes

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ABSTRACT

Glizid-M is the fixed dose combination of Gliclazide (80mg) and Metformin (500mg) indicated for the treatment of non-insulin dependent diabetes mellitus; type 2 diabetes with or without obesity in adults. The present post marketing surveillance evaluated the efficacy, safety and tolerability of Glizid-M in 497 patients with type 2 diabetes. It was an open labelled, non-comparative, multicentric study; which involved 26 investigators across the country. The total duration of protocol therapy was 4 weeks, whereas duration of study was 4-6 months. Assessment of the blood glucose levels was performed at the baseline, at 2nd week and at the end of the therapy (4th week). Safety parameters were assessed at week 2 and at the end of the therapy.

Results

There was a significant decrease in mean fasting blood glucose (from base line of 182.16mg/dl to 148.32mg/dl at week 2 and 124.9mg/dl at week 4) and post prandial blood glucose (from baseline of 262.19 mg/dl to 200.81mg/dl at week 2 and 168.24mg/dl at week 4). Moreover, 64.2% patients were able to achieve the target of blood glucose level defined by American Diabetes Association (ADA 2004) for good glycemic control, i.e. fasting blood glucose of ≤ 130 mg/dl and 2-hour post prandial blood glucose of ≤ 180 mg/dl. The combination was well tolerated in general except few suspected episodes of hypoglycaemia.

Conclusion

The fixed dose combination of Gliclazide and Metformin showed statistically significant efficacy in improving the glycemic control in type 2 diabetics. Good safety and tolerability profile of the combination was also demonstrated in the clinical trial. (The Ind. Pract. 2005; 58(5):283-291)

KEY WORDS

Glizid-M, Gliclazide, Metformin, type 2 diabetes and diabetes mellitus.

INTRODUCTION

Type 2 diabetes mellitus is the commonest form of diabetes and constitutes nearly 90% of the diabetic population in any country.

The pathogenesis of type 2 diabetes remains a subject of research and debate with one contentious issue being the relative contribution of insulin resistance and insulin secretion abnormalities in producing the condition. After meals, patients with type 2 diabetes mellitus typically exhibit an impaired first phase insulin response and delayed second phase secretion with inadequate release of insulin overall, in relation to blood glucose levels.

According to WHO estimates, the number of adults with diabetes in the world is estimated to increase by 122%, from 135 million in 1995 to 300 million in 2025. There will be a 42% increase from 51 million to 72 million, in the developed countries. India has recorded the highest increase in diabetic population over the years¹. India has around 30 million diabetes patients at present. The tally is expected to rise to about 57 million by 2025.

Most diabetologists prescribe insulin secretagogues or insulin sensitizers as the first options during the management of type 2 diabetes mellitus. Insulin secretagogues enhance insulin secretions thereby reducing hyperglycemia whereas insulin sensitizers improve insulin sensitivity through its peripheral mechanism of action and also suppresses hepatic glucose output.

Gliclazide belongs to sulfonylurea group of oral hypoglycaemic agents. It is rapidly absorbed from the GIT, and is metabolized in the liver. It appears in the blood within 1-2 hrs. It is extensively plasma protein bound (more than 90%) and peak level is achieved in 4-6 hrs. The plasma $t_{1/2}$ is 8-12 hrs and its duration of action is 12 hrs. It is indicated for type 2 diabetes (non insulin dependent diabetes mellitus). It stimulates insulin secretion by pancreatic beta cells and in the long-term reduces hepatic

gluconeogenesis, and increases insulin effects by acting at receptor or post-receptor sites. It is also found to inhibit platelet aggregation and increase fibrinolysis.

Metformin is an oral biguanide derivative that acts principally by decreasing hepatic glucose production and by increasing insulin action in muscle and fat. Preponderance of data indicates an effect on reducing gluconeogenesis.

Many patients with newly diagnosed type 2 diabetes can initially achieve adequate glycemic control with a single oral anti diabetic agent, if dietary and lifestyle interventions alone prove unsuccessful. However, as type 2 diabetes progresses, most patients eventually require the addition of a second agent, in an attempt to bring blood glucose levels close to target. Therefore, it is useful and recommended to have combinations of antidiabetic agents². Further the results with monotherapy, especially the worsening metabolic control often seen within five years after the initiation of an oral hypoglycemic agent, have led to switch over to combination therapy, where the principle behind combination therapy should be to use drugs with different mechanisms of action. It has also been stated, however, that the use of combination therapy may obviate the need for the insulin in some patients.³ Control of mealtime hyperglycemia is also important for glycemic control in type 2 diabetes, and recently it has been shown to be an independent risk factor for cardiovascular mortality⁴.

One of the combinations, which have proved to be efficacious in terms of glycemic control, is Sulfonylurea and Metformin⁵. This combination is already well established and treatment with this combination has been reported to provide satisfactory glycemic control for several years⁶. The proposed combination is the best studied combination among the choices available, it is a therapeutic approach that addresses both underlying defects in the disorder: insulin deficiency and insulin resistance⁷. It is expected to have enhanced glucose lowering effects probably because Gliclazide stimulates insulin secretion by pancreatic beta cells and in the long-term, reduces hepatic gluconeogenesis, whereas Metformin improves insulin sensitivity^{8, 9, 10}.

Efficacy and tolerability of Gliclazide and Metformin combination have been studied previously in various studies. In a study conducted by Galeone F et al, the glycemic control in 57 patients suffering from type 2 diabetes for at least 5 years was evaluated. The combination of Gliclazide and Metformin was found to be effective and well tolerated in patients with type 2 diabetes inadequately controlled with sulphonylurea monotherapy¹¹. Combination therapy with Gliclazide and Metformin, compared with monotherapy, reduces the blood glucose levels and the frequency of complications, leading to increase in quality of life for the patient and favorable pharmacoeconomic scenario.

This present study was planned with the purpose to further establish the safety and efficacy of Gliclazide –Metformin combination (Glizid-M) in wide Indian population.

PATIENTS AND METHODS

Study Objectives and Design Evaluation of efficacy, safety and tolerability of fixed dose combination of Glizid-M type 2 diabetes. An open labeled, non-comparative, and multicentric study.

Study Centers

The study was conducted across 9 cities in India: Amritsar, Bhopal, Delhi, Indore, Jabalpur, Jaipur, Lucknow, Mumbai and Noida; with 26 investigators participating in the study.

Study Duration

Duration of protocol therapy was 4 weeks. While the duration of study was 4-6 months

Study Population and Sample Size

The study was carried out in patients suffering from Type 2 diabetes mellitus inadequately controlled by diet, exercise or metformin or gliclazide alone or any combination therapy except study medication. A total of 497 patients were enrolled in the study and 339 patients were evaluated at the end of therapy.

Selection Of Subjects

Inclusion Criteria : Male and female patients with Type 2 diabetes, aged 30 to 65 years, body mass index between 20-35 kg/m², having fasting blood glucose \geq 126mg/dl and post prandial blood

glucose \geq 200mg/dl and who were willing to give written informed consent were included in the study.

Exclusion criteria

Following patients have been excluded from the study: Patients having diabetes other than Type 2 diabetes, who have been treated with insulin 12 months prior then enrolment, having a history of hypersensitivity to sulphonylureas or biguanides, having hepatic or renal impairment or acute complications (severe infections, major operations and trauma), having gastrointestinal disorders or diseases of blood or haematopoietic organs or severe cardiovascular or respiratory disease or deficiencies of vitamin B12, folic acid and iron, patients with known history of diabetic ketoacidosis or alcoholism, pregnant or breast-feeding women and patients having any concomitant medication, which may interact with hypoglycemia action of study drug.

Ethical Aspects

The study was conducted in accordance with the Declaration of Helsinki and ICHGCP guidelines. Regular monitoring was done to ensure compliance with the protocol and ICH-GCP guidelines.

Study Procedure

After taking the voluntary informed written consent, subjects were screened for inclusion/exclusion criteria. The pertinent demographic information and medical history was taken and subjects' health status was checked. Subjects who passed the screening were included in the study and given Glizid-M, fixed dose combination of Gliclazide (80mg) and Metformin (500mg) manufactured by Panacea Biotec Ltd. 1-2 tablets of Glizid-M was given to the patients, once or twice daily with meals to a maximum of 4 tablets per day (depending upon the glycemic control) for 4 weeks. Drugs were stored at a temperature of 30°C and were protected from light and moisture.

Patients were assessed on baseline (day 0) and week 2 and week 4 of the treatment period. Fasting Blood glucose and Post Prandial glucose was measured on (day 0), weeks 2 and 4. Glycosylated hemoglobin was an optional investigation at baseline (day 0) and week 2 and week 4.

Subject Compliance

Subjects taking \geq 70% of test medication over duration of therapy were said to be compliant with the protocol therapy. Subjects taking $<$ 70% of the test medication over duration of therapy were said to be noncompliant with the protocol therapy.

Concomitant Medication

The subjects were not allowed to take any other known oral hypoglycemic agent during the study. If any other concomitant drug therapy other than that specified in the protocol was administered during the period of each treatment, decision to continue or discontinue the subject was based on the pharmacology and pharmacokinetics of nonstudy medication and likelihood of drugdrug interactions thereby affecting pharmacodynamic profile of study medication.

Criteria For Evaluation Of Study Efficacy And Safety

- Criteria for Evaluation of Study Efficacy: Efficacy of the drug combination was assessed by determining reduction in Blood glucose levels (Fasting and Post Prandial glucose).
- Criteria for Evaluation of Study Safety: Suspected episodes of hypoglycaemia at all visits and adverse events at all visits (Gastrointestinal, Dermatological or any other side effect).

Serious Adverse Events

It was mentioned in the protocol that in case of a serious ADR, investigator would notify to the sponsor (within 48 hours) and take appropriate measures to safeguard the subject. Separate serious adverse event forms were also provided with each case report form.

Statistics

Descriptive statistics (Minimum, Maximum, Mean, Median, standard deviation/ standard error) for continuous variables and numbers along with percentage (%) for categorical variables were presented. Paired t-test was employed to compare pre treatment and post treatment Fasting Sugar levels and also to compare pre treatment and post treatment Post Prandial Sugar levels. McNemar's test was applied for the paired design to detect the differences in percentages of subjects reporting an adverse effect symptom.

RESULTS

A total of 497 patients were enrolled in the study and 339 patients were evaluable at the end of therapy, out of which 1 patient was dropped out at week 2 as the patient developed dermatological

adverse effect. For statistical analysis, all patients who complied with $\geq 70\%$ of test medication consumed over duration of protocol therapy were eligible for "intent to treat" (ITT) analysis. Hence, 338 patients were evaluable at the end of protocol therapy.

Demographic Data

The total number of 339 patients was evaluated, out of which 207 were males and 132 were females (Table 1). One patient was dropped out at week 2 and finally excluded from efficacy analysis. The study group comprise of both males and females with the age ranging from 35 to 65 years having type- 2 diabetes. Demographic data of the population is summarized in Table 1. Out of 338 patients, 61.1% were male and 38.9%, females. Mean age (Std. Deviation) of the patients was 50.42 (7.74) years.

Age Groups	Male N (%)	Female N (%)	Total N (%)
30 – 39	17 (56.7)	13 (43.3)	30 (100)
40 – 49	65 (54.6)	54 (45.4)	119 (100)
50 – 59	87 (64.0)	49 (36.0)	136 (100)
60 – 69	38 (70.4)	16 (29.6)	54 (100)
Total	207 (61.1)	132 (38.9)	339 (100)

Parameters	N	Min	Max	Mean	Median	Std. Deviation
BP Systolic (Baseline)	337	100	180	136.08	134	17.32
BP Systolic (Week 2)	333	100	170	131.00	130	14.19
BP Systolic (Week 4)	332	102	180	129.73	130	13.52
BP Diastolic (Baseline)	337	60	110	84.84	80	9.67
BP Diastolic (Week 2)	333	62	100	82.35	80	7.51
BP Diastolic (Week 4)	332	60	100	81.58	80	7.01

Parameter	N	Min	Max	Mean	Median	Std. Deviation
Body Weight (Baseline)	339	56	98	70.46	69	7.71
Body Weight (Week 2)	338	56	96	70.38	69	7.74
Body Weight (Week 4)	338	55	99	70.28	69	7.86

Physical Examination Findings

- Blood pressure Monitoring :Out of 339 patients evaluated, Blood pressure evaluation data is available for 337 patients at baseline, 333 patients at week 2 and 332 patients at week 4. Mean systolic and diastolic blood pressure decreased continuously from baseline to week 2 and week 4, the decrease being marginal and clinically non significant. As depicted in Table 2.
- Body weight Monitoring : All the 339 patients were assessed for body weight at baseline and 338 at subsequent visits (except for one dropped out at week 2). Mean body weight almost remained same at all visits with negligible change in variability. (Table 3)

Blood Glucose levels

- Fasting Blood Glucose Levels Out of 339 patients, 338 patient's efficacy data was

analyzed,(excluding the one, who was dropped out at week 2) for fasting blood glucose levels at baseline, week 2 and week 4 of the protocol therapy and the results indicated a statistically significant decrease in Blood glucose levels at every visit (Table 4).

Pair	PP Sugar	N	Mean	Std. Deviation	Std. Error	Mean of Difference	95% CI for Mean Difference		P value (2 tailed)
							Lower	Upper	
Pair 1	Day 0	338	182.16	38.57	2.10	33.85	30.98	36.71	< 0.001
	Week 2	338	148.32	31.44	1.71				
Pair 2	Day 0	338	182.16	38.57	2.10	57.18	53.92	60.43	< 0.001
	Week 4	338	124.99	24.28	1.32				
Pair 3	Week 2	338	148.32	31.44	1.71	23.33	21.28	25.38	< 0.001
	Week 4	338	124.99	24.28	1.32				

Pair Sugar	Fasting	N	Mean Deviation	Std. Error	Std. of Mean	Mean Difference	95% CI for Mean of Difference		P value (2 tailed)
							Lower	Upper	
Pair 1	Day 0	338	262.19	47.10	2.56	61.37	57.40	65.35	< 0.001
	Week 2	338	200.81	35.71	1.94				
Pair 2	Day 0	338	262.19	47.10	2.56	93.95	89.68	98.22	< 0.001
	Week 4	338	168.24	29.14	1.59				
Pair 3	Week 2	338	200.81	35.71	1.94	32.58	29.74	35.41	< 0.001
	Week 4	338	168.24	29.14	1.59				

- Post Prandial Glucose Levels : Out of 339 patients, 338 patient's efficacy data was analyzed, (excluding the one, who was dropped out at week 2) for Post Prandial (PP) blood glucose levels at baseline, week 2 and week 4 of the protocol therapy and the results indicated a statistically significant decrease in Blood glucose levels at every visit (Table 5).

Safety Parameters

Safety was evaluated for all the patients enrolled in the study. Gastrointestinal adverse effects (heartburn and nausea) were noticed in few patients at week 2 of the follow up, but by the end of week 4, statistically significant reduction in the number of gastrointestinal adverse effects was observed. One patient was dropped out after 4th day because of severe itching and rashes and the protocol therapy was discontinued.

Hypoglycemia was strongly suspected in few patients (during week 2 and during week 4 of therapy), their suggestive symptoms subsided by taking meals. No further episodes were recorded in these patients even though the therapy was continued. No episodes of hypoglycemic coma were recorded (Table 6).

Safety Parameters	Specific Component	Number of subjects (%)		p value**
		Week 2	Week 4	
Hypoglycemia	Sweating	6 (1.6)	2 (0.5)	0.219
	Dizziness	3 (0.8)	2 (0.5)	1.00
	Headache	8 (2.1)	4 (1.1)	0.388
	Weakness	15 (4.0)	9 (2.4)	0.070
	Palpitation	8 (2.1)	4 (1.1)	0.289
	Blurred vision	1 (0.3)	1 (0.3)	1.00
	Poor concentration	1 (0.3)	1 (0.3)	1.00
	Tremors	1 (0.1)	0	1.00
	Intense hunger	6 (1.6)	2 (0.5)	0.125
Gastrointestinal	Heartburn	15 (4.0)	6 (1.6)	0.035*
	Nausea	18 (4.7)	4 (1.1)	0.001*
	Diarrhea	5 (1.3)	1 (0.3)	0.219
	Abdominal discomfort	15 (4.0)	8 (2.1)	0.118
Dermatological	Pruritis	2 (0.5)	0	0.50
	Erythema	0	0	-
	Rash	1 (0.3)	0	1.00
	Flushing	2 (0.5)	0	0.50
CNS	Dizziness	0	1 (0.3)	1.00
	Headache	7 (1.8)	5 (1.3)	0.727

*Statistically significant
**Statistically not significant

DISCUSSION

Type 2 diabetes mellitus, is a chronic disease characterized by hyperglycemia and numerous other metabolic abnormalities. It is the most common form of diabetes that accounts for nearly 90% of the diabetic population in any country. Three major pathophysiologic abnormalities are associated with type 2 diabetes mellitus: impaired insulin secretion, excessive hepatic glucose output, and insulin resistance in skeletal muscle, liver, and adipose tissues⁵.

Four major classes of oral hypoglycemic agents are available for treatment. They act as follows at major sites of defects in type 2 diabetes mellitus: by increasing insulin availability (secretagogues, i.e., sulfonylureas and meglitinides), by suppressing excessive hepatic glucose output (biguanides, i.e., metformin), by improving insulin sensitivity (thiazolidinediones or glitazones, i.e., rosiglitazone and pioglitazone) and finally by delaying gastrointestinal glucose absorption (α -glucosidase inhibitors acarbose and miglitol).

Unfortunately, due to the progressive nature of type 2 diabetes mellitus and the continued decline in beta cell function, monotherapy eventually fails to provide adequate glucose control in most patients with type 2 diabetes mellitus. To overcome failures of monotherapy, a combined therapy of oral anti-diabetic agents with complementary mode of action should be considered¹².

The goal of combination therapy is to take advantage of the different mechanism of action of the various pharmacological agents and to create an individualized treatment plan for achieving effective glycemic control. The combination of two agents often results in a synergistic rather than mere additive glucose lowering effect. One of the combinations, which has proved to be efficacious in terms of achieving optimal glycemic control, is Gliclazide and Metformin⁵. Gliclazide belongs to the sulfonylurea group of oral hypoglycaemic agents. It is rapidly absorbed from the GIT, and is metabolised in the liver. It appears in the blood within 1-2 hrs. It is extensively plasma protein bound (more than 90%). Peak level is achieved in 4-6 hrs. The plasma $t_{1/2}$ is 8-12 hrs and its duration of action is 12 hrs. It is indicated for non insulin dependent diabetes mellitus. It stimulates insulin secretion by pancreatic beta cells. In the longterm reduces hepatic gluconeogenesis, and increases insulin effects by acting at receptor or post-receptor sites.

Metformin is the only currently available oral antidiabetic/hypoglycemic agents that act predominantly by inhibiting hepatic glucose release. As patients with type2 diabetes often have excess hepatic glucose output, use of Metformin is effective in lowering glycosylated hemoglobin (HbA1c) by 1-2 % when used as monotherapy or in combination with other blood-glucose lowering

agents¹³.

Efficacy and tolerability of Gliclazide and Metformin combination have been studied previously in various setups. Galeone. F et. al evaluated the glycemic control in 57 patients suffering from type 2 diabetes for at least 5 years, with mean age 61.0 +/- 3.4 years, with a duration of diabetes of 9.2 +/- 3.9 years, previously treated with gliclazide 240 mg/day alone. The patients were treated with Gliclazide and Metformin combination for 3 months; 24-hour glycosuria, fasting and post-prandial glycemia, were determined at the beginning and at the end of the study. After 3-month treatment, a reduction of fasting and post-prandial glycemia, glycosuria (15.0 +/- 5.3 versus 5.7 +/- 4.0 g/l, p < 0.01) was observed. The treatment was generally well tolerated. In conclusion, the combination of Gliclazide and Metformin, which could theoretically show advantages over the association of glibenclamide and metformin with regards to haemorrhologic profiles, resulted to be effective and well tolerated in patients with type 2 diabetes inadequately controlled with sulphonylurea monotherapy¹¹. The weakness of this study was that effect on HbA_{1c} and other glycemic control parameters was not seen and also the study was of short duration.

Further, it has been demonstrated through several clinical studies that administration of Metformin to patients with type 2 diabetes mellitus (on sulphonylurea therapy with inadequate glycemic control) has led to significant decrease in fasting and post prandial glucose & insulin levels.

In this current study, patients were administered fixed dose combination of Gliclazide (80mg) and Metformin (500mg) i.e. Glizid-M, 1-2 tablets once or twice daily with meals to a maximum of 4 tablets/day as per the patients blood glucose levels. Assessment of the blood glucose levels was performed at the baseline, at 2nd week and at the end of the therapy (4th week). Other efficacy and safety parameters were assessed at the baseline and at the end of the therapy. The results of the current study demonstrated a significant decrease in the mean fasting blood glucose levels from baseline of 182.16 mg/dl to 148.32 mg/dl at week 2 and it further decreased to 124.99mg/dl at week 4. The current study additionally evaluated change in 2-hour post prandial blood glucose levels, and found that the mean decreased from 262.19 mg/dl at baseline to 200.81 mg/dl at week 2 and it further decreased to 168.24mg/dl at week 4, which is statistically significant. Moreover, 71 patients (21%) at week 2 and in 217 patients (64.2%) at week 4 could achieve the current Goals For Treatment Of Type 2 Diabetes Mellitus in nonpregnant adults laid by American Diabetes Association (ADA), (i.e. fasting blood glucose of \leq 130mg/dl and 2 hour post prandial blood glucose of \leq 180 mg/dl.) The patients satisfactorily tolerated the combination of Gliclazide and Metformin with mild and infrequent adverse effects

except for one patient, who required discontinuation from the therapy because of the dermatological adverse effects and few suspected episodes of hypoglycemia.

Considering the fact, that in majority of the patients enrolled, blood glucose levels were poorly controlled on previous drug/ drugs therapy, the results of this combination (Gliclazide & Metformin) appears to be efficacious & safe in treating type 2 diabetes mellitus. This trial further illustrated the efficacy and safety of the said combination. Glizid-M has potential to be prescribed as monotherapy in newly diagnosed diabetics or as a combination/ replacement therapy in patients showing poor glycemic control with other hypoglycemic agent/agents.

CONCLUSION

The fixed dose combination of Gliclazide and Metformin showed statistically significant efficacy in improving the glycemic control in type 2 diabetics. Good safety and tolerability profile of the combination was also demonstrated in the clinical trial.

ACKNOWLEDGEMENTS

We at Panacea Biotec Ltd, would like to thank all the doctors who participated in this study and submitted back their valuable feedback about Glizid- M tablets. This study would not have been possible without their participation.

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