

Glimepiride as Add-on Therapy in Type 2 Diabetic Patients with Metformin Monotherapy: A Real-Life Study from Egypt

YEHIA GHANEM, M.D.

The Department of Internal Medicine, Unit of Diabetes, Faculty of Medicine, Alexandria University, Alexandria, Egypt

Abstract

Background: Adding glimepiride to metformin monotherapy was reported to improve the glycemic status of patients with type 2 diabetes mellitus (T2DM), with tolerable safety profile.

Aim of Work: The present real-life study aimed to investigate the safety and effectiveness of glimepiride add-on therapy in poorly controlled T2DM patients with metformin monotherapy.

Patients and Methods: In the present prospective study, we included 1050 poorly controlled T2DM patients from Egypt, and for whom the investigators decided to prescribe glimepiride in addition to metformin. Glimepiride was added to patients uncontrolled on metformin monotherapy for at least three months despite reaching the maximally tolerated dose. Regimen doses were decided by the investigators to reflect the in-practice approach. We followed the included patients for at three months and safety outcomes were measured throughout the study period.

Results: After three months of treatment, the mean HbA1c level decreased by 1.54% (95% CI: -1.61 to -1.46%), with a mean percentage reduction of 16.3% ($p < 0.001$). In addition, 31.7% of the included patients achieved the targeted HbA1c level $< 7\%$. The total number of adverse events was 15 adverse events occurred in 11 patients. Ten episodes of non-serious hypoglycemia were recorded.

Conclusion: The present real-life study confirms the efficacy of glimepiride add-on therapy to metformin monotherapy among poorly controlled T2DM patients from Egypt. Moreover, glimepiride/metformin regimen exhibits well-tolerable safety profile.

Key Words: Glimepiride – Metformin – HbA1c – Hypoglycemia – T2DM.

Introduction

TYPE 2 diabetes mellitus (T2DM) is one of the most common causes of morbidity and mortality worldwide, with major health and financial conse-

quences [1]. Poorly controlled T2DM patients may experience a wide variety of micro-and macro-vascular complications that merely affect every single organ in the body; however, early and proper control of glycemic status can minimize these consequences [2,3]. The main lines of management of T2DM consist of lifestyle modifications and oral antidiabetics (OADs). OADs are proposed to reduce the chronic hyperglycemic status of T2DM patients through reducing insulin resistance, enhancing insulin secretion, and increasing glucagon-like-peptide-1 secretion [4]. However, a growing body of evidence shows that the administration of single OAD fails to properly control the glycemic status of patients with T2DM [5,6]. Moreover, the need to reach the maximum tolerated dose with mono-therapy, in order to achieve the targeted glycemic control, was linked to increased risk of serious hypoglycemia [3]. Recently, It was recommended that OADs should be administrated in combination regimens with a complementary mechanism to achieve the targeted glycemic control in patients with poorly controlled T2DM [5].

Glimepiride is a third-generation sulfonylurea that stimulates the pancreatic B cells to enhance insulin secretion with significant improvement in both first- and second-phase insulin secretion [7]. In addition, glimepiride showed a lower incidence of hypoglycemic events compared to other sulfonylureas [8]. It has been suggested that adding glimepiride to metformin-based therapy potentially leads to more improvement in glycemic control, as metformin improves hepatic and peripheral tissue insulin resistance while glimepiride enhances insulin secretion [9]. The use of a glimepiride/metformin combination may improve patients' compliance compared with instructing the patient to multiple pills, as well [10,11]. In addition to its cost-effectiveness, glimepiride/metformin combination was reported to minimize the side effects

Correspondence to: Dr. Yehia Ghanem, The Department of Internal Medicine, Unit of Diabetes, Faculty of Medicine, Alexandria University, Alexandria, Egypt

that may result from instructing T2DM patients to a high-dose of OAD mono-therapy [11].

According to the Diabetes Atlas 2014, Egypt is considered the 8th country in the International Diabetes Federation's top 10 countries for adults (20-70 years) with diabetes. Egypt has around 7.5 million patients with diabetes; where the diabetes comparative prevalence according to the WHO standard is 16.62% [12]. Despite the worldwide consensus recommendations, we lack the published literature from Egypt that assess the real-life efficacy of glimepiride/metformin combination in the management of patients with T2DM. In this regards, the present prospective study aimed to evaluate the safety and efficacy of prescribing glimepiride to Egyptian patients with poorly controlled T2DM on metformin monotherapy.

Patients and Methods

In the present observational prospective study, patients in 76 active sites from different governorates in Egypt between November 2013 and May 2016. Were included if they met the following criteria: (1) Adult patients (≥ 21 years) with poorly controlled T2DM despite being on the maximum tolerated dose, (2) Patients who received metformin monotherapy only, and (3) Patients whose physicians decided to prescribe glimepiride as add-on therapy to metformin. We excluded patients with severe hepatic or renal disorders, and patients with reported hypersensitivity to glimepiride or metformin.

The physicians were randomly selected according to their specialties. Each participating physician was asked to include consecutive patients during the recruitment period, starting from the initiation date at each site, to limit bias related to physician-led patients selection. For every participating patient, the following data were collected: Demographic characteristics, medical history, and baseline HbA1c levels. The included participants were then followed for three months and HbA1c levels were measured at the end of the follow-up. Safety outcomes were measured throughout the course of treatment. All adverse events, whether related to the glimepiride/metformin combination or not, were recorded from the first day of therapeutic administration. The seriousness of the adverse events and corrective interventions were also monitored.

The primary endpoints of the present study were the mean change in HbA1c after three months of treatment with glimepiride/metformin combination. Secondary endpoints included: The percentage

of patients who reached the target HbA1c $\leq 7\%$ after three months of treatment; the mean change in fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and body weight (Kg) at the end of the study; and the incidence of adverse events.

Data entry, verification, and validation were carried out using standard computer software. A double-entry method was used to ensure that the data were transferred accurately from the case report forms to the database. Data were analyzed using the software, Statistical Package for Social Science (SPSS Inc. Released 2009, PASW Statistics for Windows, Version 18.0: SPSS Inc., Chicago, Illinois, USA), then processed and tabulated. Frequency distribution with its percentage and descriptive statistics with mean and standard deviation were calculated. Chi-square, *t*-test, correlations were done whenever needed. *p*-values of less than 0.05 were considered significant.

The study was conducted in full accordance with the guidelines for good clinical practice and the Declaration of Helsinki, and data for each patient were collected only after obtaining that patient's signed written data release forms.

Results

Initially, we screened a total of 1050 patients from Egypt with poorly controlled T2DM, for whom the investigators decided to add glimepiride to metformin monotherapy. Out of those 1050 initially enrolled patients, 12 patients did not meet the eligibility criteria, while 83 patients were excluded for loss to follow-up. Thus the efficacy analysis included only 955 patients. The dosing regimens and the need to add insulin or other medications were left to the investigators to experience the real-life practice.

The majority of subjects (60.8%) had T2DM since 1-5 years. The mean age of the included patients was 48.2 ± 11.4 years with an average weight of 88.2 ± 12.9 kg. Slightly more than half (53.9%) (of the patients) were males. The baseline systolic blood pressure was 130.4 ± 15 mmHg, diastolic blood pressure 82.5 ± 8 , and heart rate of 79.5 ± 7.9 beat/minute. Almost 80% of patients reported a positive family history of diabetes, and 41.6% of the patients had medical or surgical complications rather than diabetes. The majority of patients were instructed to ≤ 2000 mg daily of metformin. After the baseline visit, all patients were instructed to glimepiride, and most of the patients were prescribed to ≤ 4 g daily. Notably, a total of 10 (9.6%) patients needed add-on basal

insulin, 3 (0.3%) patients needed rapid-acting insulin, and 6 (0.6%) patients needed other OADs (Table 1).

Table (1): Baseline characteristics of the included patients.

Characteristics	Frequency, (%) (Total=1038)
Age (mean ± SD) years	48.2±11.4
<i>Male:</i>	
Sex	559 (53.9)
Female	478 (46.1)
Baseline weight (mean ± SD) Kg	88.2±12.9
Baseline SBP (mean ± SD) mmHg	130.4±15
Baseline DBP (mean ± SD) mmHg	82.5±8
Baseline HR (mean ± SD)/minute	79.5±7.9
<i>Duration of T2DM:</i>	
Less than one year	141 (13.6)
1-5 years	631 (60.8)
More than 5 years	119 (7.9)
Positive family history	724 (80.0)
Medical or surgical history	397 (41.6)
<i>Smoking habits:</i>	
Never	651 (62.8)
Current	251 (24.3)
Former	133 (12.9)
Baseline HbA1c (mean ± SD) %	8.96 (1.38)%
Baseline FPG (mean ± SD), mg/dL	186.25 (49.29)
<i>Baseline PPG (mean ± SD), mg/dL:</i>	
<i>Metformin total daily dose (mg):</i>	
500	47 (4.5)
800	45 (4.3)
1000	299 (28.9)
1500	96 (9.3)
1700	153 (14.7)
2000	330 (31.9)
2550	51 (4.9)
3000	12 (1.2)
4500	1 (0.1)
<i>Glimepiride total daily dose (g):</i>	
1	152 (14.6)
1.5	1 (0.1)
2	381 (36.8)
3	265 (25.6)
4	159 (15.4)
6	50 (4.9)
8	24 (2.3)
9	1 (0.1)
12	1 (0.1)

SBP : Systolic blood pressure. T2DM : Type 2 diabetes mellitus.
 DBP : Diastolic blood pressure. FPG : Fasting plasma glucose.
 HR : Heart rate. PPG : Post-prandial plasma.

After three months of treatment, the HBA1c decreased significantly from 8.96±1.38% to 7.4±1.1%. The mean change in HBA1c level at the end of follow-up was -1.54% (95% CI: -1.61 to 1.46%), and the mean relative reduction was 16.3% (p<0.001). At the final visit, 31.7% of patients achieved the targeted HbA1c level ≤7%

Fig. (1). The mean change in FPG level was 56.8mg/dL (95% CI: 59.75 to 53.85mg/dL) at month three, while the mean relative reduction was 27.9% (p<0.001). The PPG level decreased significantly by a mean of 90.4mg/dL (95% CI: 94.69 to 86.10mg/dL) at the end of study period (p<0.001). While the mean change in body weight was 0.87kg (95% CI: 1.11 to -0.63kg) (p<0.001). (Table 2).

Throughout the study period, 11 patients (1.06%) experienced a total of 15 adverse events. Mild hypoglycemia occurred in six subjects with no incidence of severe hypoglycemia. Hyperglycemia occurred in two cases, both were mild and were not considered as treatment-related. The incidence of adverse events throughout the study period are shown in Table (3).

Table (2): Mean change in primary and secondary outcomes at the end of study.

Endpoints	Baseline	Month 3	p-value
<i>HbA1c level:</i>			
Mean (SD)	8.96 (1.38)	7.43 (1.07)	<0.001
Mean change from baseline (SD)	-1.54 (95% CI: -1.61 to -1.46)		
<i>FPG level, mg/dL:</i>			
Mean, 95% CI	186.25 (49.29)	129.54 (34.59)	<0.001
Mean change from baseline (SD)	-56.8 (95% CI: -59.75 to -53.85)		
<i>PPG level, mg/dL:</i>			
Mean, 95% CI	266.88 (74.3)	176.53 (51.02)	<0.001
Mean change from baseline (SD)	-90.4 (95% CI: -94.69 to -86.10)		
<i>Body Weight Kg:</i>			
Mean, 95% CI	87.92 (12.57)	87.09 (12.08)	<0.001
Mean change from baseline (SD)	-0.87 (95% CI: -1.11 to -0.63)		

FPG : Fasting plasma glucose.
 PPG : Post-prandial plasma.

Table (3): Reported acute adverse events among the included patients.

Adverse events	Frequency (%) (Total=1038)
Hypoglycemia	10 (1.4)
Hyperglycemia	2 (0.2)
GIT Upsets	2 (0.2)
Pregnancy	1 (0.1)

*Every subject may have more than one AEs/ADRs.
 GIT: Gastrointestinal system.

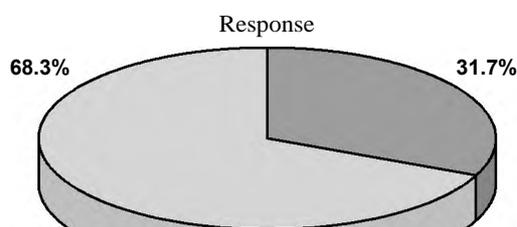


Fig. (1): The percentage of patients who responded to treatment after 3 months.

Discussion

Glimepiride and metformin are one of the most commonly prescribed OADs worldwide. Metformin improves insulin resistance in peripheral tissue and hepatic cells, making it widely recommended as the first OAD of choice, particularly for newly diagnosed patients with T2DM. On the other hand, glimepiride is a third generation Sulfonylurea that enhances insulin secretion through stimulating pancreatic B cells. Glimepiride, in comparison to other sulfonylureas, can selectively target the pancreatic ATP-sensitive potassium channel leading to an improvement in glucose transport [13]. When Metformin mono-therapy fails to control the hyperglycemic status of T2DM patients, glimepiride can be prescribed as add-on therapy. In the present real-life study, 31.7% of patients, who were prescribed to glimepiride/metformin free combination, achieved the targeted HbA1c $\leq 7\%$ after three months of treatment. In addition, the mean HbA1c level showed a statistically significant reduction by 1.54%. In addition, FPG, PPG, and body weight decreased significantly at the end of the study. Glimepiride/metformin free combination exhibited a tolerable safety profile as well.

According to 2012 ADA/EASD position statement, adding a second agent to metformin is expected to reduce HbA1c level by 1.5% in patients with poorly controlled T2DM [14]. In the present study, we observed a significant reduction in HbA1c by 1.54% after the prescription of glimepiride/metformin free combination. In concordance with our results, a growing evidence of the published literature reported the clinically significant efficacy of glimepiride/metformin combination. Pareek and colleagues conducted a prospective study to evaluate the efficacy of glimepiride/metformin free combination on 93 patients with uncontrolled T2DM, they reported that HbA1c decreased significantly after three months of treatment (mean change = -0.7 ± 1.55); a similar significant reduction was observed in FPG and PPG levels [9]. González-Ortiz and colleagues, a study on 76 patients with

uncontrolled T2DM, reported that a total of 44.6% of the patients in glimepiride/metformin combination group achieved the targeted HbA1c level after 12 months of treatment [15].

Glimepiride/metformin fixed-dose combination was reported to be effective as well. Kim and colleagues [16] conducted a randomized controlled trial on 209 patients with T2DM, they concluded that glimepiride/metformin fixed-dose combination therapy was more effective in glycemic control than metformin up-titration, with similar safety profile. The targeted HbA1c level was achieved in 74.7% of the patients (versus 46.6% patients in metformin group), with a significantly greater reduction in mean HbA1c level at the end of treatment. Another report showed that the fixed dose combination of glimepiride/metformin achieved 3% reduction in mean HbA1c level after three months, while half of the patients showed a HbA1c reduction of at least 1% [17].

Hypoglycemia is a major concern when using sulfonylureas. However, glimepiride was reported to be associated with lower rates of severe hypoglycemia than other sulfonylureas, which may be attributed to its potentially controllable effect on insulin secretion [18]. Pareek and colleagues [19] reported an incidence rate of 2% of symptomatic hypoglycemia. Another report showed a higher proportion of hypoglycemic events were observed in the glibenclamide group compared to glimepiride group (28.9% vs. 17%, respectively) [15]. The Korean study by Kim and colleagues [16] reported a high incidence of hypoglycemia in glimepiride/metformin combination group (41%), while metformin group showed an incidence of (5%). However, in the present study, hypoglycemia occurred in 6 (0.5%) patients only, with no reported severe hypoglycemic event.

In this observational study conducted in Egypt, the addition of glimepiride to metformin monotherapy in patients with uncontrolled T2DM was associated with an improved glycemic control and was well-tolerated.

Acknowledgments:

The study was sponsored and funded by Sanofi, which played no role in analyzing or interpreting the data. A statistical analysis was provided by RAY Contract Research Organization. Editorial support was provided by Ahmed Elgebal, Reham Elgarhy and Fady Adel of RAY Contract Research Organization and was funded by Sanofi.

Authors' COI:

The author has no conflicts of interest to declare.

References

- 1- TURNER R.: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*, 352: 854-865. doi: 10.1016/S0140-6736(98)07037-8, 1998.
- 2- TURNER R.: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352: 837-53. doi: 10.1016/S0140-6736(98)07019-6, 1998.
- 3- HOLMAN R.R., PAUL S.K., BETHEL M.A., et al.: 10-year follow-up of intensive glucose control in type 2 diabetes. *N. Engl. J. Med.*, 359: 1577-89. doi: 10.1056/NEJMoa0806470, 2008.
- 4- TURNER R.C., CULL C.A., FRIGHI V. and HOLMAN R.R.: Glycemic control with diet, sulphonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA*, 281: 2005-12. doi: 10.1017/CB O9781107415324.004, 1999.
- 5- HERMANN L.S., SCHERSTEN B., BITZÉN P.O., et al.: Therapeutic comparison of metformin and sulphonylurea, alone and in various combinations: A double-blind controlled study. *Diabetes Care*, 17: 1100-9. doi: 10.2337/diacare.17.10.1100, 1994.
- 6- WRIGHT A.D., CULL C.A., HOLMAN R.R. and TURNER R.C.: UKPDS 28: A randomized trial of efficacy of early addition of metformin in sulphonylurea-treated type 2 diabetes. *Diabetes Care*, 21: 87-92. doi: 10.2337/diacare.21.1.87, 1998.
- 7- ROSENKRANZ B.: Pharmacokinetic basis for the safety of glimepiride in risk groups of NIDDM patients. *Horm. Metab. Res.*, 28: 434-9. doi: 10.1055/s-2007-979833, 1996.
- 8- DRAEGER E.: Clinical profile of glimepiride. *Diabetes Res. Clin. Pract.*, 28: S139-S146. doi: 10.1016/0168-8227(95)01072-L, 1995.
- 9- PAREEK A., CHANDURKAR N.B., SALKAR H.R., et al.: Evaluation of efficacy and tolerability of glimepiride and metformin combination: A multicentric study in patients with type-2 diabetes mellitus, uncontrolled on monotherapy with sulphonylurea or metformin. *Am. J. Ther.*, 17: 559-565. doi: 10.1097/MJT.0b013e3181ff7c63, 2010.
- 10- ZHU H., ZHU S., ZHANG X., et al.: Comparative efficacy of glimepiride and metformin in monotherapy of type 2 diabetes mellitus: Meta-analysis of randomized controlled trials. *Diabetol. Metab. Syndr*, 5: 70. doi: 10.1186/1758-5996-5-70, 2013.
- 11- MELIKIAN C., WHITE T.J., VANDERPLAS A., et al.: Adherence to oral antidiabetic therapy in a managed care organization: A comparison of monotherapy, combination therapy, and fixed-dose combination therapy. *Clin. Ther.*, 24: 460-7. doi: 10.1016/S0149-2918(02)85047-0, 2002.
- 12- FEDERATION I.D.: IDF Diabetes Atlas Sixth edition. idf.org 1-2. doi: 2-930229-80-2, 2014.
- 13- GEISEN K., VÉGH A., KRAUSE E. and PAPP J.G.: Cardiovascular effects of conventional sulphonylureas and glimepiride. *Horm. Metab. Res.*, 28: 496-507. doi: 10.1055/s-2007-979841, 1996.
- 14- INZUCCHI S.E., BERGENSTAL R.M., BUSE J.B., et al.: Management of hyperglycemia in type 2 diabetes: A patient-centered approach: Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*, 35: 1364-79. doi: 10.2337/dc12-0413, 2012.
- 15- GONZÁLEZ-ORTIZ M., GUERRERO-ROMERO J.F., VIOLANTE-ORTIZ R., et al.: Efficacy of glimepiride/metformin combination versus glibenclamide/metformin in patients with uncontrolled type 2 diabetes mellitus. *J. Diabetes Complications*, 23: 376-9. doi: 10.1016/j.jdiacomp.2008.09.002, 2009.
- 16- KIM H. SOON, KIM D. MAN, CHA B. SOO, et al.: Efficacy of glimepiride/metformin fixed-dose combination vs metformin uptitration in type 2 diabetic patients inadequately controlled on low-dose metformin monotherapy: A randomized, open label, parallel group, multicenter study in Korea. *J. Diabetes Investig.*, 5: 701-8. doi: 10.1111/jdi.12201, 2014.
- 17- GONZÁLEZ-ORTIZ M., MARTÍNEZ-ABUNDIS E., GUERRERO ROMERO C.F., et al.: Eficacia y seguridad de la terapia hipoglucemiante oral combinada de glimepirida más metformina en una sola forma farmacéutica en pacientes con diabetes mellitus tipo 2y falla secundaria a monoterapia con glibenclamida. *Rev. Investig. Clin.*, 56: 327-33, 2004.
- 18- HOLSTEIN A., PLASCHKE A. and EGBERTS E.H.: Lower incidence of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. *Diabetes Metab. Res. Rev.*, 17: 467-73. doi: 10.1002/dmrr.235, 2001.
- 19- PAREEK A., CHANDURKAR N.B., SALKAR H.R., et al.: Evaluation of Efficacy and Tolerability of Glimepiride and Metformin Combination. *Am. J. Ther.*, 20: 41-7. doi: 10.1097/MJT.0b013e3181ff7c63, 2013.

جليمبيريد كعلاج إضافي لمرض السكر من النوع الثانى على متفورمين وحده: دراسة واقعية من مصر

الخلفية: تم الإبلاغ عن أن إضافة عقار جليمبيريد إلى العلاج الأحادى بعقار ميتفورمين يؤدي إلى تحسين حالة سكر الدم للمرضى الذين يعانون من مرض السكرى من النوع (٢)، مع تحقيق ملف أمان مقبول.

الهدف من العمل: هدفت الدراسة الفعلية القائمة إلى التحقق من أمان وفعالية العلاج الإضافى بعقار جليمبيريد فى المرضى الذين يعانون من مرض السكرى من النوع (٢) غير المتحكم به بشكل جيد مع العلاج الأحادى بعقار ميتفورمين.

المرضى وطرق العلاج: فى الدراسة الاستطلاعية القائمة، قمنا بإلحاق ١٠٥٠ مريضاً ممن يعانون من مرض السكرى من النوع (٢) غير المتحكم به بشكل جيد من مصر، والذين قرر الباحثون وصف عقار جليمبيريد بالإضافة إلى الميتفورمين. تم إضافة عقار جليمبيريد للمرضى غير المتحكم بحالتهم باستخدام عقار ميتفورمين كعلاج أحادى لمدة لا تقل عن ثلاثة أشهر على الرغم من الوصول إلى الجرعة القصوى التى يمكن تحملها. حدد الباحثون نظام الجرعات لعكس النهج عملياً. قمنا بمتابعة المرضى الذين تم إلحاقهم لمدة ثلاثة أشهر وتم قياس نتائج الأمان على مدار فترة الدراسة.

النتائج: بعد ثلاثة أشهر من العلاج، انخفض متوسط مستوى الهيموجلوبين السكرى بنسبة ١.٥٤٪ (نطاق ثقة ٥٩٪ - ١.٦١ إلى ١.٤٦٪)، مع وجود متوسط إنخفاض بالنسبة قدره ١٦.٣٪ (القيمة الاحتمالية > ٠.٠٠١). بالإضافة إلى ذلك، وصل ٣١.٧٪ من المرضى الملتحقين إلى المستوى المستهدف للهيموجلوبين السكرى والذي يبلغ $\geq 7\%$. بلغ العدد الإجمالى للأثار الجانبية ١٥ أثراً جانبياً أصيب بها ١١ مريضاً تم تسجيل ١٠ حالات من حدوث نقص غير خطير بسكر الدم.

الخلاصة: تؤكد الدراسة الفعلية القائمة فعالية العلاج الإضافى بعقار جليمبيريد إلى العلاج الأحادى بعقار ميتفورمين بين المرضى المصريين الذين يعانون من مرض السكرى من النوع (٢) غير المتحكم به بشكل جيد. علاوة على ذلك، أظهر نظام العلاج بعقار جليمبيريد/ميتفورمين ملف أمان مقبولاً بشكل جيد.