A Statistical Review on the Active Substance Gliclazide and a Detailed Interpretation of its Adverse Drug Reaction Reports

Contract Research Organization / Terzetto Pharma Metrics

SHRUTHI SURENDRAN AND BANU PRIYA

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Introduction

Gliclazide is a second generation Sulfonylurea's oral hypoglycemic agent which stimulates insulin secretion. Chemical structure:

![Chemical Structure of Gliclazide](image)

Chemical Formula: C15-H21-N3-O3-S

Molecular Weight: 323.41054 g/mol

IUPAC name: 1-(3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-2-yl)-3-(4-methylphenyl)sulfonylurea
It is intended to treat and improve the defective insulin secretion in patients with non-insulin-dependent diabetes mellitus (NIDDM). It reduces blood glucose levels by stimulating insulin secretion from the β cells of the islets of Langerhans. In addition to metabolic properties such as increase in postprandial insulin and C-peptide secretion which can persist after two years of treatment it also has haemovascular properties.

**Mechanism of action**
Gliclazide binds to the β cell sulfonylurea receptor (SUR1). This binding subsequently blocks the ATP sensitive potassium channels. The binding results in closure of the channels and leads to a resulting decrease in potassium efflux leads to depolarization of the β cells. This opens voltage-dependent calcium channels in the β cell resulting in calmodulin activation, which in turn leads to exocytosis of insulin containing secretory granules. It is rapidly and well absorbed with peak plasma concentrations occurring within 4-6 hours of oral administration.

**Patents**
The US Patent US6733782B1 is on the Core tablet for controlled release of gliclazide after oral administration published on 11-05-2004 by Les Laboratoires Servier, France. The patent expires in 2024. The sustained-release formulation of gliclazide was patented by Disphar International on 05-05-2010. It was first patented by Servier Canada and then approved for therapeutic use by the name of Diamicron® MR.

Patent no. EP1148871 – European patent on Core tablet for controlled release of gliclazide after oral administration published on 31.10.2001 by Les Laboratoires Servier, France in EU. The patent expires on October 2019. Gliclazide BGR 30 mg MRT (Modified Release Tablet) from Les Laboratoires Servier was given a marketing authorization on June, 5th, 2008 in Europe.

Indian patent no. 211372 - Matrix Tablet for the Prolonged Release of Gliclazide and Process for the Preparation Thereof published on 09-11-2007. The patent expires in 2027. In India Gliclazide was manufactured under the brand name Diamicron by Serdia Pharmaceuticals (India) Private Limited. About 187 pharmaceutical companies manufactured Gliclazide containing drugs in India. In the Indian
pharmacopeia scenario, gliclazide has 4 formulations i.e. 30mg, 40mg, 60mg, 80mg and 2.5mg with an eminent price percentage variation (in Rs.) of 946.73 implying a wide price variation in its affordability.

Method of data collection
The drug substance information was extracted and compiled from the European database of suspected adverse drug reaction reports (website: www.adrreports.eu). The information on Gliclazide was updated within years 2013 to 2016. The information available in the above website was collected from adverse drug reactions of substances, stating the data available for gliclazide. The data was segregated into individual cases and cases based on reaction groups such as age, sex, reporter group and geographic origin.

Interpretation
Based on the data retrieved from the website adrreports.eu for the drug substance gliclazide, it can be observed that the total number of ADR cases reported was 1,815. Among these cases, under age group, the highest frequency of cases was seen in 65-85 years (48.3%). Higher number of cases was reported for the female group – 820 cases (45.2%) showing a significant difference with the male group (40.6%). European economic areas have reported a significant number of ADR cases i.e. 1,208 out of the total (66.6%) than non European economic areas.

System Organ Classification (SOC)
A SOC is the highest level of the hierarchy that provides the broadest concept for data retrieval. There are a total of 26 SOCs and they comprise groupings by:

- Etiology (e.g., SOC Infections and infestations)
- Manifestation site (e.g., SOC Gastrointestinal disorders)
- Purpose (e.g., SOC Surgical and medical procedures)

Based on SOCs the following interpretations were made for the data retrieved.

The total number of cases reported is 3,828. Among 26 SOCs, the SOC Metabolism and nutrition disorders was found to have the maximum number of cases reported – 730. With highest number of cases reported under the age group 65-85 years.
(49.31%). Also the highest number of cases was reported in the female group (48.08%) than the male counterpart. The largest reporter group was the healthcare professionals forming 92.88% of the total. The highest frequency of cases was depicted in the European economic areas – 67.67%.

The second highest cases reported are in the SOC Nervous system disorders with 395 cases. Highest number observed in the age group 65-85 years (49.37%). Also the highest number of cases was reported in the female group (49.11%), a slight increase from the male group (40.25%). Largest reporter group comprised the healthcare professionals forming 88.35% majority. The highest frequency of cases was depicted in the European economic areas – 61.77%.

The SOC - General disorders and administration site conditions have 356 cases reported. Highest number of cases observed in the age group 65-85 years (50.56%). Also the highest number of cases was reported in the female group (48.31%), a slight increase from the male group (43.26%). Largest reporter group comprised the healthcare professionals forming 82.02% majority. The highest frequency of cases was depicted in the European economic areas – 56.74%.

The SOC - Investigations have 284 cases reported. Highest number of cases observed in the age group 65-85 years (47.89%). Also the highest number of cases was reported in the female group (47.89%). Largest reporter group comprised the healthcare professionals forming 82.39 % majority. The highest frequency of cases was depicted in the Non European economic areas – 51.06% which was a deviation from the previous SOCs.

The SOC – Gastrointestinal disorders have 266 cases reported. Highest number observed in the age group 65-85 years (44.74%). Also the highest number of cases was reported in the female group (47.37%), a slight increase from the male group. Largest reporter group comprised the healthcare professionals forming 86.84% majority. The highest frequency of cases was depicted in the European economic areas – 60.53 %.

225 cases were reported in the SOC Skin and subcutaneous tissue disorders. Highest number observed in the age group 65-85 years (56 %). The maximum number of cases was reported in the female group (54.67%). Largest reporter group comprised the healthcare professionals forming 91.11% majority. The highest frequency of cases was depicted in the European economic areas – 67.56 %.
Consequently the remaining SOCs are depicted with the total number of cases for each class: Blood and lymphatic system disorders 163; Cardiac disorders 97; Eye disorders 41; Hepatobiliary disorders 185; Infections and infestations 88; Injury, poisoning and procedural complications 202; Musculoskeletal and connective tissue disorders 88; Neoplasms benign, malignant and unspecified (incl cysts and polyps) 60; Psychiatric disorders 130; Renal and urinary disorders 198; Respiratory, thoracic and mediastinal disorders 120 and Vascular disorders 98.

Of the mentioned SOCs, Blood and lymphatic system disorders, Cardiac disorders, Hepatobiliary disorders, Infections and infestations, Psychiatric disorders, Renal and urinary disorders, Respiratory, thoracic and mediastinal disorders and Vascular disorders all fall in the percentage range of 44.73 – 54.54 for majority reports in age group 65-85 years. The remaining SOCs fall in a lower percentage range of 37.12 – 43.18. Eye disorders was the only SOC showing majority cases in age group 18-64 years (48.78%).

Ranging from 46.96 – 61.22 percent the female group is dominant over its male counterpart with maximum cases reported for the above mentioned SOCs, except in three SOCs where number of cases is higher in the male group; Blood and lymphatic system disorders (47.85%), Hepatobiliary disorders (41.62%) and Neoplasms benign, malignant and unspecified (incl cysts and polyps) (53.33%).

The largest reporter group reporting maximum number of cases is found to be the healthcare professionals ranging from 63.41 – 97.54 percentages.

The most number of cases is reported from the European economic area in the range of 51.54 – 70.55 percentages. Infections and infestations (51.14%) and Musculoskeletal and connective tissue disorders (55.68%) cases are reported from Non European areas.

These are SOCs that fall in the category of minority number of cases reported: Congenital, familial and genetic disorders 4; Ear and labyrinth disorders 13; Endocrine disorders 12; Immune system disorders 24; Pregnancy, puerperium and perinatal conditions 11; Product issues 9; Reproductive system and breast disorders 7; Social circumstances 6 and Surgical and medical procedures 16.
Conclusion

The data observed shows higher number of cases reported for age groups 18-64 years and 65-85 years in the percentage range of 37.5 – 66.67 except for Congenital, familial and genetic disorders in which majority cases were unspecified (75%). Most number of cases reported for the female group and lie in the percentage range of 53.84 - 66.67 percentages. Cases reported under the SOC Reproductive system and breast disorders has slight increase in the male group (57.14%) and Congenital, familial and genetic disorders had majority cases which were unspecified (75%) in the gender category. All cases reported by healthcare professionals fall in the range of 75 – 100 percentages. Of the nine SOCs mentioned above, five had most cases reported from the European economic areas in the range 54.16 – 75 percentages; while Endocrine disorders, Product issues, Reproductive system and breast disorders and Surgical and medical procedures have most number of cases from the non European areas in the range 55.55 – 71.42 percentages.
THANK YOU.
FOR MORE INFORMATION CONTACT: Shruthi
info@tpmet.com