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Quality and Behavior of Glimepiride Generics Versus Amaryl Under Stressed Conditions

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ABSTRACT

Background: The use of generic versions of drugs, such as those for glimepiride [Amaryl®, Amarel®, Solosa® (sanofi-aventis, Paris, France)], a third-generation sulfonylurea, can reduce healthcare costs. However, the quality and performance of these generics should be carefully evaluated.

Methods: We compared the quality and behavior of 23 marketed generic forms with Amaryl (all 2 mg) under stressed conditions. Deblistered samples were stored at 60°C for 21 days in order to mimic temperature-stressed conditions. Samples were analyzed at Days 0, 7, and 21 for content of active compound, levels of impurities, levels of residual solvent (Day 0 only), and dissolution profile, and results were compared against Amaryl specifications.

Results: Levels of the degradation product glimepiride sulfonamide were ≤1% in all products at Day 0 but increased to above Amaryl specifications (≤2.5%) in two generics at Day 7 and in four generics at Day 21. Total levels of other impurities and levels of residual solvents were above Amaryl specifications (≤1.0% and >1,400 ppm, respectively) in two generics at Day 0. At Day 0, the dissolution of 12 generics (52%) failed to meet Amaryl specifications (≥85% dissolved in 15 min); this trend was confirmed at Day 21. Overall, 74% (17 of 23) of the generics were not of equivalent quality or performance compared with Amaryl.

Conclusions: This study indicates that a relevant percentage of glimepiride generics may offer reduced quality and performance when compared with the original drug.

INTRODUCTION

THE EXPIRY OF PROPRIETARY PATENTS on therapeutics presents other pharmaceutical companies with an opportunity to produce and commercialize their own version of the compound. The use of generic versions of drugs also provides an opportunity to reduce healthcare costs.[1]

Although the exact details of the production of the therapeutics are made available, manufacturing standards and methods may differ among pharmaceutical companies, which, consequently, can lead to differences in the quality and performance of the generic versions.[2] Therefore, assessing the equivalence of generics is essential for predicting both therapeutic efficacy and potential toxicity.[2–4] This is of particular importance with therapeutics used in the treatment of chronic diseases for which daily, long-term therapy is required.

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Glimepiride [Amaryl®, Amarel®, Solosa® (sanofi-aventis, Paris, France)] is a third-generation, once-daily sulfonylurea manufactured by sanofi-aventis for the treatment of Type 2 diabetes. Type 2 diabetes is a progressive disease characterized by insulin resistance and a loss of insulin secretion associated with a progressive failure of beta cell function.[5] Glimepiride is demonstrated to offer therapeutic advantages over other sulfonylureas in terms of glucose-dependent insulinotropic action and hypoglycemic risk.[6,7]

There are many commercially available generic glimepiride products, the quality and performance of which should be carefully evaluated. Analytical comparisons of the short-term stability of generic compounds compared with Amaryl production specifications have yet to be performed. The aim of this study was to evaluate the quality and behavior of 23 marketed glimepiride generics in terms of the levels of active compound (glimepiride), degradation products, other impurities, residual solvents, and the dissolution profile with those of Amaryl.

MATERIALS AND METHODS

Reagents and samples

Samples of Amaryl and 23 glimepiride generics (all 2 mg) were included in this study; the commercial names, manufacturers, and country of origin of each product are listed in Table 1. Samples were stored at 60°C for 21 days to mimic temperature-stressed conditions. In order to avoid interferences from different packaging material, unpacked tablets of

Table 1. Glimepiride Sample Characteristics

Sample	*Dosage*	*Batch number*	*Product*	*Manufacturer (country of origin)*
1	2 mg	D569	Amaryl	Aventis Scoppito, sanofi-aventis group (Italy)
2	2 mg	L3540	Adiamyl	Lancasco (Guatemala)
3	2 mg	OO A6022	Amadiab-2	Lapi Laboratories (Indonesia)
4	2 mg	403309	Bioglic	Biolab Sanus (Brazil)
5	2 mg	4DIG001	Diagril	Bukwang (South Korea)
6	2 mg	MT 595	Diabold	Barrett Hodgson (Pakistan)
7	2 mg	12762800	Diameprid	Abdi Ibrahim Pharmaceuticals (Turkey)
8	2 mg	040623/030762	Dolcyl	Medical Union Pharmaceuticals (Egypt)
9	2 mg	3G109/3M102	Evopride	Pharmevo (Pakistan)
10	2 mg	0410128	Hanall glimepiride	Han All Pharmaceutical (Republic of Korea)
11	2 mg	040202 (caps)	Geliemeiniao Jiaonang	Pudu Pharmaceuticals (China)
12	2 mg	4001	GLA-DM	Yuhan (Republic of Korea)
13	2 mg	4P15	Glimepibal	Laboratorios Baldacci (Brazil)
14	2 mg	4G 121	Glimax	Ali Raif (Turkey)
15	2 mg	3001	Glimepiride (Boryung)	Boryung (Republic of Korea)
16	2 mg	H40004	Glimepiride (Hanni)	Hanni (Republic of Korea)
17	2 mg	0303	Glimepirida	Laboratorios La Sante Sa (Columbia)
18	2 mg	GTB-3002	Glimepirida (Esterlina)	Esterlina (Brazil)
19	2 mg	L41028	Glimepirida (Eurofarma)	Eurofarma (Brazil)
20	2 mg	N7304001	Glimulin-2	Glenmark Pharmaceuticals (India)
21	2 mg	DD161 0306	Glusafe	Genovate Biotechnology Company (Taiwan)
22	2 mg	BN627006T	Metrix	Kalbe Farma (Indonesia)
23	2 mg	L001/003	Panabutol	Panalab (Argentina)
24	2 mg	90223	Taboss	Okasa Pharma (Guatemala)

Table 2. Sanofi-Aventis Shelf-Life Specifications for the Manufacture of Amaryl

	Shelf-life specification
Impurities	
GS	≤2.5%
Other impurities (each)	≤0.5%
Total other impurities	≤1.0%
Total impurities	≤3.5%
Glimepiride content	1.8–2.1 mg
Dissolution	≥85%
Residual solvent	
Methanol	≤1,400 ppm
Ethanol	Absent

each batch were separately stored in glass beakers and used for the study.

On Days 0, 7, and 21, all samples were analyzed to determine the amount of active compound and the levels of impurities. Levels of residual solvents were measured on Day 0 only, and dissolution profiles were determined on Days 0 and 21. All analytical results were compared against the specifications for the manufacture of Amaryl as defined by sanofi-aventis (Table 2).

Apparatus

Storage of samples was undertaken in a Function Line T12 oven (Heraeus® Kendro, Asheville, NC). The liquid chromatographic analyses were carried out using two high-performance liquid chromatography (HPLC) systems. The first system comprised a Shimadzu (Kyoto, Japan) model LC2010C, which included a compact low-pressure gradient HPLC system with $1\frac{1}{2}$ plunger pump equipped with a Peltier oven, monochromatic ultraviolet detector, autosampler with a Peltier cooler unit, and Class-VP 6.12 acquisition system. The second system comprised a Shimadzu model HPLC10Avp, which included a modular high-pressure gradient system with two $1\frac{1}{2}$ plunger pump equipped with ventilation oven, monochromatic ultraviolet detector, noncooling autosampler, and Class-VP 4.3 acquisition system. Gas chromatography was performed using an Agilent (Palo Alto, CA) 6890 gas chromatograph equipped with a flame ionization detector detector and a headspace sampler (model HP7694, Agilent). Pharmatest (Hainburg, Germany) (model PTW S 3) and ER-

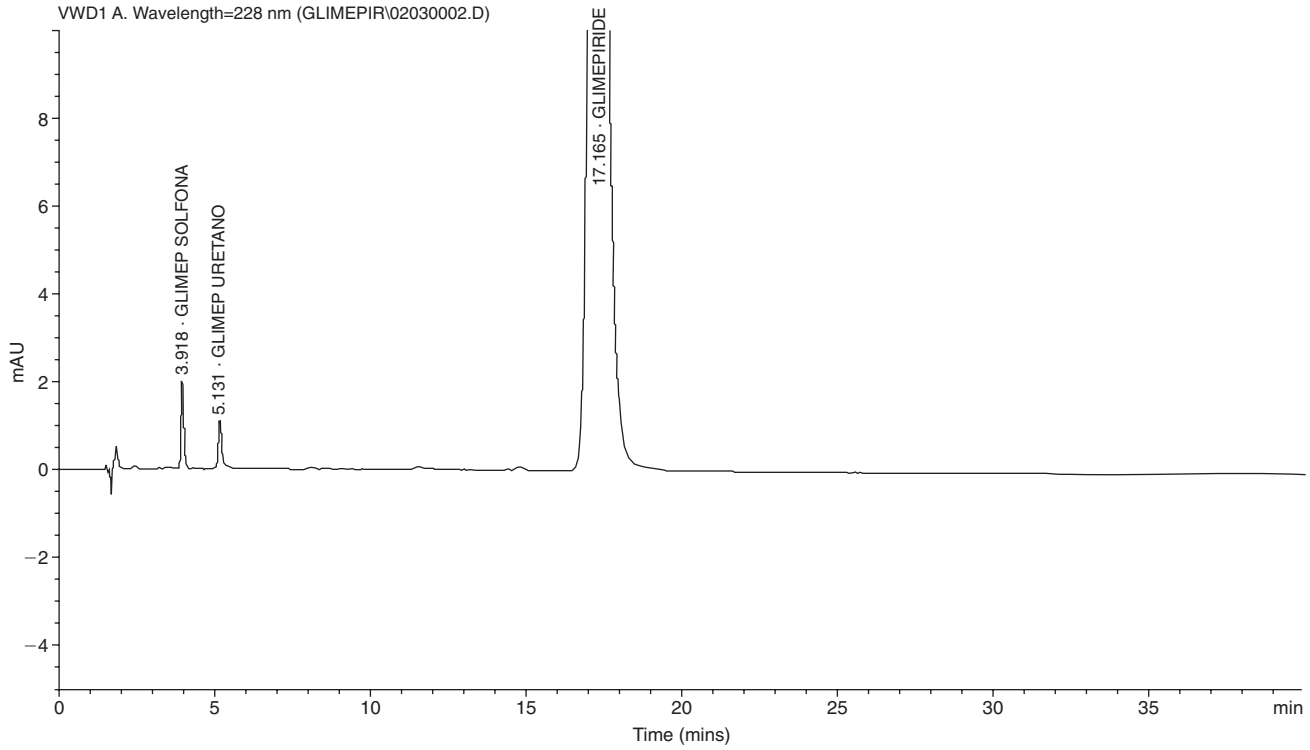

FIG. 1. Typical chromatogram. mAU, milli arbitrary units.

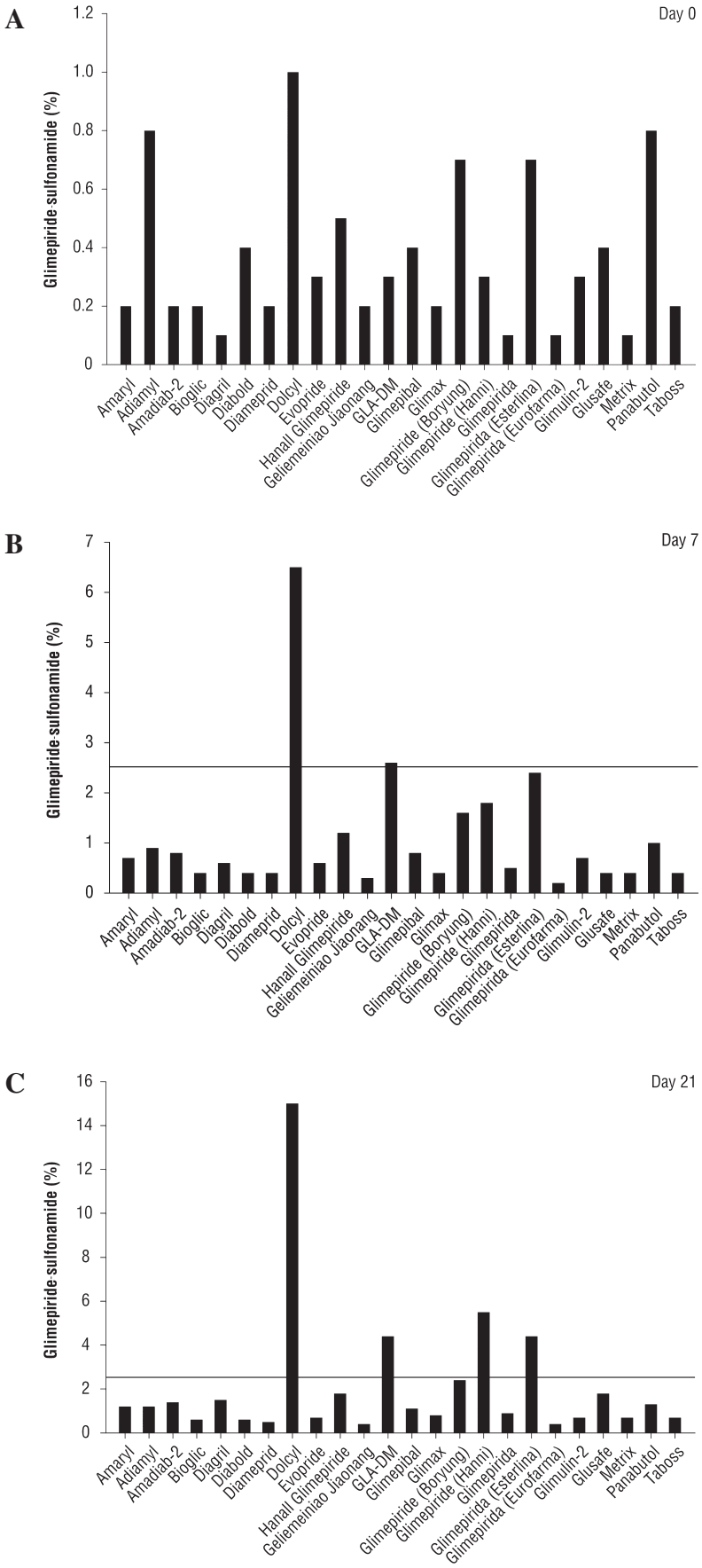

FIG. 2. Levels of the degradation product GS at Day 0 (**A**), Day 7 (**B**), and Day 21 (**C**) in 23 generics of Amaryl versus Amaryl.

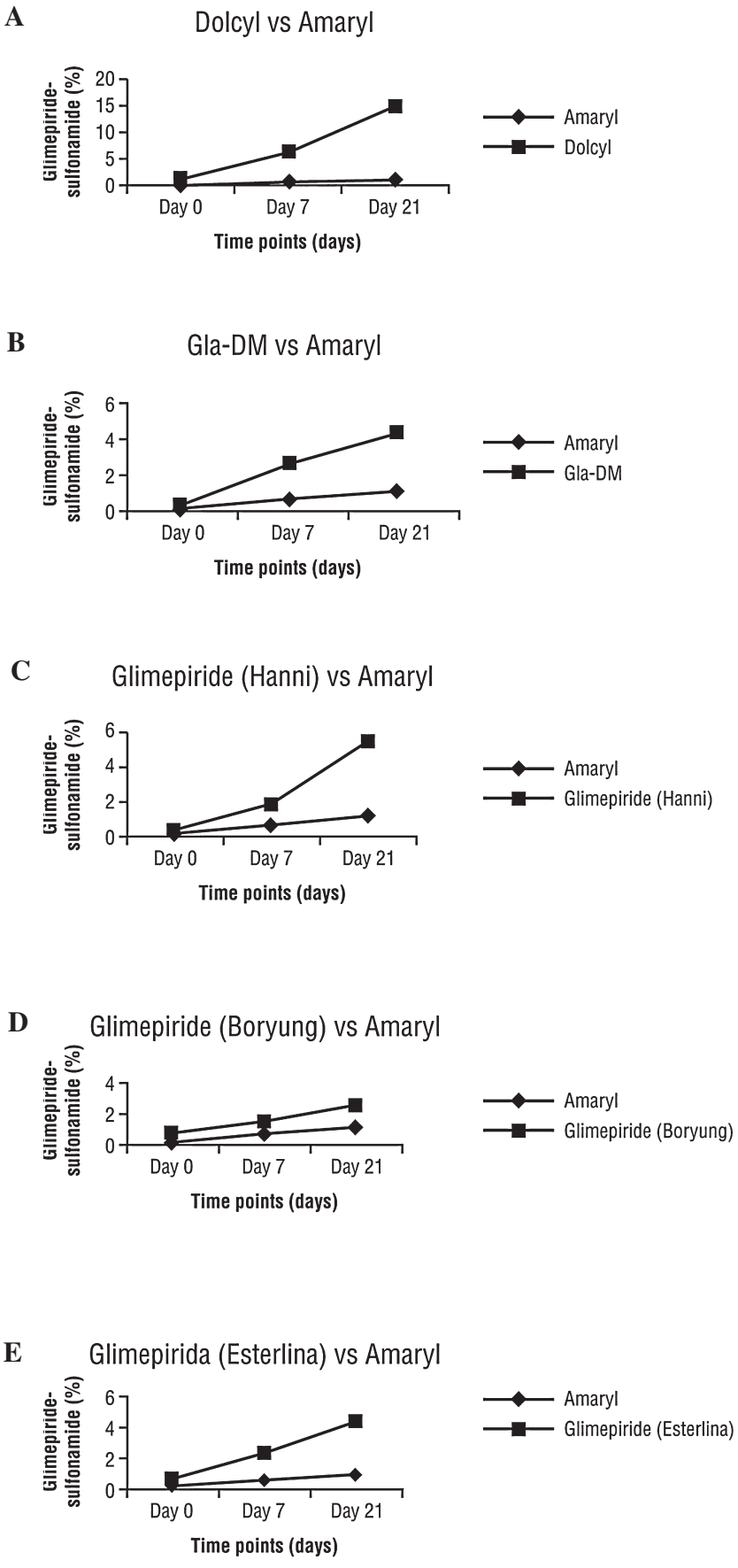

FIG. 3. Dissolution profiles for the accumulation of GS in Dolcyl (**A**), GLA-DM (**B**), glimepiride (Hanni) (**C**), glimepiride (Boryung) (**D**), and glimepirida (Esterlina) (**E**) versus Amaryl.

WEKA® (Düsseldorf, Germany) (model DT 60 and DT 700) dissolutor testers were used for in vitro dissolution.

Liquid/gas chromatography and dissolution

Liquid chromatography was used to assay the content of the active compound, glimepiride, as well as the major degradation product, glimepiride sulfonamide (GS), and other related impurities. An example chromatogram can be seen in Figure 1. Gas chromatography was performed to assay the amount of the following residual solvents: methanol, isopropanol, and ethanol. Dissolution analyses on Days 0 and 21 were used to assay the amount of glimepiride dissolved in vitro after 5, 10, 15, and 20 min in the dissolution medium.

RESULTS

Liquid chromatography: quality assessment

At Day 21, the mean content of active compound was below Amaryl specifications (1.8–2.1 mg) in only one generic, Dolcyl.

Levels of the degradation product GS were ≤1% in all products at Day 0; however, GS levels increased to above Amaryl specifications in two generics at Day 7 (Dolcyl and GLA-DM) and in four generics at Day 21 [Dolcyl, GLA-DM, glimepiride (Hanni), and glimepirida (Esterlina)] (Fig. 2). GS levels were fivefold greater for Dolcyl versus Amaryl at Day 0 (1% vs. 0.2%) and 12.5-fold greater at Day 21 (15% vs. 1.2%) (Fig. 2A and C). The greatest increase in the major degradation product (GS) was observed for the generic compounds Dolcyl, Gla-DM, glimepiride (Hanni), glimepiride (Boryung),

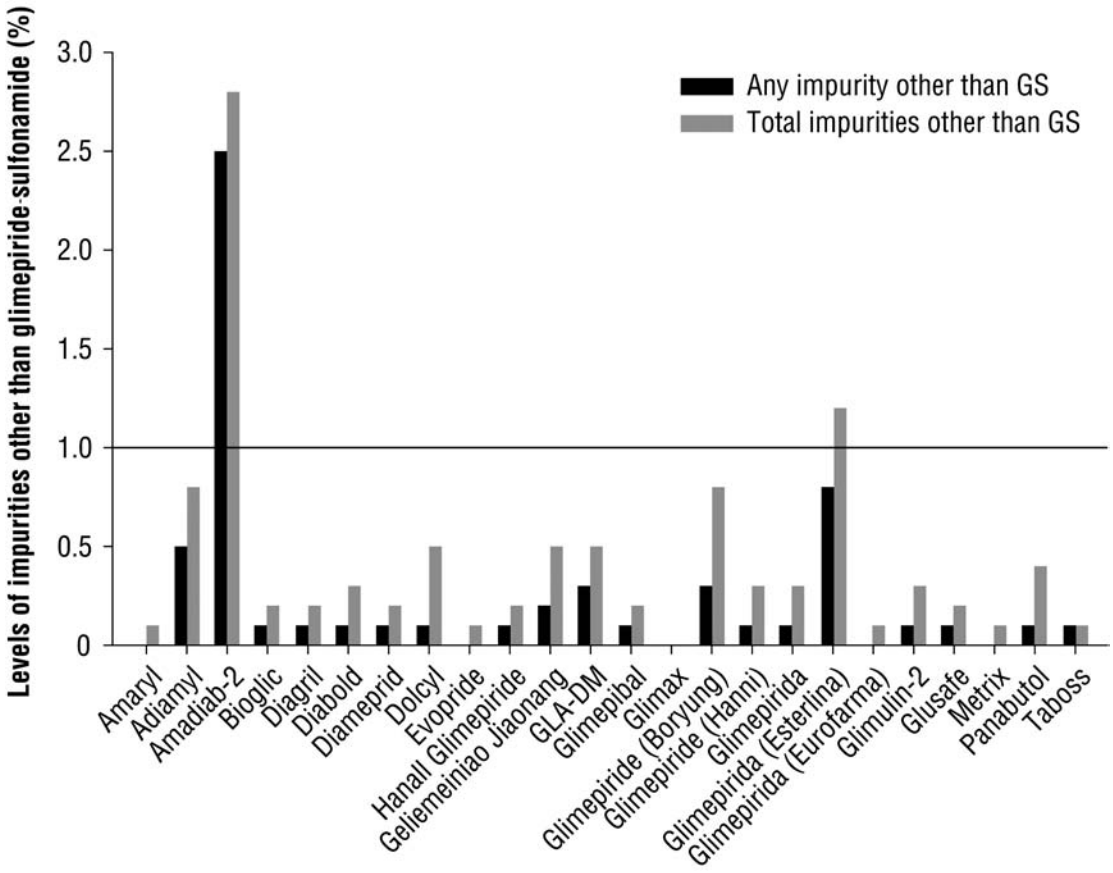

FIG. 4. Level of other impurities at Day 0 in 23 generics of Amaryl versus Amaryl.

and glimepirida (Esterlina) after 21 days in stressed conditions (Fig. 3).

Total levels of other impurities were above Amaryl specifications in two generics [Amadiab-2 and glimepirida (Esterlina)] at Day 0; Amadiab-2 contained 2.8% total other impurities versus 0.1% for Amaryl (Fig. 4).

Gas chromatography: evaluation residual solvents

The levels of residual methanol in all generic products tested were within the Amaryl specifications; however, high levels of residual ethanol were detected in both glimepirida (La Sante) and Metrix (Fig. 5).

Dissolution profile: performance assessment

At Day 0, the dissolution of 12 generics (52%) failed to meet Amaryl specifications (≥85% dissolved in 15 min); this trend was confirmed at Day 21 (Fig. 6). The dissolution profiles of 15 generic products (65%) were not considered comparable to that of Amaryl (Fig. 6).

Evaluation of stability performance, together with dissolution profiles, indicates that only six of the 23 (26%) generics evaluated [Adiamyl, Diagril, Evopride, Hanall glimepiride, glimepirida (Eurofarma), and Taboss] are comparable with Amaryl (Table 3).

DISCUSSION

The World Health Organization has reported numerous examples of inferior quality for copies of original pharmaceutical products and that these differences in formulation can lead to differences in bioavailability between products.[2] This study evaluated the quality and performance of generics of Amaryl, a third-generation sulfonylurea for the treatment of Type 2 diabetes. The quality of 23 glimepiride generics of Amaryl was evaluated by measuring the amounts of active compound (glimepiride), its major degradation product, GS, and the levels of other impurities at the start of the study, and

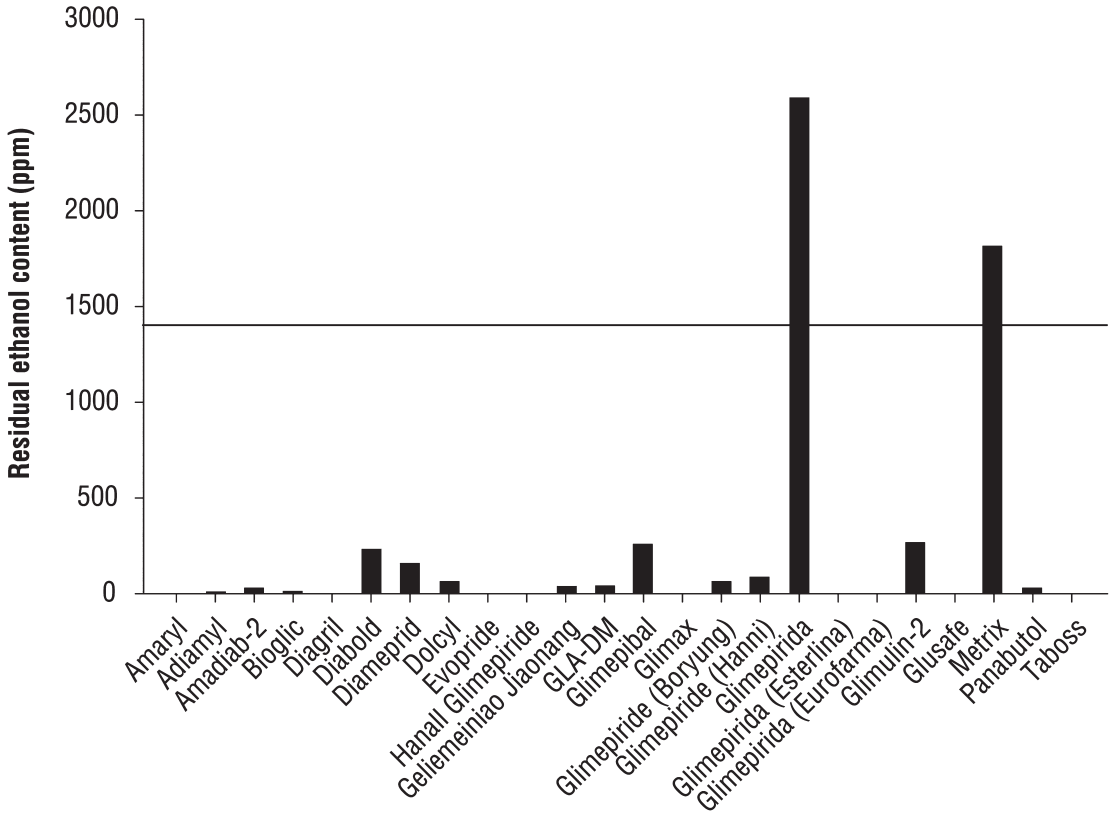

FIG. 5. Amount of residual ethanol in 23 generics of Amaryl versus Amaryl.

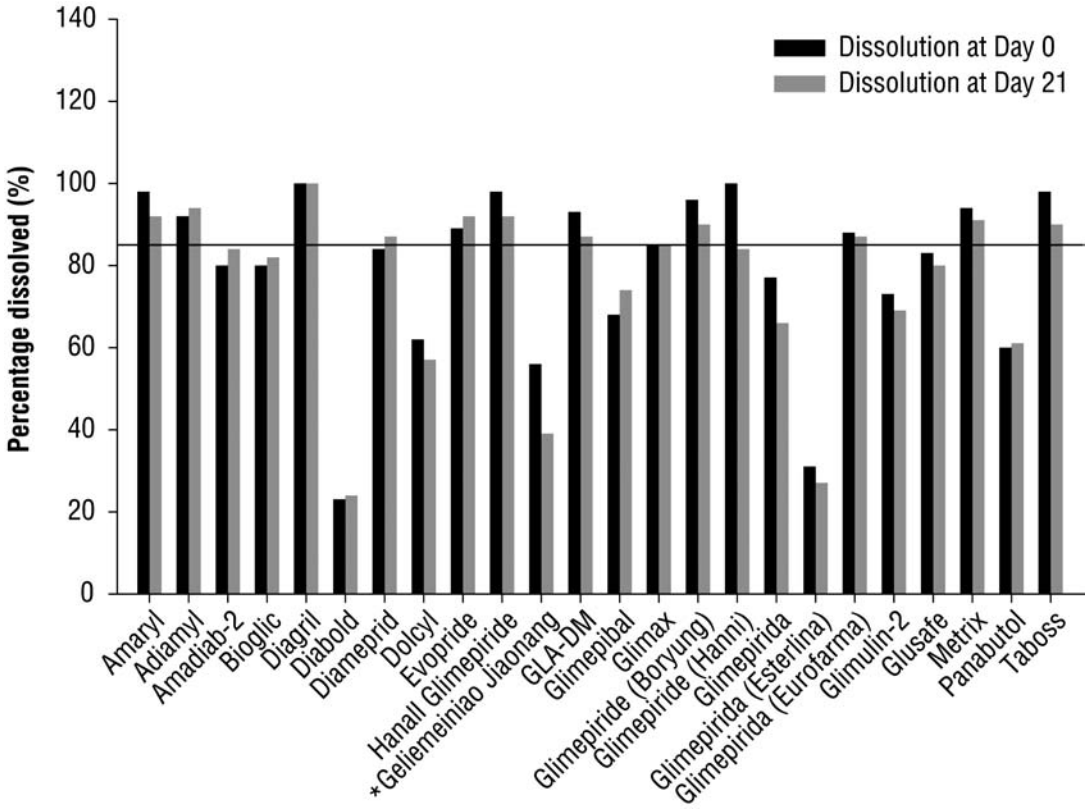

FIG. 6. Dissolution profiles at Day 0 and Day 21 in 23 generics of Amaryl versus Amaryl. *Not directly comparable owing to caplet formulation.

TABLE 3. COMPARABILITY OF GENERICS TO AMARYL

Sample	*Product*	*Dissolution*	*Level of impurities*	*Residual solvents*	*Conclusion*
1	Adiamyl	+	+	+	+
2	Amadiab-2	−	−	+/−	−
3	Bioglic	−	+	+	+/−
4	Diagril	+	+	+	+
5	Diabold	−	+	+/−	−
6	Diameprid	+/−	+	+/−	+/−
7	Dolcyl	−/−	−/−	+/−	−
8	Evopride	+	+	+	+
9	Hanall glimepiride	+	+	+	+
10	Geliemeiniao Jiaonang	−/−	+	+	−
11	GLA-DM	+	−	+	−
12	Glimepibal	−/−	+	+	−
13	Glimax	+/−	+	+	+/−
14	Glimepiride (Boryung)	+	+/−	+	+/−
15	Glimepiride (Hanni)	+/−	−	+	−
16	Glimepirida	−/−	+	−	−
17	Glimepirida (Esterlina)	−/−	−	+	−
18	Glimepirida (Eurofarma)	+	+	+	+
19	Glimulin-2	−/−	+	+/−	−
20	Glusafe	+/−	+	+	+/−
21	Metrix	+	+	−	+/−
22	Panabutol	−/−	+	+	−
23	Taboss	+	+	+	+

Ratings were on the following scale: +, good performance; −, not comparable; −/−, poor performance; +/−, average performance.

then 7 and 21 days after storage at 60°C. These data provided evidence of the integrity of each compound and its tendency to degrade under stressed storage conditions.

The results demonstrate that, regarding overall performance of the compounds (based on stability performance, dissolution profiles, and levels of impurities), only 26% of the generics tested were comparable to Amaryl.

With regard to quality assessment, although the majority of generics met Amaryl specifications for the mean content of active compound after 21 days in stressed conditions, one generic, Dolcyl, failed to reach this specification. Similarly, despite comparable levels of GS in all products at the start of the study, after 7 days in stressed conditions, GS levels had risen above those specified for Amaryl in 9% of generics by Day 7 and in 17% of generics at the end of the study. The greatest increase in product degradation after 21 days was observed in the Dolcyl generic, which exhibited levels of GS approximately 10-fold higher than those observed with Amaryl, thus demonstrating the large inherent variability between Amaryl and its generic versions.

Our findings reveal that substantial differences in active compounds and degradation exist between generic preparations and Amaryl. These differences will likely impact on bioavailability and pharmacokinetics, and, consequently, the generic products may not necessarily provide a similar safety and efficacy profile to that observed with Amaryl. It is possible that even small differences in levels of active ingredient and product degradation between formulations could alter the clinical efficacy and safety profiles relative to Amaryl. Furthermore, appropriate dosing of sulfonylureas is particularly important in order to prevent under- and overdosing, which could result in hyper- and hypoglycemia, respectively[8]; the large variations in formulations demonstrated here could make accurate dosing problematic.

In addition, two generics, Amadiab-2 and glimepirida (Esterlina), had high levels of impurities compared with Amaryl. It is unknown whether these impurities could interact with the active agent to alter bioavailability or whether they are toxic; further studies are required to establish the nature of these impurities and their potential impact on efficacy and safety. Levels of residual solvent provide some indication of the general quality of the drug product. Residual solvent does not provide any therapeutic benefit, and thus Good Manufacturing Practices and general quality-based requirements recommend limiting the amount of residual solvent in the drug as much as possible. The high levels of residual ethanol detected in both glimepirida (La Sante) and Metrix should be taken into account when considering the quality of these products.

Stability performance of the generics was evaluated through the dissolution profiles at 5-, 10-, 15-, and 20-min intervals, obtained at the start (Day 0) and end (Day 21) of the stressed conditions. The ability of the agents to dissolve adequately will impact their bioavailability and levels of inherent variability; as such, the dissolution properties of a drug are a critical factor in determining the reliability of a pharmaceutical agent. Here we demonstrate that more than 50% of generics tested failed to meet Amaryl specifications of $\geq$85% dissolution within 15 min and that an even greater proportion (65%) were not considered comparable to that of Amaryl. These data suggest that the lower level of dissolution observed in many of the generic compounds we tested could alter the bioavailability of the drug and potentially reduce efficacy.

It is recognized that the disintegration/dissolution profiles in vivo may differ from those reported here, and, as such, the magnitude and extent of the differences reported between the generics and Amaryl remain uncertain in the clinical setting since clinical data have yet to be published. In view of these uncertainties, further research is warranted to evaluate the pharmacokinetic and safety profiles of these generic products to determine if they are therapeutically equivalent to Amaryl.

In conclusion, our study indicates that a considerable percentage of the glimepiride generics of Amaryl are of reduced quality in terms of active compound content, levels of impurities, residual solvent, and dissolution profile when compared with the original drug. These results indicate that not all standards for manufacturing glimepiride are equivalent to those

of sanofi-aventis. Such divergent standards may result in production of glimepiride with reduced efficacy.

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