

Memorandum

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Food and Drug Administration
Center for Drug Evaluation and Research**

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SUBJECT: One Year Post-Pediatric Exclusivity Post-marketing Adverse Event Review: Drug Use Data
Metformin Hydrochloride / Glyburide (Glucovance[®]) Tablets: NDA 21-178

****This document contains proprietary data from IMS Health and Caremark which cannot be shared outside of FDA without clearance from IMS Health and Caremark obtained through the Office of Drug Safety.****

EXECUTIVE SUMMARY

This consult examines drug utilization trends for metformin/glyburide tablets (Glucovance[®]) in the pediatric population (ages 0-16 years). Sales data were examined for the four-year period from November 1, 2000 – October 31, 2004 with a primary focus on sales patterns 12 months before and 12 months following the granting of Pediatric Exclusivity for Glucovance[®] on October 8, 2003. Outpatient drug utilization patterns were examined for the 3-year period from November 2001 - October 2004, with a primary focus on utilization patterns during the year before and after the granting of pediatric exclusivity. Because over 91% of Glucovance[®] sales are into the retail channels, inpatient drug utilization patterns are not addressed.

Outpatient prescriptions of all oral antidiabetic products combined increased by 10% during November 2001 – October 2002 to November 2003 – October 2004 (Table 2). Antidiabetic combination products accounted for 6.7% and 9.2% of all prescriptions dispensed for oral antidiabetic products during November 2001 - October 2002 and November 2003 - October

2004, respectively. During the 3 years of this analysis, prescriptions for all oral antidiabetic combination products increased by 52%.

Glucovance[®] was the most commonly dispensed product compared to other oral antidiabetic combination products in this analysis, accounting for 7 million (86% of the prescriptions for oral antidiabetic combination products) and 4.4 million (45% of the prescriptions for oral antidiabetic combination products) prescriptions dispensed during November 2002-October 2003 and November 2003 – October 2004, respectively. A generic glyburide/metformin product was introduced in February 2004 and accounted for 2.4 million prescriptions (24% of oral combination antidiabetic products) dispensed during November 2003 – October 2004 and contributed substantially to the decline in Glucovance[®] prescriptions. The combined number of prescriptions dispensed for the brand and generic products totaled over 6.8 million prescriptions and accounted for approximately 68.9% of the market share for antidiabetic combination products. Taken together, this represented a 2% decline in dispensed prescriptions for the combination glyburide/metformin products during the post exclusivity period.

The top two prescriber specialties for Glucovance[®] from November 2003 through October 2004 were internal medicine and family practice. Of all specialties, pediatricians were ranked 13th in prescribing Glucovance[®] during this period and accounted for less than 1% of the prescriptions dispensed in each of the 3 one-year periods of this analysis. In general, prescribing patterns for Glucovance[®] dispensed in outpatient retail pharmacy settings showed no substantial change across provider specialties during the 36-month study period.

Among a large, insured patient population managed by Caremark, pediatric patients age 1-16 accounted for no more than 0.06% of the claims for oral antidiabetic products in each of the 3 one-year periods from November 2001 - October 2004. Due to the low use of Glucovance in patients age 1-16 years, we were unable to obtain a reliable national estimate of the number of prescriptions dispensed to this population.

The most common diagnosis associated with a mention of Glucovance[®] in office based physician-patient encounters was diabetes without complications (ICD-9 250.0) which accounted for 96% of mentions during the pre-exclusivity period (November 2002 - October 2003) and 97% during the post-exclusivity (November 2003 - October 2004). Due to the small numbers, we were not able to analyze the diagnoses associated with members in the pediatric population.

In conclusion, the use of this product in pediatric patients was low as 0.05% of all claims for oral antidiabetic products and does not appear to have changed over the three-year period examined.

INTRODUCTION

On January 3, 2001, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of the BPCA requires the reporting of adverse events associated with the use of a drug in children during the one-year period following the date on which the drug received pediatric marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee on the drug utilization patterns

and adverse events associated with the use of the drug on a quarterly basis. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

Glucovance[®] (NDA 21-178) is an oral antihyperglycemic combination product consisting of glyburide and metformin hydrochloride. The product is available in tablet form containing 1.25mg glyburide/250mg metformin, 2.5mg glyburide/500mg metformin, or 5mg glyburide/500mg metformin. Glucovance[®] was approved on July 31, 2000 for initial therapy of adult patients with type 2 diabetes uncontrolled by diet and exercise alone, or for second-line therapy in patients who do not achieve adequate control with diet, exercise and treatment with a sulfonylurea or metformin. According to the approved labeling of March, 2004; the recommended starting dose for initial therapy in adults is one 1.25/250mg tablet once daily increasing up to the minimum effective dose necessary to achieve adequate blood glucose control. In clinical trials of Glucovance[®] as initial therapy there was no experience with total daily doses greater than 10mg/2000mg daily. The recommended starting dose for second-line therapy in adults is 2.5mg/500mg or 5mg/500mg twice a day to a maximum of 20mg/2000mg daily. On March 15, 2004, Glucovance[®] was approved for use in the pediatric population under NDA 21-178/S-007. The revised label included a summary of a 26-week randomized trial, which found no statistically significant superiority of Glucovance[®] treatment in 167 pediatric patients when compared to metformin and glyburide alone. In addition, no unexpected safety findings were associated with Glucovance[®] in this trial.

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Glucovance[®] (NDA 21-178) on October 8, 2003.

This review describes outpatient drug usage of Glucovance[®] in the pediatric population as compared to the adult population. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

DATA SOURCES

This review describes the annual sales and drug use patterns of Glucovance[®] in the pediatric population as compared to the adult population in several years before and one year after the granting of pediatric exclusivity. Proprietary drug use databases licensed by the Agency were used to conduct this analysis. The data sources for this analysis are described in detail below.

IMS HEALTH, NATIONAL PRESCRIPTION AUDIT PLUS™ (NPA PLUS™)

NPA Plus™ measures the retail dispensing of prescriptions, or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. These retail pharmacies include chain, independent, food store, mail order, discount houses, and mass merchandiser pharmacies, as well as nursing home (long-term care) pharmacy providers. Information on the specialty of the prescribing physician can also be collected, except for in the long-term care and mail order pharmacy settings.

The number of dispensed prescriptions is obtained from a sample of approximately 22,000 pharmacies throughout the U.S. and projected nationally. The pharmacies in the database account for approximately 40% of all pharmacy stores and represent approximately 45% of prescription coverage in the U.S.

Data for this analysis included all prescriptions dispensed from November 1, 2001 – October 31, 2004 inclusive.

IMS HEALTH, NATIONAL SALES PERSPECTIVES™

IMS Health National Sales Perspectives™ measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into retail and non-retail markets. The volume of drug products transferred to these markets is expressed in terms of sales dollars, vials, and market share. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. These data are based on national projections.

For this analysis, the sales trend for Glucovance® was examined from November 1, 2000 – October 31, 2004 inclusive (the most current data available at the time of this analysis).

CAREMARK™

Caremark is one of the largest pharmacy benefit manager (PBM) companies in the US, currently covering over 70 million lives, and processing over 545 million prescription claims annually. FDA has access to Caremark's Dimension Rx™ database consisting of a subset of total Caremark paid claims representing 350 million claims per year for prescriptions filled in 57,000 pharmacies across the country. Participants whose claims are processed by Caremark are covered under various types of insurance plans, including health maintenance organizations (HMOs), employers' self-insured health plans, selected managed care plans, and other selected traditional health insurers. Caremark's Dimension Rx™ system represents participants from all 50 states and includes special populations such as the elderly, children, and women of childbearing age. The representativeness of those included in Caremark's Dimension Rx™ system to all persons receiving dispensed prescriptions in the U.S., however, is not known.

For this analysis, prescription claims in the Caremark Dimension Rx™ system were examined from November 1, 2001 – October 31, 2004 inclusive.

IMS HEALTH, NATIONAL DISEASE AND THERAPEUTIC INDEX™ (NDTI™)

The National Disease and Therapeutic Index™ (NDTI™) is an ongoing survey designed and conducted by IMS Health to provide descriptive information on the patterns and treatment of disease encountered in office-based practices in the continental U.S. The data are collected from a panel of approximately 3,000 office-based physicians who complete and submit a survey of their practice patterns to IMS Health for two consecutive days per quarter. These data may include profiles and trends of diagnoses, patients, drug products mentioned, and treatment patterns. These data are projected nationally to reflect national prescribing patterns.

NDTI™ uses the term drug uses for mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a drug use does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

For this analysis, we examined annual mentions of Glucovance® during office-based physician visits during the time period from November 1, 2001 – October 31, 2004 inclusive.

RESULTS

I. Sales and Distribution Channels

Sales of Glucovance® were examined from November 2000 through October 2004. Retail channels are the largest purchasers of Glucovance®, representing at least 91% of the total sales of Glucovance® in each of the four one-year periods of this analysis. Total sales of Glucovance® increased by a relative 31% over the 4 years of this analysis from 331 million tablets sold during November 2000 – October 2001, peaked during November 2002 – October 2003 at 656 million tablets sold, then declined to 432 million tablets sold during November 2003 – October 2004 (Table 1). Compared to the pre-exclusivity period (November 2002 – October 2003), sales in the post exclusivity period (November 2003 – October 2004) declined by 34% from 656 million tablets to 432 million tablets sold.

The decrease in Glucovance sales was likely due to the introduction of two generic products in 2004. The generic products had 252 million tablets sold during November 2003 – October 2004 which represented 37% of brand and generic glyburide/metformin sales during November 2003 – October 2004. Sales of the brand and generic products combined increased by two fold over the 4 years of this analysis from 331 million tablets sold during November 2000 – October 2001 to 685 million tablets sold during November 2003 – October 2004. Sales of brand and generic products increased by 4% from the pre-exclusivity period (November 2002 – October 2003) to the post exclusivity period (November 2003 – October 2004).

Table 1. Total Number of Tablets (in thousands) of Glucovance® and Glyburide/Metformin Sold to U.S. Distribution Channels During November 2000 - October 2004

	November 2000 - October 2001		November 2001 - October 2002		November 2002 - October 2003		November 2003 - October 2004		Percent Change November 2000 - October 2004 %
	N (%)		N (%)		N (%)		N (%)		
Glucovance	331,096	(100)	585,152	(100)	655,523	(100)	432,354	(100)	31
Retail*	309,390	(93)	544,715	(93)	609,308	(93)	392,576	(91)	27
Non-Retail**	21,705	(7)	40,437	(7)	46,215	(7)	39,778	(9)	83
Glyburide/Metformin (Generic)							252,378		
Retail*							247,045	(98)	
Non-Retail**							5,333	(2)	
Total	331,096		585,152		655,523		684,732		107
Retail*	309,390	(93)	544,715	(93)	609,308	(93)	639,621	(93)	107
Non-Retail**	21,705	(7)	40,437	(7)	46,215	(7)	45,111	(7)	108

* Retail includes chain, independent, mail order, long term care and food store pharmacies

**Non-retail includes Non-federal hospitals, federal facilities, clinics, HMOs, home health care, prisons, universities, and other

IMS Health, National Sales Perspectives™ Combined, Data Extracted 01-2005

(File:NSPC Glucovance® 01-05 Sales Channels 0501glu2.xls)

II. Dispensed Prescriptions

Outpatient prescriptions of all oral antidiabetic products combined increased by 10% during November 2001 – October 2004, rising from 97 million prescriptions dispensed in the 12-month period from November 2001 – October 2002 to 107 million prescriptions in the 12-month period from November 2003 – October 2004 (Table 2). Antidiabetic combination products accounted for 6.7% (6.5 million prescriptions) and 9.2% (9.9 million prescriptions) of all prescriptions dispensed for oral antidiabetic products during November 2001 – October 2002 and November 2003 – October 2004, respectively. During the 3 years of this analysis, prescriptions for all oral antidiabetic combination products increased by a relative 52%.

Glucovance® was the most commonly dispensed product compared to other oral antidiabetic combination products in this analysis, accounting for 7 million (86% of the prescriptions for oral antidiabetic combination products) and 4.4 million (45% of the prescriptions for oral antidiabetic combination products) prescriptions dispensed during November 2002-October 2003 and November 2003 – October 2004, respectively. A generic glyburide/metformin product was introduced in February 2004 and accounted for 2.4 million prescriptions (24% of the prescriptions for oral antidiabetic combination products) dispensed during November 2003 – October 2004 and likely contributed substantially to the decline in Glucovance® prescriptions. The combined number of prescriptions dispensed for the brand and generic products totaled over 6.8 million prescriptions and accounted for approximately 68.9% of the market share for antidiabetic combination products. Taken together, this represented a 2% decline in dispensed

prescriptions for the combination glyburide/metformin products during the post exclusivity period.

Table 2: Total Number of Prescriptions Dispensed (in thousands) in Retail Pharmacies Nationwide for Oral Anti-Diabetic Products During November 2001 – October 2004

	November 2001 - October 2002		November 2002 - October 2003		November 2003 - October 2004	
	N	(%)	N	(%)	N	(%)
Total oral antidiabetic products	97,382	(100)	102,300	(100)	107,323	(100)
Insulin secretagogues	40,223	(41)	39,916	(39)	39,956	(37)
Biguanides	32,358	(33)	34,417	(34)	36,543	(34)
Insulin Sensitizers	17,645	(18)	19,300	(19)	20,356	(19)
Combination Diabetes Therapy	6,519	(7)	8,076	(8)	9,900	(9)
Glucovance	6,519		6,969		4,429	
Avandamet	00		804		2,556	
Glyburide/Metformin (generic)	00		00		2,393	
Metaglip	00		303		522	
Alpha-glucosidase inhibitors	636	(1)	591	(1)	566	(1)

IMS Health, NPA *Plus*™ data extracted 11-2004 (File: NPA Glucovance® 11-04 TRx Market 0411glu1.xls)

The top two prescriber specialties prescribing Glucovance® from November 2003 through October 2004 were internal medicine and family practice (Table 3). Of all specialties, pediatricians were ranked 13th in prescribing Glucovance® during this period and accounted for less than 1% of the prescriptions dispensed in each of the 3 one-year periods of this analysis. In general, prescribing patterns for Glucovance® dispensed in outpatient retail pharmacy settings showed no substantial change across provider specialties during the 36-month study period.

Table 3: Total Number of Prescriptions Dispensed for Glucovance® Nationwide by Physician Specialty (excludes Mail Order and Long Term Care) During November 2001 – October 2004

Prescriber specialty	November 2001 - October 2002		November 2002 - October 2003		November 2003 - October 2004	
	N	(%)	N	(%)	N	(%)
All prescribers	5,947	(100)	6,288	(100)	3,976	(100)
Internal Medicine	2,109	(35)	2,230	(35)	1,431	(36)
Family Practice	1,763	(30)	1,894	(30)	1,194	(30)
Osteopathic Medicine	601	(10)	629	(10)	386	(10)
Endocrinology	349	(6)	341	(5)	214	(5)
General Practice	222	(4)	228	(4)	143	(4)
Other Practices (46)	905	(15)	962	(15)	607	(15)

IMS Health NPA *Plus*™ Data extracted 11-2004 (file: NPA Glucovance® 11-04 MD specialty 0411glu3.xls)

III. Patient Demographics

Among a large, insured population managed by Caremark, pediatric participants age 1-16 years accounted for no more than 0.06% of the claims for oral antidiabetic products in each of the 3 one-year periods from November 2001 – October 2004¹. Due to the low use of Glucovance in participants age 1-16 years, we were unable to obtain a reliable national estimate of the number of prescriptions dispensed to this population.

The most common diagnosis associated with a mention of Glucovance[®] in office based physician-patient encounters was diabetes without complications (ICD-9 250.0) which accounted for 96% of mentions during the pre-exclusivity period (November 2002 – October 2003) and 97% of mentions during the post-exclusivity (November 2003 – October 2004) period (Table 4). Due to the small number of visits, we were not able to analyze the diagnoses associated with members in the pediatric population.

Table 4. Top Diagnoses Associated with Mentions of Glucovance[®] (in thousands) for Pediatric and Adult Patients Combined During November 2001 - October 2004

ICD-9 Code	November 2001 - October 2002	November 2002 - October 2003	November 2003 - October 2004
	N (%)	N (%)	N (%)
Glucovance[®] Total Uses*	2,870 (100.0)	3,311 (100.0)	2,775 (100.0)
250.0 Diabetes mellitus w/o Complications	2,810 (97.9)	3,186 (96.2)	2,699 (97.3)
250.8 Diabetes with Other Specified Manifestations	7 (0.3)	04 (0.1)	14 (0.5)
250.6 Diabetes with Neurological Manifestations	4 (0.1)	38 (1.2)	12 (0.4)
790.2 Abnorm Glucose Tolerance Test	--- ---	14 (0.4)	12 (0.4)
277.7 Dysmetabolic Syndrome X	--- ---	45 (1.3)	11 (0.4)

IMS National Disease and Therapeutic IndexTM, November 2001 - October 2004. Data extracted 12-2004 (File NDTI Glucovance[®] d030616 diags.dvw)

*The combination product glyburide-metformin did not appear in this database.

DISCUSSION

Based on the databases used for this consult, sales of Glucovance[®] to retail and non-retail channels combined increased by 31% over the 4 years from November 2000 through October 2004. Yet, sales in the post exclusivity period (November 2003 - October 2004) declined by 34% compared to the pre-exclusivity period (November 2002 - October 2003). The decline was likely due to a market shift to the generic glyburide/metformin product which was introduced on February 2004. The generic products and accounted for 37% of the total sales of brand and generic products combined during November 2003 – October 2004. Sales of brand and generic products combined increased by 4% from the pre-exclusivity period (November 2002 – October 2003) to the post exclusivity period (November 2003 – October 2004.)

¹ Caremark Dimension RxTM-Data Extracted 11-2004 (file: APCS Glucovance[®] by age 11-04.xls)

Outpatient prescriptions of all oral antidiabetic products combined increased by 10% during November 2001 - October 2003. The increase in the prescriptions for oral antidiabetic products is consistent with studies reporting an increase in the prevalence of type 2 diabetes in the U.S.^{2,3}

Glucovance[®] and its generic version appears to be the most commonly dispensed oral antidiabetic combination product in this analysis. Nonetheless, antidiabetic combination products consist of only about 10% of all prescriptions dispensed for oral antidiabetic products during November 2003 - October 2004. The two major prescriber specialties for Glucovance[®] were internal medicine and family practice. Pediatricians accounted for less than 1% of the prescriptions dispensed during the study period. In general, prescribing patterns for Glucovance[®] dispensed in outpatient retail pharmacy settings showed no substantial change across provider specialties during the 36-month study period. The use of this product appears to be almost exclusively in the adult population.

Findings from this consult should be interpreted in the context of the known limitations of the databases used. NPA Plus[™] data provide an estimate of the total number of prescriptions dispensed in the U.S. However, NPA Plus[™] does not include complete historical demographic information, such as age and gender. The inclusion of prescriber specialty data in this report does not include mail order and long-term care channels.

NDTI[™] data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly when use is not prevalent in the pediatric population, as in the case of Glucovance[®].

Caremark Dimension Rx[™] data cannot be projected to provide national estimates, but its large sample size can be helpful for replicating demographic findings in IMS Health's NDTI[™], where sample sizes are often small. Although the data from Caremark's Dimension Rx[™] system may not be nationally representative, they provide a useful description of prescription drug use in the U.S. for a large proportion of the population with prescription drug coverage. Estimates of the number of prescriptions dispensed nationally to pediatric populations based on the proportion dispensed to pediatric participants in the Caremark Dimension Rx[™] system are dependent upon the assumption that these patterns are similar across populations with and without prescription drug coverage. The accuracy of this assumption is not known at this time. In addition, reliable information for participants less than the age of 1 year is not available from this data source.

CONCLUSION

The outpatient prescriptions of all oral antidiabetic products combined increased by 10% during the two 12-month periods November 2001 – October 2002 and November 2003 - October 2004.

² Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the United States. *JAMA* 2001; 286(10):1195-1200.

³ Gregg EW, Cadwell BL, Cheng YJ, Cowie CC, Williams DE, Geiss L et al. Trends in the prevalence and ratio of diagnosed to undiagnosed diabetes according to obesity levels in the U.S. *Diabetes Care* 2004; 27(12):2806-2812.

Glucovance[®] and its generic version appears to be the most commonly dispensed oral antidiabetic combination product in this analysis. The combined number of prescriptions dispensed for the brand and generic products totaled over 6.8 million prescriptions and accounted for approximately 68.9% of the market share for antidiabetic combination products during November 2003 - October 2004. Taken together, this represented a 2% decline in dispensed prescriptions for the combination glyburide/metformin products during the post exclusivity period (November 2003 - October 2004), compared to the pre-exclusivity period (November 2002 - October 2003). Nonetheless, antidiabetic combination products consist of approximately 10% of all prescriptions dispensed for oral antidiabetic products during November 2003 - October 2004.

The two major prescriber specialties for Glucovance[®] were internal medicine and family practice. Pediatricians accounted for less than 1% of the prescriptions dispensed during the study period. The use of this product appears to be almost exclusively in the adult population.

Among a large, insured population managed by Caremark, pediatric participants age 1-16 years accounted for no more than 0.06% of the claims for oral antidiabetic products in each of the 3 one-year periods from November 2001 – October 2004⁴. Due to the low use of Glucovance in participants age 1-16 years, we were unable to obtain a reliable national estimate of the number of prescriptions dispensed to this population.

The most common diagnosis associated with a mention of Glucovance[®] in office based physician-patient encounters was diabetes without complications (ICD-9 250.0) which accounted for 96% of mentions during the pre-exclusivity period (November 2002 - October 2003) and 97% of mentions during the post-exclusivity period (November 2003 - October 2004).

⁴ Caremark Dimension RxTM.-Data Extracted 11-2004 (file: APCS Glucovance[®] by age 11-04.xls)

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