Title: Evaluation of Glucose Administration Recommendation in Bioequivalence Studies to Support Generic Oral Antidiabetic Drug Development

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BACKGROUND

Several classes of oral antidiabetic drugs (OADs) have been approved in the U.S. One of the most common adverse events of OADs is hypoglycemia. These OADs have different mechanisms of action (MOA) and thus the risk of hypoglycemia varies. Prevention of hypoglycemia is important, particularly for the protection of healthy subjects participating in bioequivalence (BE) studies who may be at a greater risk for hypoglycemia than those who require treatment with OADs. Product-specific guidances (PSGs)[1] for OADs generally recommend administration of glucose to reduce the risk of hypoglycemia in BE study subjects irrespective of MOA of OADs. The current study aimed to derive a risk-based recommendation for glucose administration in PSGs of OADs.

METHODS

We investigated the in-house data of four classes of OADs from generic drug applications and collected the following information: glucose administration recommendation in PSGs; study designs; actual glucose administration; and hypoglycemia events in BE studies.
For studies with hypoglycemic events, we further explored whether a high pre-dose blood glucose concentration (BGC) (>90 mg/dL) would avoid hypoglycemia events. We defined hypoglycemia as a BGC of ≤60 mg/dL.

RESULTS

The incidence rates of hypoglycemia as observed in BE studies for four drug classes are presented in **Table 1**. It should be noted that this does not represent the complete landscape for OADs because certain classes have not been fully investigated.

For the evaluation of the impact of pre-dose BGC on hypoglycemia incidence, we analyzed BE studies that reported pre-dose BGC and post-dose BGC.

- Products in **Table 1** were excluded for further analysis if they do not contain all the needed data.
- Products were not included in the data analysis if subjects were given lollipops when the BGC dropped below 80 mg/dL.
- Three product drug applications (from different classes of OADs) containing all the needed information were further analyzed with results presented in **Tables 2 & 3**.

Table 1. Incidence rate of hypoglycemia* in BE studies with different levels of glucose administration for the investigated drug products

OAD Class	Dosage Form	Glucose Administered, g	% of Subjects with Hypoglycemia
Biguanide	Extended release (ER) & Immediate release (IR) tablet	0	7.7
		240	0.0 ~ 0.6
DPP-4 inhibitor	IR tablet	0	0.0 ~ 10.8
		96 ~ 240	0.0 ~ 3.6
Thiazolidinedione	IR tablet	240	0.3
		48	2.2
Sulfonylurea	IR tablet	240	0.0

**Incidence of hypoglycemia is defined by clinical investigators of each application.*

Table 2. Comparison of incidence rates of hypoglycemia (BGC ≤60 mg/dL) in subjects with different pre-dose BGC in BE studies with no glucose administration

Product	Product A	
Dose	Dose 1	
Pre-dose BGC (mg/dL)	≤90	>90
% Subjects with post-dose BGC ≤60 mg/dL**	3.7	0.0

*** Note: post-dose BGCs were measured for a time period of 3 hours to 12 hours following dosing.*

Table 3. Comparison of incidence rates of hypoglycemia (BGC ≤60 mg/dL) in subjects with different pre-dose BGC in BE studies with 240 g glucose administration

Product	Product B				Product C	
Dose	Dose 2		Dose 3		Dose 4	
Pre-dose BGC (mg/dL)	≤90	>90	≤90	>90	≤90	>90
% Subjects with post-dose BGC ≤60 mg/dL	5.8	5.3	3.3	2.9	20.8	6.3

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RESULTS

- Our study suggested that for the limited number of products that we investigated, the incidence rate of hypoglycemia tended to be lower in BE studies enrolling healthy subjects who had co-administration of 240 g glucose compared with the studies enrolling healthy subjects with lower than co-administration of 240 g or no glucose administration, irrespective of MOA of OADs.
- The data suggested that having a higher pre-dose BGC (>90 mg/dL) may decrease the risk for hypoglycemic events in healthy subjects enrolling in BE studies and the relative decreased risk may be dependent on MOA of OADs.

CONCLUSIONS

- Given the observed varied risk of hypoglycemia, MOA-based glucose administration may be recommended for BE studies with different classes of OADs.
- Selecting study subjects based on their baseline glucose in blood may be an alternative to reduce hypoglycemia risk based on MOA of OADs.

REFERENCE:

1.FDA Product-Specific Guidance Database: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

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