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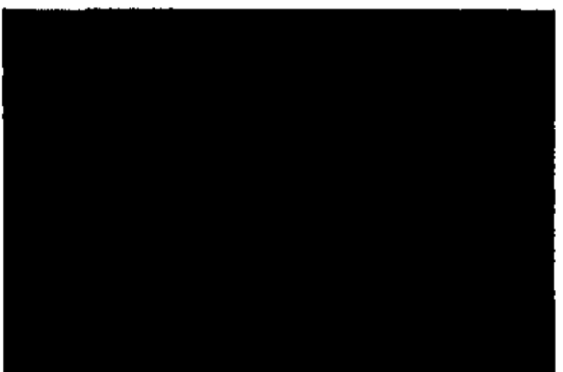
Pharmaceuticals and Medical Devices Agency

Revisions of the Precautions in the Package Insert of Blood Glucose Meters, etc.

1. Blood Glucose Meters

Blood glucose levels are measured using a combination of in vitro diagnostics for blood glucose measurements and blood glucose meters. In vitro diagnostics for blood glucose measurements include glucose assay kits for blood tests and glucose assay kits for self-monitoring; blood glucose meters include glucose analyzers, automated analyzers, and self-monitoring blood glucose (SMBG) meters. The measurement principles for blood glucose are as shown in Table 1.

Hereinafter, the following medical devices and in vitro diagnostics for blood glucose measurements are referred to as “blood glucometers, etc.”

		
SMBG Meters + Glucose assay kits for self-monitoring	Glucose analyzers + Glucose assay kits for blood tests	Automated analyzers + Glucose assay kits for blood tests

<Table 1> Measurement Principles for Blood Glucose

Type of Measurement Principles	
Enzymatic electrodes	Glucose oxidase (GOD) method
	Glucose dehydrogenase (GDH) method
Enzyme colorimetric assays	Hexokinase (HX) method
	Glucose oxidase/peroxidase (GOD/POD) method

Cases of observed false high values have been reported when measuring blood glucose levels using blood glucose meters, etc. in patients who are being administered pralidoxime methyl iodide (PAM-I). Validation results suggest that errors in blood glucose measurements dependent on PAM concentration occur because the ultraviolet absorption characteristics of PAM changes depending on pH in enzyme colorimetric assays and because the iodide ions within PAM-I molecules generate an electric signal due to the voltage load during measurement using enzymatic electrodes.

Based on these results, Pharmaceutical and Food Safety Bureau (PFSB)/Safety Division (SD) Notification No. 0907001 “Regarding Instructions on Revisions of the “Precautions” in the Package Insert of Blood Glucose Meters” (Material 1) was issued for blood glucose meters, and PFSB/SD Notification No. 0907003 “Regarding Revisions of the “Precautions” in the Package Inserts” (Material 2) was issued for in vitro diagnostics for blood glucose measurements and PAM-I. Both notifications were issued in September 2007. In accordance with these notifications, “Higher values than actual blood glucose levels may be seen in patients being administered pralidoxime iodide” was added to the Warning section of package inserts for blood glucose meters, etc., while “Important Precautions” section was newly

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added to the package insert of PAM-I. "Higher values than actual blood glucose levels may be seen in patients being administered this product" was added to the Important Precautions section.

2. Current cases reported

1) Research report

There was a research report on the influence of PAM-I on in vitro diagnostics for blood glucose measurements in May 2013 by XXXX (Product investigated: XXXX). Details of the report are as follows.

[Device Used]

POCT: Antsense II

SMBG: Glutest Every, Glutest Ace-R, Ascensia Breeze 2, OneTouch Ultra

[Details]

Glucose levels increased depending on the concentration of PAM-I added to the blood samples when measured with blood glucose meters using enzymatic electrodes. Furthermore, similar results were observed when potassium iodide (KI) was added to the blood samples. On the other hand, adding pralidoxime methyl chloride (PAM-Cl) or potassium chloride (KCl) to blood samples did not affect the measured glucose levels. Based on the above observations, iodide ions are considered to influence measurements of blood glucose meters using enzymatic electrodes¹⁾.

<Table 2> Influence of Drugs on Measured Values for Each Type of Blood Glucose Meter

	POCT (GOD method)	SMBG (GOD method)	Hitachi 7600 Enzyme colorimetric assay* ²
PAM-I	↑	↑	↑
KI	Cannot be measured* ¹	↑	No influence

*1 The specific membrane filter of the meter used influenced the values, and measurements could not be made.

*2 The reason why values of large-scale analyzers using enzyme colorimetric assays are influenced by PAM-I is that the PAM salts rather than the iodide ions influence the measured levels at wavelength 340 nm.

2) Malfunctions reported

In December 2013, there was a case report by XXXX that blood glucose levels measured using XXXX were different from the measured values using blood gas analyzers (XXXX). It was suggested that the cause of the differences was a false high value with XXXX due to contamination with residual iodine antiseptics on the patient's skin when collecting blood. Furthermore, an investigation revealed that, as cases similar to the reported malfunction, increased serum iodide concentrations were reported in patients with thermal burn due to the use of iodine antiseptics^{2) 3)}.

3. Future Safety Measures

Although past reports on false high values in actual clinical practice were found only in cases administered PAM-I, when considering the aforementioned research results and malfunction reports, further revisions to the package inserts of blood glucose meters, etc. is necessary to provide clearer information with regards to the risk of high false values due to iodide ions with blood glucose measurements using enzymatic electrodes.

On the other hand, according to the aforementioned research report, glucose measurements increased depending on serum iodide ion concentration, and it is considered that glucose measurements are not significantly affected when serum iodide ion concentrations are low. Given that injectable or oral drugs including iodine other than PAM-I are unlikely to influence glucose measurements based on the actual iodine content in the product or the dosage administered overall, it was considered that revisions in package inserts of drugs including iodine (injectables or orals) and caution when measuring blood glucose in patients using such products were unnecessary. Furthermore, based on the aforementioned malfunction reports, while topical preparations including iodine may influence glucose measurements by contaminating the blood sample, revisions to package inserts for such topical preparations was also considered unnecessary as this risk can be avoided by giving the alert regarding blood collection methods.

Given the above conclusions, it is considered desirable to instruct Marketing Authorization Holders dealing with blood glucose meters using enzymatic electrodes and in vitro diagnostics for blood glucose measurements to add the following description to package inserts as well as to alert medical institutions using such products to exercise caution.

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1) Glucose analyzers and SMBG meters that use enzymatic electrodes

- In the “Important Precautions” section in the Precautions in the package insert, the following text should be added:
Avoid collecting blood from sites using topical preparations that include iodine. [It may cause false high values.]

2) Automated analyzers, etc. that use enzymatic electrodes to measure blood glucose

- In the “Important Precautions” section in the Precautions in the package insert, the following text should be added:
Avoid collecting blood from sites using topical preparations that include iodine when measuring blood glucose. [It may cause false high values.]

3) In vitro diagnostics used when enzymatic electrodes are used to measure blood glucose

- In the “Operating Precautions” of the package insert, the following text should be added as an interfering substance:
If there is a substance that releases iodide ions in the measured sample, it may result in false high values.

[References]

1. Nagase S, et al. (2013). Interference by Pralidoxime (PAM) salts in clinical laboratory tests. *Clinica Chimica Acta*. 416, 72-79.
2. John L, et al. (1980). A Critical Evaluation of Povidone-iodine Absorption in Thermally Injured Patients. *The Journal of Trauma*. 20 (2), 127-129.
3. John P., Jonathan L.M. (1976). Complications of Povidone-iodine Absorption in Topically Treated Burn Patients. *The Lancet*. Feb.7, 280-282.