This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Summary of investigation results

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

September 15, 2015

Non-proprietary name

a. Canagliflozin hydrate
b. Dapagliflozin propylene glycolate hydrate
c. Empagliflozin
d. Ipragliflozin L-proline
e. Luseogliflozin hydrate
f. Tofogliflozin hydrate

Brand name (Marketing authorization holder)

a. Canaglu Tablets 100 mg (Mitsubishi Tanabe Pharma Corporation)
b. Forxiga Tablets 5 mg and 10 mg (AstraZeneca K.K.)
c. Jardiance Tablets 10 mg and 25 mg (Nippon Boehringer Ingelheim Co., Ltd.)
d. Suglat Tablets 25 mg and 50 mg (Astellas Pharma Inc.)
e. Lusefi Tablets 2.5 mg and 5 mg (Taisho Pharmaceutical Co., Ltd.)
f. Apleway Tablets 20 mg (Sanofi K.K.) and Deberza Tablets 20 mg (Kowa Company, Ltd.)

Indications

Type 2 diabetes mellitus

Summary of revision

1. Precautions regarding ketoacidosis should be added in the Important Precautions section for the above products from a to f.
2. “Ketoacidosis” should be newly added in the Clinically significant adverse reaction section for the above products from a to f.
3. “Sepsis” should be added to the “Pyelonephritis” subsection in the Important Precautions section for the above products from a to f.

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4. “Sepsis” should be added to the “Pyelonephritis” subsection in the Clinically significant adverse reaction section for the above products from a to f.
5. “Patients with urinary tract infection and/or genital infection” should be newly added in the Careful Administration section for the above products a to c.

Background of the revision and investigation results

- Ketoacidosis

Cases of ketoacidosis have been reported in patients treated with SGLT2 inhibitors in Japan. Following an investigation result based on the opinions of expert advisors and the available evidence, the MHLW/PMDA concluded that precautions that related ketoacidosis should be revised in the Important precautions and should be added in the Clinically adverse reaction section of the package insert was necessary.

- Sepsis

(1) Cases of sepsis from pyelonephritis have been reported in patients treated with some SGLT2 inhibitors in Japan, and (2) similar risks are assumed in the same class of drugs given the mechanism of action of SGLT2 inhibitors. Following an investigation result based on the opinions of expert advisors and the available evidence, the MHLW/PMDA concluded that precautions related to sepsis should be revised in the Important precautions and Clinically significant adverse reaction section of all package inserts and that “patients with urinary tract and/or genital infection” should be added to the Careful Administration section for package inserts that do not already note this.

The number of reported adverse reactions and fatal cases in the last 3 fiscal years in Japan

- Ketoacidosis associated cases
  a. Canagliflozin hydrate
     A total of 4 cases associated with ketoacidosis have been reported (including 2 cases for which a causal relationship to the product could not be ruled out; however, 1 case was for a condition not included in the approved indications). No fatality has been reported.
  b. Dapagliflozin propylene glycolate hydrate
     A total of 7 cases associated with ketoacidosis have been reported (including 5

cases for which a causal relationship to the product could not be ruled out; however, 1 case was for a condition not included in the approved indications). No fatality has been reported.

c. Empagliflozin

A case associated with ketoacidosis has been reported (a causal relationship to the product could not be established for this patient). No fatality has been reported.

d. Ipragliflozin L-proline

A total of 15 cases associated with ketoacidosis have been reported (including 9 cases for which a causal relationship to the product could not be ruled out). No fatality has been reported.

e. Luseogliflozin hydrate

A case associated with ketoacidosis has been reported (a causal relationship to the product could not be ruled out for this patient). No fatality has been reported.

f. Tofogliflozin hydrate

A total of 5 cases associated with ketoacidosis have been reported (including 2 cases for which a causal relationship to the product could not be ruled out). No fatality has been reported.

- Sepsis associated cases

a. Canagliflozin hydrate

No case associated with sepsis has been reported.

b. Dapagliflozin propylene glycolate hydrate

A total of 5 cases associated with sepsis have been reported (including 3 cases for which a causal relationship to the product could not be ruled out). No fatality has been reported.

c. Empagliflozin

No case associated with sepsis has been reported.

d. Ipragliflozin L-proline

A total of 8 cases associated with sepsis have been reported (including 6 cases for which a causal relationship to the product could not be ruled out). No fatality has been reported.

e. Luseogliflozin hydrate

No case associated with sepsis has been reported.

f. Tofogliflozin hydrate

A total of 3 cases associated with sepsis have been reported (including 3 cases for which a causal relationship to the product could not be ruled out). No fatality has been reported.