



Summary of investigation results

Sodium-glucose co-transporter 2 (SGLT2)

Inhibitors and combination products

containing SGLT2 inhibitors

May 9, 2019

Non-proprietary name

- a. Ipragliflozin L-proline
- b. Dapagliflozin propylene glycolate hydrate
- c. Tofogliflozin hydrate
- d. Luseogliflozin hydrate
- e. Canagliflozin hydrate
- f. Empagliflozin
- g. Teneligliptin hydrobromide hydrate/canagliflozin hydrate
- h. Sitagliptin phosphate hydrate/ipragliflozin L-proline
- i. Empagliflozin/linagliptin

Branded name (Marketing authorization holder)

- a. Suglat Tablets 25 mg, 50 mg (Astellas Pharma Inc.)
- b. Forxiga Tablets 5 mg, 10 mg (AstraZeneca K.K.)
- c. Apleway Tablets 20 mg (Sanofi K.K.), Deberza Tablets 20 mg (Kowa Company, Ltd.)
- d. Lusefi tab. 2.5 mg, 5 mg (Taisho Pharmaceutical Co., Ltd.)
- e. Canaglu Tablets 100 mg (Mitsubishi Tanabe Pharma Corporation)
- f. Jardiance Tablets 10 mg, 25 mg (Boehringer Ingelheim Japan, Inc.)
- g. Canalia Combination Tablets (Mitsubishi Tanabe Pharma Corporation)
- h. Sujanu Combination Tablets (MSD K.K.)
- i. Tradiance Combination Tablets AP, BP (Boehringer Ingelheim Japan, Inc.)



Indications

a, b

Type 2 diabetes mellitus, Type 1 diabetes mellitus

c – f

Type 2 diabetes mellitus

g

Type 2 diabetes mellitus, but only if treatment with co-administration of teneligliptin hydrobromide hydrate and canagliflozin hydrate is considered appropriate.

h

Type 2 diabetes mellitus, but only if treatment with co-administration of sitagliptin phosphate hydrate and ipragliflozin L-proline is considered appropriate.

i

Type 2 diabetes mellitus, but only if treatment with co-administration of empagliflozin and linagliptin is considered appropriate.

Summary of revision

1. A cautionary statement regarding Necrotising fasciitis of the external genitalia or perineum (Fournier's gangrene) should be added to the language concerning urinary tract infection and genital infection in the Important Precautions section.
2. "Necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene)" should be added to the Clinically Significant Adverse Reactions section.

Investigation results and background of the revision

MHLW/PMDA concluded that a cautionary statement regarding necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) should be added based on the results of their investigation of the currently available evidence and in consultation with expert advisors, taking into consideration the following:

- A case of Fournier's gangrene for which a causal relationship with SGLT2 inhibitors could not be ruled out has been reported in Japan.
- Cases of this event observed following administration of SGLT2 inhibitors have been reported overseas.
- The disproportionality analysis using the WHO Individual Case Safety Reports (ICSRs)



Global Database (VigiBase)* statistically shows higher numbers of adverse reaction of Fournier's gangrene or necrotising fasciitis reported for multiple SGLT2 inhibitors (in patients treated with dapagliflozin, canagliflozin, or empagliflozin) than would be expected for the entire database. On the other hand, data from other antidiabetic drugs have not shown such a trend†.

- Although the mechanism of necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) when SGLT2 inhibitors are administered has not been elucidated, the pharmacological effect of SGLT2 inhibitors (the action that promotes glucose excretion into urine) cannot be ruled out.

*The information comes from a variety of sources, and the probability that the suspected adverse reaction is drug-related is not the same in all cases.

†The information does not represent the opinion of the Uppsala Monitoring Centre or the World Health Organization.

Number of adverse reactions and patient mortalities reported in Japan during the previous 3 fiscal years

a to e, and, g to i

No cases involving necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) have been reported to date.

f

One case involving necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) has been reported to date. (A causal relationship to the product could not be ruled out in this case.)

No patient mortalities have been reported to date.