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藥物不良反應工作小組藥物安全警訊通告 107.09

美國食品藥物管理署(FDA)用藥安全資訊風險溝通：SGLT-2抑制劑可能引起罕見的嚴重生殖器感染之風險

摘要說明：

美國食品藥物管理署(FDA)提出警告，用於治療第二型糖尿病的 SGLT-2 抑制劑有可能會發生罕見的嚴重生殖器感染，亦稱為會陰部壞死性筋膜炎或福耳尼埃氏壞疽(Fournier's gangrene)。此藥物不良反應的進程很快，病患若於生殖器區域會感到紅腫、壓痛，甚至發燒，應立即就醫，給予廣效性抗生素，並視情況執行外科清創手術。

於 FAERS 資料庫裡，自 2013 年 3 月至 2018 年 5 月已經發生 12 例的案件(7 男，5 女)，多為服用數月後(平均 9.2 個月)，皆住院治療並接受外科手術，其中一名病患死亡。糖尿病本身即為發生 Fournier's gangrene 的危險因子，調查 1984-2018 年間有另外 Fournier's gangrene 的 6 位男性案例，與近年發生的情況相比，SGLT-2 抑制劑導致的藥物不良反應較為明顯，但是其統計上的意義仍為有限。

目前 SGLT-2 抑制劑的成份有 dapagliflozin、ertugliflozin、canagliflozin 及 empagliflozin，本院使用的產品為 Forxiga®(Dapagliflozin)，於仿單中於警示及注意事項和不良反應項目亦有說明 Forxiga® 有增加泌尿道感染及生殖器黴菌感染的風險，於臨床試驗中男女生殖器黴菌感染佔不良反應的百分比分別為 1.5%及 0.3%，女性主要為外陰陰道黴菌感染，男性主要為龜頭炎。此藥物不良反應與會陰部壞死性筋膜炎不同，不會發燒或感到全身不適，但是會有生殖器分泌物異常、紅癢的症狀。

SGLT-2 抑制劑以減少葡萄糖再吸收而達到降血糖甚至減輕體重的目的。但是會使尿液變成微生物喜歡的環境，這導致泌尿道和生殖器感染的風險明顯上升，故在使用本類藥品時應衛教病患適量補充水分，特別在夏季時。

醫療人員注意事項：

1) 醫療人員應提醒病患若發現從生殖器至肛門區域感到紅腫、壓痛，甚至發燒>38℃、全身無力時應立即就醫，若懷疑為嚴重生殖器感染，應給予廣效性抗生素並視情況執行外科清創手術。
2) 病患若因藥物不良反應停藥，應密切監測病患血糖指數並選擇其他類降血糖藥物控制，同時注意病患有可能會發生其他併發症的風險。
3) 醫療人員若懷疑病人因為使用藥品導致不良反應發生時，請立即線上通報藥物不良反應及登入於藥物過敏/不良反應記錄中。

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Drug Safety Communications

FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes

Safety Announcement

[8-29-2018] The U.S. Food and Drug Administration (FDA) is warning that cases of a rare but serious infection of the genitals and area around the genitals have been reported with the class of type 2 diabetes medicines called sodium-glucose cotransporter-2 (SGLT2) inhibitors. This serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene. We are requiring a new warning about this risk to be added to the prescribing information of all SGLT2 inhibitors and to the patient Medication Guide.

SGLT2 inhibitors are FDA-approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes. SGLT2 inhibitors lower blood sugar by causing the kidneys to remove sugar from the body through the urine. First approved in 2013, medicines in the SGLT2 inhibitor class include canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin (see FDA-Approved SGLT2 Inhibitors). In addition, empagliflozin is approved to lower the risk of death from heart attack and stroke in adults with type 2 diabetes and heart disease. Untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease.

Patients should **seek medical attention immediately** if you experience any symptoms of tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, and have a fever above 100.4 F or a general feeling of being unwell. These symptoms can worsen quickly, so it is important to seek treatment right away.

Health care professionals should assess patients for Fournier's gangrene if they present with the symptoms described above. If suspected, start treatment immediately with broad-spectrum antibiotics and surgical debridement if necessary. Discontinue the SGLT2 inhibitor, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Fournier's gangrene is an extremely rare but life-threatening bacterial infection of the tissue under the skin that surrounds muscles, nerves, fat, and blood vessels of the perineum. The bacteria usually get into the body through a cut or break in the skin, where they quickly spread and destroy the tissue they infect. Having diabetes is a risk factor for developing Fournier's gangrene; however, this condition is still rare among diabetic patients. Overall published literature about the occurrence of Fournier's

gangrene for men and women is very limited. Publications report that Fournier's gangrene occurs in 1.6 out of 100,000 males annually in the U.S., and most frequently occurs in males 50-79 years (3.3 out of 100,000).[1-3] In our case series, however, we observed events in both women and men.

In the five years from March 2013 to May 2018, we identified 12 cases of Fournier's gangrene in patients taking an SGLT2 inhibitor. This number includes only reports submitted to FDA* and found in the medical literature,[4-6] so there may be additional cases about which we are unaware. In 2017, an estimated 1.7 million patients received a dispensed prescription for an SGLT2 inhibitor from U.S. outpatient retail pharmacies.[7] Although most cases of Fournier's gangrene have previously been reported in men, our 12 cases included 7 men and 5 women. Fournier's gangrene developed within several months of the patients starting an SGLT2 inhibitor and the drug was stopped in most cases. All 12 patients were hospitalized and required surgery. Some patients required multiple disfiguring surgeries, some developed complications, and one patient died. In comparison, only six cases of Fournier's gangrene (all in men) were identified in review of other antidiabetic drug classes over a period of more than 30 years.

To help FDA track safety issues with medicines, we urge patients and health care professionals to report side effects involving SGLT2 inhibitors or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

*The cases were reported to the FDA Adverse Event Reporting System (FAERS).

FDA-Approved SGLT2 Inhibitors

Brand Name	Active Ingredient(s)
Invokana	canagliflozin
Invokamet	canagliflozin and metformin
Invokamet XR	canagliflozin and metformin extended-release
Farxiga	dapagliflozin
Xigduo XR	dapagliflozin and metformin extended-release
Qtern	dapagliflozin and saxagliptin
Jardiance	empagliflozin
Glyxambi	empagliflozin and linagliptin
Synjardy	empagliflozin and metformin
Synjardy XR	empagliflozin and metformin extended-release
Steglatro	ertugliflozin
Segluromet	ertugliflozin and metformin
Steglujan	ertugliflozin and sitagliptin

Facts about SGLT2 Inhibitors

- SGLT2 inhibitors are a class of prescription medicines approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes.

- Medicines in the SGLT2 inhibitor class include canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. They are available as single-ingredient products and also in combination with other diabetes medicines such as metformin (see FDA-approved SGLT2 Inhibitors).
- SGLT2 inhibitors lower blood sugar by causing the kidneys to remove sugar from the body through the urine.
- Common side effects of SGLT2 inhibitors include yeast infections, urinary tract infections, and low blood sugar when combined with other prescription diabetes medicines.
- In 2017, an estimated 1.7 million patients received a dispensed prescription for an SGLT2 inhibitor from U.S. outpatient retail pharmacies.[7]

Additional Information for Patients

- Cases of a rare but serious infection of the genitals and areas around them have been reported with the class of type 2 diabetes medicines called sodium-glucose cotransporter-2 (SGLT2) inhibitors. This serious condition, called necrotizing fasciitis of the perineum or Fournier's gangrene, can progress quickly and must be treated immediately because it can cause severe damage to the tissues around the genital area.
- Seek medical attention immediately if you experience any symptoms of tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, and have a fever above 100.4 F or a general feeling of being unwell. These symptoms can worsen quickly.
- SGLT2 inhibitors can also cause local genital fungal infections, also known as yeast infections. Yeast infections are different from necrotizing fasciitis of the perineum (Fournier's gangrene) because they cause limited local symptoms like vaginal or penile discharge, itching, or redness, and are not associated with fever or generally feeling unwell.
- Read the patient Medication Guide every time you receive a prescription for an SGLT2 inhibitor because there may be new or important additional information about your drug. The Medication Guide explains the benefits and risks associated with the medicine.
- To help FDA track safety issues with medicines, report side effects from SGLT2 inhibitors or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- Cases of necrotizing fasciitis of the perineum, also known as Fournier's gangrene, have been reported in patients with type 2 diabetes receiving SGLT2 inhibitors. This adverse event is a life-threatening infection requiring urgent antibiotics and surgical intervention.
- Cases in patients receiving SGLT2 inhibitors have occurred in both females and males in almost equal frequency.
- Serious outcomes have included hospitalization, multiple surgeries, and death.

- Assess patients for Fournier's gangrene if they present with tenderness, erythema, swelling in the genital or perineal area, fever, malaise, and have pain out of proportion to the physical exam.
- If Fournier's gangrene is suspected, institute prompt treatment with antibiotics and surgical debridement, if appropriate. Discontinue the SGLT2 inhibitor, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.
- Counsel patients to promptly seek medical attention if they experience any symptoms of tenderness, erythema, or swelling in the genital or perineal area, fever, or malaise.
- Encourage patients to read the Medication Guide they receive with their SGLT2 inhibitor prescriptions.
- To help FDA track safety issues with medicines, report adverse events involving SGLT2 inhibitors or other medicines to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of this page.

Data Summary

Overall published literature about the incidence of Fournier's gangrene in men and women is very limited. Publications using the U.S. State Inpatient Database (SID) from 593 civilian hospitals of 13 states in 2001 and 21 states in 2004 reported that Fournier's gangrene occurs in 1.6 out of 100,000 males annually in the U.S., with the highest incidence occurring in males 50-79 years (3.3 out of 100,000). Although the publications reported 39 female Fournier's gangrene cases, the investigators restricted analysis for females descriptively without incidence inference because the identification and ascertainment of Fournier's gangrene in females and males were different (i.e., there is no Fournier's gangrene code for females but a specific code for males) and low yield number of female Fournier's gangrene cases preclude any meaningful incidence analysis.[1-3]

A search of the FDA Adverse Event Reporting System (FAERS) database from March 2013, when the first SGLT2 inhibitor was approved, to February 2018 and the medical literature through May 2018 identified 12 cases of Fournier's gangrene in patients taking an SGLT2 inhibitor.[4-6] The patients ranged in age from 38-78 years. Seven cases were reported in men and five in women. The average time to onset was 9.2 months (range 7 days to 25 months). All drugs in the SGLT2 inhibitor class except ertugliflozin had associated Fournier's gangrene. As the most recently approved SGLT2 inhibitor, there is insufficient patient use to assess the risk of Fournier's gangrene with ertugliflozin. However, it would be expected to have the same risk for this rare and serious infection as other SGLT2 inhibitors.

Among the 12 cases, all patients were hospitalized and one patient died. All 12 required surgical debridement, five of which required more than one surgery and one required skin grafting. The clinical course for four patients was complicated by diabetic ketoacidosis, acute kidney injury, and septic shock, prolonging their hospitalizations or leading to death. Two patients were transferred to a rehabilitation hospital. The SGLT2 inhibitor

was discontinued in eight cases; one patient died; and information on drug continuation or discontinuation was not included in three cases.

Because diabetes is a known risk factor for Fournier's gangrene, we also searched FAERS for cases with several other classes of antidiabetic agents (insulins, biguanides, sulfonylureas, and dipeptidyl peptidase-4 inhibitors) to help assess whether the cases of Fournier's gangrene with the SGLT2 inhibitors are more likely to be associated with the underlying condition of diabetes as opposed to the drug. In the 34 years between 1984 and 2018, we identified only six additional cases of Fournier's gangrene in FAERS). All six patients were males and their median age was 57 years (range 42-71). Five of these patients were hospitalized and one died. This contrasts with the findings for Fournier's gangrene with the SGLT2 inhibitors where more cases were reported over a shorter timeframe, and cases involved both males and females. FAERS data have limitations. Many factors can influence whether or not an event will be reported.

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Related Information

Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors

Necrotizing Fasciitis

The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective

Think It Through: Managing the Benefits and Risks of Medicines

Risks associated with SGLT2 Inhibitors: An Overview

Article *in* Current Drug Safety · February 2018

DOI: 10.2174/1574886313666180226103408

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REVIEW ARTICLE

Risks Associated with SGLT2 Inhibitors: An Overview

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ARTICLE HISTORY

Received: December 08, 2017
Revised: February 15, 2018
Accepted: February 19, 2018

DOI:
10.2174/1574886313666180226103408

Abstract: Sodium glucose co-transport 2 inhibitors (SGLT2-i) are the new class of anti-diabetic medications which are recently approved (2013) by the Food and Drug Administration (FDA) for the treatment of diabetes. These inhibitors block the SGLT2 protein which involved glucose reabsorption from proximal renal tubule resulting in increased glucose excretion and lower blood glucose levels. These inhibitors exert favourable effects beyond glucose control such as consistent body weight, blood pressure and serum uric acid reductions. Canagliflozin, Dapagliflozin and empagliflozin belong to the class of SGLT2 inhibitors. All these drugs are giving promising results in the treatment of diabetes mellitus, but emerging data from post-marketing studies indicate their adverse effects such as diabetic ketoacidosis, genital and urinary tract infection, cancer, bone fracture and foot and leg amputation. Thus, there is a need for better understanding the risk profile of SGLT2 inhibitors. In this review, we have compiled the risk profile of SGLT2 inhibitors by collecting information from various sources such as case reports, published literature and from various regulatory websites. Further, the proposed mechanism of risks has also been discussed.

Keywords: Gliflozin, SGLT2 inhibitor, adverse drug reactions, diabetes mellitus.

1. INTRODUCTION

Diabetes mellitus is defined as the chronic disorder characterized by the elevated blood sugar level of the body which causes as a result of insulin deficiency, impaired insulin action or insulin resistance [1]. It is generally classified into 3 major types: (i) Insulin-dependent Diabetes mellitus, (ii) Non- insulin dependent Diabetes Mellitus and (iii) Gestational Diabetes mellitus [2]. It is the rapidly growing disorder in all age groups all over the world which leads to enormous social, economic and health-related consequences.

In 2010, approximately 285 million people (6.4% of adult population) were suffering from diabetes mellitus which is estimated to be increased up to 642 million by 2040 [3]. About 50% of the putative diabetics were not diagnosed until 10 years after the onset of disease. Some of the main reasons for diabetes mellitus are aging and obesity among the adult population. The prevalence of the diabetes mellitus worldwide is very high which should be controlled with proper care and treatment [4]. About 69.1 million adult cases of diabetes mellitus were reported in India till 2015, but this number will be expected to reach 109 million by 2035 [5].

There are various classes of drugs available in the market for the treatment of Diabetes mellitus. These classes are Non-sulfonylureas (Metformin), Thiazolidines (Rosiglitazone and pioglitazone), Sulfonylureas (Chlorpropamide, Glibenclamide, Glimepiride, Glipizide, Tolazamide and Tolbutamide), Meglitinides (Nateglinide and Repaglinide)], Alpha-glucosidase inhibitors (Acarbose and miglitol), Incretins mimetic (Exenatide, Liraglutide, Albiglutide and Dulaglutide), DPP4 inhibitors (Linagliptin, Alogliptin, Sitagliptin and Saxagliptin)] and Amylin analogs (Pramlintide) [6]. These classes of drugs are presented in Fig. (**1**). However, various side effects are observed regarding the use of these medications for *e.g*. Thiazolidinediones lead to liver disease, fluid retention, weight gain, increased risk of fractures and bladder cancer, DPP-4 inhibitors lead to hypoglycemia, headache, nasopharyngitis, urinary tract infection and facial swelling, Biguanides lead to stomach discomfort, upset stomach and decreased appetite, Sulfonylureas lead to skin rash, liver disease, upset stomach and drop in RBC count and Alpha-Glucosidase inhibitors lead to gas, bloating, upset stomach and diarrhoea as presented in Table **1** [7].

SGLT2 inhibitors are the recently approved therapy for the treatment of diabetes mellitus. At present, Canagliflozin, Dapagliflozin and Empagliflozin are the three drugs approved by FDA for the treatment of type 2 diabetes mellitus. Serum Glucose Co- transporter inhibitors result in significant lowering of blood plasma glucose level by increasing the excretion of glucose in the urine which further results in body weight loss and reducing blood pressure level of the body [8]. However, emerging reports indicated the various adverse drug reactions related to SGLT2 inhibitors. Thus, in this article, we tried to summarize the risk associated with SGLT2 inhibitors.

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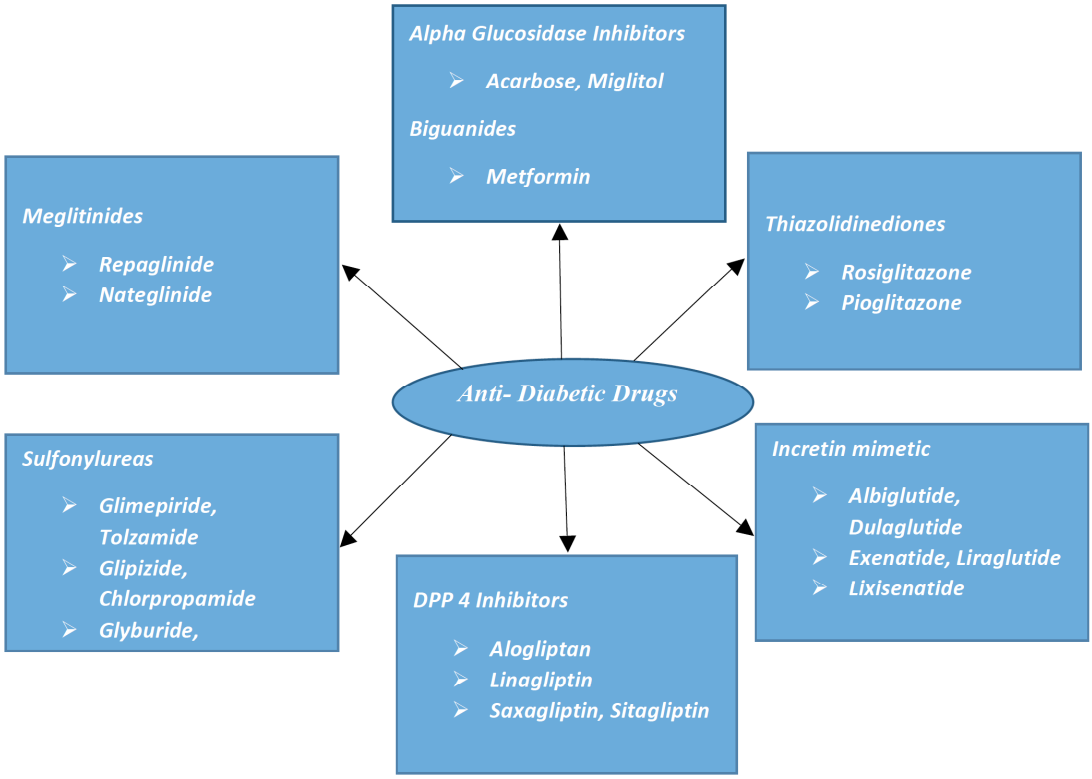

Fig. (1). Various classes of Anti-Diabetic drugs.

Table 1. Various adverse drug reactions (ADRs) of anti-diabetic medications.

Drug Class	Drug Name	Adverse Drug Reactions (ADRs)
Thiazolidinediones	Pioglitazone	Upper RTIs, bronchitis, sinusitis, bladder cancer, anaemia, hypersensitivity reactions.
	Rosiglitazone	Headache, cough, back pain, heart attack and back pain.
Dipeptidyl peptidase-4 (DPP-4)	Sitagliptin	Hypersensitivity reactions, headache, dizziness, hypoglycaemia, constipation, acute pancreatitis, pruritus.
	Linagliptin	Nasopharyngitis, hypoglycaemia, pancreatitis, constipation, angioedema.
Biguanides	Metformin	Taste disturbances, nausea, vomiting, liver dysfunction, pruritus, urticarial.
Sulfonyl ureases	Glimepiride	Mild hypersensitivity reactions, fall in blood pressure, pancytopenia, hypoglycaemia, visual disturbances.
	Glipizide	Hypoglycaemia, tremor, dizziness, blurred vision, eczema, jaundice cholestatic.
	Tolbutamide	Ear and labyrinth disorders.
Alpha-Glucosidase Inhibitors	Acarbose	Flatulence, diarrhoea, dyspepsia.
Serum Glucose Co-Transporter inhibitors	Canagliflozin, Dapagliflozin, Empagliflozin	Cancer, Bone fracture risk, Diabetic Ketoacidosis, Genital and Urinary tract infection and foot and toe amputation.

2. RISKS ASSOCIATED WITH SGLT2 INHIBITORS

Serum Glucose Co-transport inhibitors are recently approved FDA class of drugs for the treatment of diabetes mellitus. These inhibitors show enormous beneficial effects in the Type-2 diabetes mellitus patients as compared to currently approved drugs but still, there are various risks associated with the use of these inhibitors in the treatment of Diabetes mellitus. However, emerging reports indicated various risks associated with these inhibitors which are summarized below.

2.1. Diabetic Ketoacidosis (DKA)

2.1.1. Literature

Diabetic ketoacidosis is the life-threatening medical condition where the increased amount of ketone bodies (acid) is detected as a result of the burning of fatty acids in the body to fulfil the insulin requirements. In literature, emerging reports are pointing out the risk of diabetic ketoacidosis with the use of SGLT2 inhibitors.

Recently, Fadini *et al*. (2017)[9]analyzed the Diabetic ketoacidosis reports from the FDA ADR event reporting system regarding SGLT2 inhibitors association with diabetic ketoacidosis. Based on these reports, they have concluded that the SGLT2inhibitors are associated with DKA, and this association is not limited to any particular demographic or comorbid subpopulation and can occur at any duration of SGLT2i use. Further, FDA adverse event monitoring has also been analyzed by Blau *et al*. (2017)[10] and concluded the incidence of diabetic ketoacidosis with the use of SGLT2 inhibitors. Further, in this study, the incidence of Diabetic ketoacidosis in patients who are taking SGLT2 inhibitors and DPP4 inhibitors is compared and concluded that the risk of diabetic ketoacidosis is more in SGLT2 inhibitors as compared to DPP4 inhibitors. Monami *et al*. (2017)[11] conducted a meta-analysis to evaluate the risk of diabetic ketoacidosis with SGLT2 inhibitors and found that 09 patients were diagnosed with at least one event of diabetic ketoacidosis out of 72 trials and concluded that risk should be negligible if prescribed properly. Turner *et al*. (2016)[12] reported a case of sudden onset of diabetic ketoacidosis regarding the use of canagliflozin in an elder woman with positive dechallenge.

Diabetic ketoacidosis is considered as the serious adverse effect when 20 patients with Type 2 Diabetes Mellitus were hospitalized after the administration of SGLT2 inhibitors in a period of fourteen months (Rosenstock *et al*. 2015)[13]. Hayami *et al*. (2015)[14] reported an adult diabetic female patient who develops diabetic ketoacidosis on the administration of SGLT2 inhibitors and concluded that SGLT2 inhibitors cause Diabetic ketoacidosis in diabetic patients when low carbohydrate diet was taken with these inhibitors. Storgaard *et al*. (2015)[15] reported an obese diabetic patient with poorly controlled Type 2 diabetes mellitus which causes diabetic ketoacidosis within 5 days after the administration of SGLT2 inhibitors. Redford *et al*. (2015)[16] reported an elder woman diagnosed with Type 2 diabetes mellitus treated with Dapagliflozin which causes severe ketoacidosis after withdrawn of insulin therapy.

Crespo *et al*. (2016)[17] analyzed the various adverse event reporting system database of Food and Drug Administration (FDA) and recorded 73 cases of euglycemic ketoacidosis caused by SGLT2 inhibitors in between the year 2013 and 2015. Bader *et al*. (2016)[18] reported a case of a female patient with Type 1 diabetes mellitus having euglycemic diabetic ketoacidosis after the administration of canagliflozin with positive dechallenge. Taylor *et al*. (2015)[19] reviewed various literature published in PubMed or Google to correlate the incidence of diabetic ketoacidosis with SGLT2 inhibitors and concluded that SGLT2 inhibitors decrease the ketone excretion in urine and hence, lead to Ketoacidosis. Peters *et al*. (2015)[20] analyzed various cases of diabetic ketoacidosis occurring incidentally in patients taking SGLT2 inhibitors and concluded that these inhibitors should be prescribed with proper counselling and close monitoring in Type 1 Diabetes mellitus. Erondu *et al*. (2015)[21] analyzed reports from the randomized studies from canagliflozin and concluded that the events of diabetic ketoacidosis, ketosis occurred at a low frequency in type 2 diabetes mellitus in comparison to Type 1 diabetes mellitus. Tahir *et al*. (2015)[22] analysed that off-label use of SGLT2 inhibitor is increased for Type 1 diabetes mellitus as it was FDA approved for Type 2 diabetes mellitus and concluded that diabetic ketoacidosis occurs more commonly in patients diagnosed with type I diabetes mellitus and off-label use of SGLT 2 inhibitors should be avoided. The various risks associated with these inhibitors are summarized in Table **2**.

2.1.2. Clinical Trials

Regarding safety concern of SGLT2 inhibitors, a total of 04 clinical trials are conducted, out of which 2 are completed and remaining 2 are still not completed. The details regarding clinical trial are summarized in Table **3**.

Table 2. Various risks associated with SGLT2 inhibitors.

Sr. No.	Drug Name	Risk	Type	References
1.	Canagliflozin, Dapagliflozin, Empagliflozin.	Diabetic ketoacidosis	FDA ADR event reporting system	[9]
2.	Canagliflozin, Dapagliflozin, Empagliflozin.	Diabetic ketoacidosis	FDA ADR event reporting system	[10]
3.	Canagliflozin, Dapagliflozin, Empagliflozin.	Bone fracture	Published literature	[23]
4.	Canagliflozin	Bone fracture	Clinical studies	[25]
5.	Dapagliflozin	Urinary tract infection	Case report	[38]
6.	Dapagliflozin	Genital fungal infection	Clinical studies	[39]
7.	Empagliflozin	Bladder Cancer	Randomized controlled trials	[28]
8.	Canagliflozin, Dapagliflozin, Empagliflozin.	Diabetic ketoacidosis	FDA ADR event reporting system	[17]
9.	Canagliflozin, Dapagliflozin, Empagliflozin.	Bone fracture	Published literature	[26]
10.	Canagliflozin	Diabetic ketoacidosis	Case report	[18]
11.	Canagliflozin	Foot and toe amputation	FDA Drug safety communication	[42]
12.	Canagliflozin, Dapagliflozin, Empagliflozin.	Bone fracture	Randomized controlled trials	[27]
13.	Canagliflozin	Diabetic ketoacidosis	Case report	[12]

(Table 2) Contd…

Sr. No.	Drug Name	Risk	Type	References
14.	Canagliflozin, Dapagliflozin, Empagliflozin.	Urinary tract infection and genital mycotic infection	Clinical studies	[36]
15.	Dapagliflozin	Diabetic ketoacidosis	Case report	[14]
16.	Dapagliflozin	Diabetic ketoacidosis	Case report	[16]
17.	Canagliflozin, Dapagliflozin, Empagliflozin.	Diabetic ketoacidosis	Case report	[15]
18.	Canagliflozin, Dapagliflozin, Empagliflozin.	Diabetic ketoacidosis	Case reports	[20]
19.	Canagliflozin	Diabetic ketoacidosis	Randomized studies	[21]
20.	Canagliflozin, Dapagliflozin, Empagliflozin.	Diabetic ketoacidosis	Case reports	[22]
21.	Canagliflozin	Urinary tract infection	Randomized controlled trials	[32]
22.	Dapagliflozin	Breast Cancer	Preclinical studies	[29]
23.	Canagliflozin	Leydig cell tumour	Preclinical animal studies	[30]
24.	Canagliflozin, Dapagliflozin, Empagliflozin.	Urinary tract infection	Clinical studies	[33]
25.	Canagliflozin, Dapagliflozin, Empagliflozin.	Urinary tract infection	Clinical studies	[34]
26.	Dapagliflozin	Urinary tract infection	Multi trial safety data	[4]

Table 3. Clinical trials investigated risks of diabetic Ketoacidosis and bone fracture with SGLT2 inhibitors.

Sr. No.	Drug Name	Phase of Clinical Trial	Study design	No. of Volunteers	Status of Trial	Duration	Observed Results
1.	Empagliflozin	Phase 3	Cohort and retrospective	15000 (approx.)	Still recruiting	26 months	Not completed yet.
2.	Dapagliflozin	Phase 3	Randomized crossover interventional clinical trial	2	Completed	9 months	Not compiled
3.	Dapagliflozin	Phase 3	Case series and retrospective	200	Still recruiting	6 months	Not completed yet
4.	SGLT2 inhibitors	Phase 3	Observational and Retrospective	200000	Completed	21 months	Not compiled yet
5.	Canagliflozin	Phase 1	Randomized interventional crossover trial	175 (approx.)	Still recruiting	4 years and 7 months	Not completed yet.

2.1.3. Proposed Mechanism of Diabetic Ketoacidosis

Serum glucose co transporter (SGLT 2) inhibitors act directly on the proximal-distal tubule of the kidney and block the tiny filters of the nephron which result in the inhibition of reabsorption of glucose in blood plasma. Thus, the excess of glucose has been excreted in urine. Further, it also decreases the reabsorption of sodium in blood plasma.

However, when SGLT2 inhibitors are used for longer period of time, the decreased amount of glucose in blood increases lipolysis which further leads to the production of free fatty acids in body to complete body's energy requirements. β-oxidation then, leads to increased amount of ketones in the body called as euglycemic diabetic ketoacidosis. In pregnancy, diabetic ketoacidosis may occur as a result of ketogenic changes in metabolism during pregnancy. The proposed mechanism of SGLT2 inhibitors induced Diabetic ketoacidosis is shown in Fig. (**2**).

2.2. Bone Fracture Risk

2.2.1. Literature

Emerging reports have also indicated the bone fracture risk regarding the use of SGLT2 inhibitors. Wolverton *et al*. (2017)[23] reviewed various published literature regarding the risk of bone fracture and concluded that SGLT2 inhibitor may elevates the risk of bone fracture and decreases the total hip bone mineral density. However, the meta-analysis conducted by Ruanpeng *et al*. (2017)[24] evaluates the risk of bone fracture risk with SGLT2 inhibitors and concluded that increased bone fracture risk in type 2 diabetes mellitus patients was not observed in comparison to the placebo patients. This might be observed due to short duration of therapy. Further, TC Blevins *et al*. (2017)[25] analyzed various clinical studies to predict the incidence of bone fracture risk in patients treated with Canagliflozin and reported that Canagliflozin leads to increase in serum collagen type 1 β- carboxy telopeptide (β-CTX) which results in resorption of bone and decrease bone mineral density (BMD). Egger *et al*. (2016)[26] reviewed various published literature to check the incidence of bone fracture risk with SGLT2 inhibitors and concluded that SGLT2 inhibitors cause alteration in calcium and phosphate homeostasis and lead to decrease in bone mineral density. Tang *et al*. (2016)[27] analyzed various randomized controlled trials (RCT) from various sources to analyze bone fracture risk of SGLT2 inhibitors and concluded that these RCT data did not support the bone fracture risk but future monitoring for the same should be done.

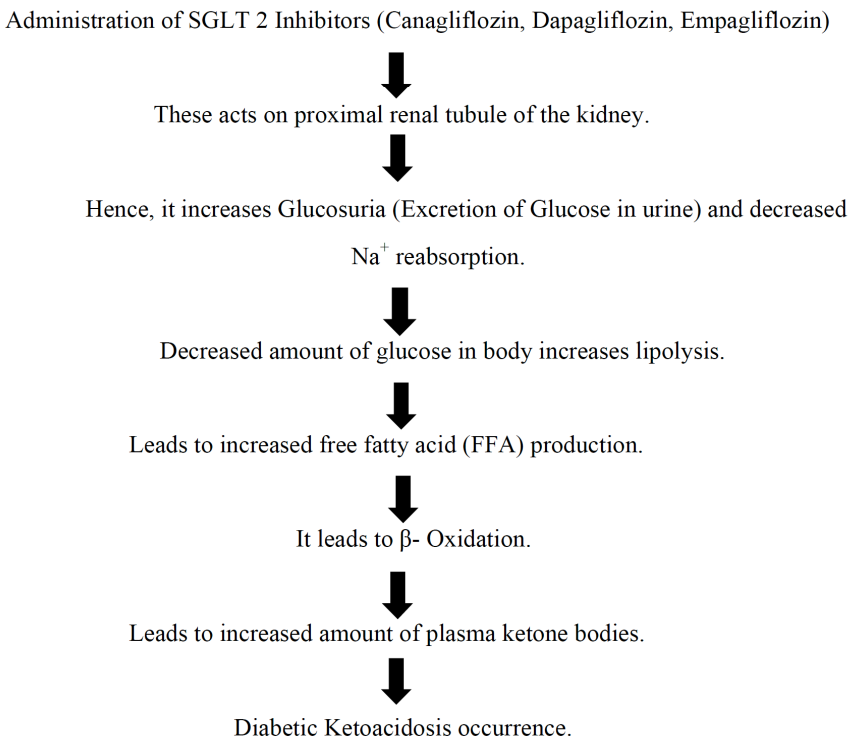

Fig. (2). Proposed Mechanism of SGLT2 inhibitors induced Diabetic Ketoacidosis.

2.2.2. Clinical Trials

Regarding safety concern of SGLT2 inhibitors, only one clinical trial is conducted which is still recruiting patients. The detail about the clinical trial is summarized in Table **2**.

2.2.3. Proposed Mechanism of Bone Fracture Risk During SGLT2 Therapy

The mechanism by which SGLT2 inhibitors can lead to bone fracture risk is still unclear. However, various pathways can play a major role. SGLT2 inhibitors can increase tubular reabsorption of phosphate which results in increased level of serum phosphate concentration in the blood. The increased serum phosphate concentration can lead to sustained release in parathyroid hormone which controls the calcium level in the blood which further stimulates the bone resorption and causes risk for the bone fractures. These SGLT2 inhibitors are also related with increased fibroblast growth factor 23 concentration which leads to bone disease and it lowers the 1, 25-dihydroxyvitamin D which further causes the loss of calcium absorption from gastrointestinal tract and impair calcification of bones. The proposed mechanism by which SGLT2 inhibitors could induce bone fracture is shown in Fig. (**3**).

2.3. Cancer Risk

Serum glucose co transporter (SGLT2) inhibitors could also induce the risk of cancer.

2.3.1. Literature

Tang *et al*. (2017)[28] analyzed various randomized controlled trials of SGLT2 inhibitors associated with risk of cancer and concluded that bladder cancer risk is associated with the Empagliflozin. However, the results are not promising as these are short-term trials. Further, these trials have also concluded that Canagliflozin are helpful in preventing gastrointestinal cancer. HW Lin *et al*. (2014)[29] analyzed various published literature from various sources and concluded that the increased risk of female breast cancer and male bladder cancer was observed in preclinical studies with SGLT2 inhibitor Dapagliflozin.

2.3.2. Preclinical study

Jonghe *et al*. (2014)[30] reported the carcinogenic effect in rats after the administration of Canagliflozin at 10, 30 and 100 mg/kg, and concluded that the use of Canagliflozin leads to increase the chances of the renal tubular tumour and testicular Leydig cell tumour in rats due to glucose malabsorption in a body.

2.4. Genital and Urinary Tract Infection

2.4.1. Literature

Johnnsen *et al*. (2013)[31] analysed the multi-trial safety data related to Dapagliflozin and concluded that once daily dose of Dapagliflozin was accompanied with the increased risk of urinary tract infection. Nicolle *et al*. (2015)[32] analysed various persons in two set of pooled datasets and concluded that Canagliflozin was associated with increased risk of incidence of urinary tract infection in type 2 Diabetes mellitus patients but there was no risk of serious or upper urinary tract infection. Geerlings *et al*. (2014)[33] analysed various patients of type 2 diabetes mellitus treated with SGLT2 inhibitors and concluded that glucosuria induced by SGLT2 inhibitors may lead to incidence of urinary tract infection to a lesser extent. Schneeberger *et al*. (2014)[34] analyzed the patients of type 2 diabetes mellitus treated with SGLT2 in-

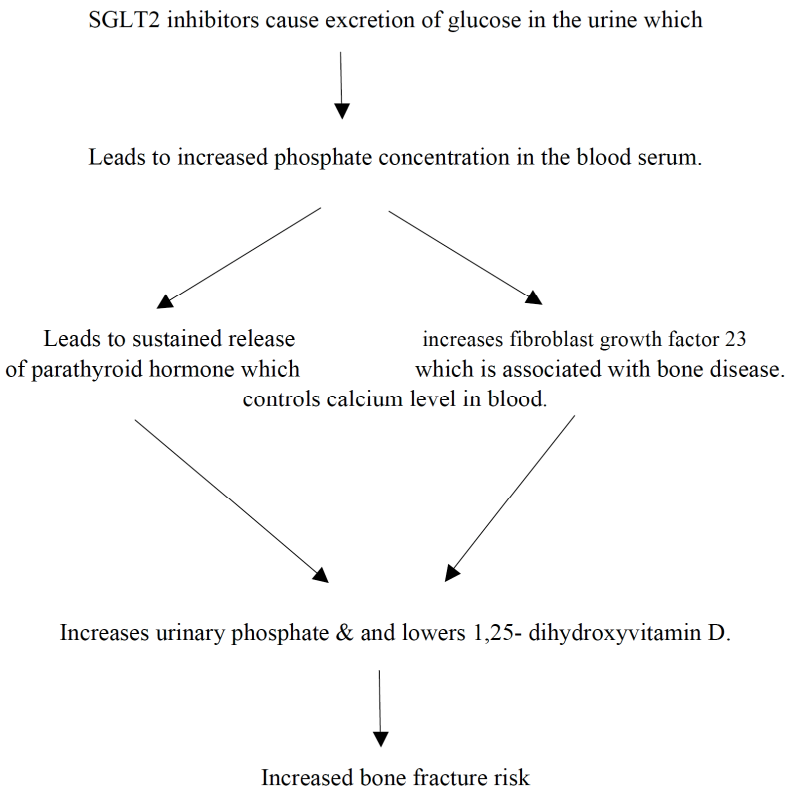

Fig. (3). Proposed Mechanism of SGLT2 inhibitors induced increased bone fracture risk.

hibitor during pregnancy and concluded that SGLT2 inhibitors are associated with the incidence of urinary tract infection to a lesser extent. Dandan Li *et al*. (2016)[35] conducted a meta-analysis to evaluate the risk of genital and urinary tract infection in type 2 diabetes mellitus patients treated with SGLT2 inhibitors and concluded that these inhibitors showed significantly higher incidence of genital and urinary tract infection among the type 2 diabetes mellitus patients in comparison to placebo and other active treatments. Arakaki *et al*. (2016)[36]analysed various patients on SGLT2 inhibitor therapy for type 2 diabetes mellitus and concluded that SGLT2 inhibitors were linked with the increased incidence of urinary tract infection and genital mycotic infections. Rizzi *et al*. (2016)[37] analyzed the various published literature to check the prevalence and the incidence of UTI infections during SGLT2 inhibitor therapy and concluded that the patients are at non-significant high risk of producing Urinary tract infection because of the increased glucose excretion in urine. Recently, Hall *et al*. (2017)[38] analyzed a patient (admitted with Urinary Tract Infection) after the initiation of dapagliflozin and concluded that the episodes of Urinary tract infection were ceased after the cessation of dapagliflozin. Thong *et al*. (2017)[39] analysed various patients of type 2 diabetes mellitus treated with Dapagliflozin to check the incidence of various genital fungal infection and concluded that patients and women having previous occurrence of genital mycotic infection are at higher risk of developing urinary tract infection and genital mycotic infection.

2.4.2. Preclinical study

In literature, one preclinical study has been found which indicated the risk of UTI with SGLT2 inhibitors. Suzuki *et al*. (2014)[40] analysed the relationship between glucosuria and Urinary tract infection with SGLT2 inhibitors in mice and concluded that the increased urine concentration of glucose increases the susceptibility of urinary tract infection.

2.5. Foot and Toe Amputation

In literature, Zhong *et al*. (2017)[41] conducted a retrospective cohort study to evaluate the risk of incidence of amputations among type 2 diabetes mellitus patients treated with SGLT2 inhibitors and concluded that the risk of below knee leg amputations was relatively low and there was no increased risk for the new users of canagliflozin. However, recently on 18th May, 2016, FDA in its drug safety communication indicates the increased risk of leg and foot amputation with the use of canagliflozin in type 2 Diabetes Mellitus patients on the basis of two large clinical trials. These trials showed that leg and foot amputations occurred about twice as often in patients treated with canagliflozin compared to patients treated with placebo, which is an inactive treatment.

Further, on 24 February 2017, European medicine agency (EMA) has been given the same recommendation regarding the use of SGLT2 inhibitors.

CONCLUSION

In conclusion, the current evidence showed that SGLT2 inhibitors increase the risk of Diabetic ketoacidosis, bone fracture, cancer and genital and urinary tract infection and foot and toe amputation. However, the impact of SGLT2 inhibitors on these risks remains uncertain; the upcoming major trials may provide important insights on these issues.

When their results are available, an updated review is warranted.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Authors are thankful to Shri. Praveen Garg, Chairman, Indo-Soviet Friendship College of Pharmacy (ISFCP), for providing research facility.

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福適佳 膜衣錠 5毫克、10毫克
Forxiga Film-coated Tablets 5mg, 10mg

本藥須由醫師處方使用
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1 適應症
第二型糖尿病【見臨床研究(14)】。

1.1 使用限制
不建議Forxiga用於第一型糖尿病或糖尿病酮酸中毒之治療。

2 用法用量

2.1 建議劑量
Forxiga可單獨使用亦可與metformin、sulfonylurea、thiazolidinedione、DPP-4抑制劑(併用或不併用metformin)、metformin加一種sulfonylurea、或胰島素合併使用，做為附加於飲食控制及運動之外的治療藥物，藉以改善第二型糖尿病患的血糖控制效果。
Forxiga的建議起始劑量是5mg每天1次，早晨服用，隨餐或空腹服用皆可。在耐受Forxiga 5mg每天1次的患者，需要額外血糖控制時，劑量可增至10mg每天1次。
在血容量不足患者，建議在開始Forxiga之前矯正這種情況【見警語和注意事項(5.1)，在特殊族群中使用(8.5，8.6)，和患者用藥指導資料(17)】。

2.2 腎功能不全患者
建議在開始Forxiga治療前和治療期間定期評估腎功能。
在eGFR低於60mL/min/1.73m²的患者，不應開始Forxiga。
在有輕度腎功能不全患者(eGFR為60mL/min/1.73m²或更大)無須調整劑量。
當eGFR持續地低於60mL/min/1.73m²，應停用Forxiga【見警語和注意事項(5.3)和在特殊族群中使用(8.6)】。

3 劑型和規格
Forxiga 5mg錠是黃色的雙凸圓形膜衣錠，一面刻有“5”，另一面刻有“1427”。
Forxiga 10mg錠是黃色的雙凸菱形膜衣錠，一面刻有“10”，另一面刻有“1428”。

4 禁忌
- 對Forxiga嚴重過敏反應病史。【見不良反應(6.1)】。
- 嚴重腎功能不全、末期腎病(ESRD)、或透析患者【見在特殊族群中使用(8.6)】。

5 警語和注意事項

5.1 低血壓
Forxiga導致血管內容積收縮。開始Forxiga後，可能發生症狀性低血壓【見不良反應(6.1)】，尤其是腎功能不全的患者(eGFR小於60mL/min/1.73m²)、老年患者或使用環利尿劑(loop diuretics)的患者。
在有一種或更多上述特徵的患者開始Forxiga前，應該評估和矯正血容量狀態。開始治療後監測低血壓的徵象和症狀。

5.2酮酸中毒
服用Forxiga等SGLT2抑制劑的第一型和第二型糖尿病患者，有出現酮酸中毒(包括糖尿病性酮酸中毒)的上市後通報案例，然而因果關係尚未建立。Forxiga不適用於第一型糖尿病患者的治療。
使用Forxiga治療的患者，若出現符合酮酸中毒的徵兆和症狀，包括噁心、嘔吐、腹痛、全身無力、呼吸急促，即使血糖值低於14mmol/l (250mg/dl)，仍應評估發生酮酸中毒之可能性。如果懷疑是酮酸中毒，應考慮停用或暫時中斷Forxiga，並且立即評估患者狀況。
誘發酮酸中毒的因子包括胰臟疾病(例如第一型糖尿病，胰臟炎的病史或胰臟手術)導致的低β細胞功能儲備量，減少胰島素劑量，熱量攝入減少或由於感染、疾病或手術導致的胰島素需求增加和酒精濫用。對於這些患者應慎用Forxiga。

5.3 腎功能不全
Forxiga增加血清肌酸酐並減少eGFR。老年患者和腎功能不全患者可能對這些變化更敏感。開始Forxiga後可能發生與腎功能有關的不良反應【見不良反應(6.1)】。開始Forxiga前和治療期間應定期評估腎功能。

5.4 與胰島素和胰島素分泌促進劑同時使用伴隨的低血糖
已知胰島素和胰島素分泌促進劑會導致低血糖。當與胰島素或胰島素分泌促進劑併用，Forxiga可能會增加低血糖風險【見不良反應(6.1)】。因此，當這些藥與Forxiga併用時，可能需要使用較低劑量的胰島素或胰島素分泌促進劑，以減少低血糖風險。

5.5 尿路敗血症和腎盂腎炎
接受Forxiga和其他的SGLT2抑制劑的患者，有發生需要住院之嚴重泌尿道感染，包括尿路敗血症和腎盂腎炎的上市後通報案例。使用SGLT2抑制劑治療會增加尿路感染的風險。如有需要，評估患者有無泌尿道感染的徵兆和症狀，並且及時治療。

5.6 生殖器黴菌感染
Forxiga增加生殖器黴菌感染風險。有生殖器黴菌感染病史的患者更易發生生殖器黴菌感染【見不良反應(6.1)】。應適當地監測和治療。

5.7 低密度脂蛋白膽固醇(LDL-C)升高
使用Forxiga會發生LDL-C升高【見不良反應(6.1)】。開始Forxiga後，監測LDL-C並依照護標準治療。

5.8 膀胱癌
跨越22個臨床研究，報導的新診斷膀胱癌病例在用Forxiga治療的患者中有10/6045例(0.17%)，在用安慰劑/對照品治療的患者中有1/3512例(0.03%)。排除診斷膀胱癌時暴露於研究藥物不到1年的患者後，有4例使用Forxiga，無病例使用安慰劑/對照品。在基線時，治療組之間膀胱癌的危險因子和血尿(已經存在腫瘤的潛在指標)平衡。病例數太少，不能確定這些事件的出現是否與Forxiga有關。
沒有足夠的數據來確定Forxiga是否對已存在的膀胱腫瘤有影響。因此在有活動性膀胱癌的患者，不應使用Forxiga。在有膀胱癌病史的患者，應考慮使用Forxiga的血糖控制效益與癌症復發未知風險。

5.9 大血管病變結果
沒有臨床研究確定用Forxiga或任何其他降血糖藥物減低大血管風險的結論性證據。

6 不良反應
下列重要不良反應描述如下和說明書的其他部分：
- 低血壓【見警語和注意事項(5.1)】
- 酮酸中毒【見警語和注意事項(5.2)】
- 腎功能不全【見警語和注意事項(5.3)】
- 與胰島素和胰島素分泌促進劑同時使用伴隨的低血糖【見警語和注意事項(5.4)】
- 尿路敗血症和腎盂腎炎【見警語和注意事項(5.5)】
- 生殖器黴菌感染【見警語和注意事項(5.6)】
- 低密度脂蛋白膽固醇(LDL-C)升高【見警語和注意事項(5.7)】
- 膀胱癌【見警語和注意事項(5.8)】

6.1 臨床試驗經驗
因為臨床試驗是在廣泛不同情況下進行的，臨床試驗觀察到的不良反應率不能與另一種藥的臨床試驗發生率直接比較，而且可能不會反映臨床作業中觀察到的發生率。

12項Forxiga 5和10mg安慰劑對照研究的合併
表1的數據來自12項為期12至24週的安慰劑對照研究。Forxiga在4項研究被用作單一治療，在8項研究Forxiga被附加於背景降血糖治療或作為與metformin合併治療【見臨床研究(14)】。
這些資料反映2338名患者暴露於Forxiga的平均暴露時間為21週。患者接受安慰劑(N=1393)、Forxiga 5mg (N=1145)、或Forxiga 10mg (N=1193)每天1次。群體平均年齡55歲，2%大於75歲；50%是男性；81%為白種人，14%為亞裔，3%為黑人或非裔美國人。在基線時，群體平均罹患糖尿病6年，平均血紅素A1c (HbA1c)為8.3%，21%已有糖尿病的小血管併發症。92%患者的基線腎功能正常或輕度受損，8%患者中度受損(平均eGFR 86mL/min/1.73m²)。
表1顯示使用Forxiga常見的不良反應。這些不良反應在基線不存在，使用Forxiga比使用安慰劑更常見，而且發生在至少2%使用Forxiga 5mg或Forxiga 10mg治療的患者。

〔表1〕在安慰劑對照研究使用Forxiga治療的患者中報導≥2%的不良反應

不良反應	患者%		
	12項安慰劑對照研究的合併		
	安慰劑 N=1393	Forxiga 5mg N=1145	Forxiga 10mg N=1193
女性生殖器黴菌感染*	1.5	8.4	6.9
鼻咽炎	6.2	6.6	6.3
尿路感染†	3.7	5.7	4.3
背痛	3.2	3.1	4.2
排尿增加‡	1.7	2.9	3.8
男性生殖器黴菌感染§	0.3	2.8	2.7
噁心	2.4	2.8	2.5
流感	2.3	2.7	2.3
血脂異常	1.5	2.1	2.5
便秘	1.5	2.2	1.9
排尿不適	0.7	1.6	2.1
肢體疼痛	1.4	2.0	1.7

* 生殖器黴菌感染包括下列不良反應，按通報頻率順序列出，女性：外陰陰道黴菌感染、陰道感染、外陰陰道念珠菌病、外陰陰道炎、生殖器感染、生殖器念珠菌病、黴菌性生殖器感染、外陰炎、生殖泌尿道感染、外陰膿瘍、細菌性陰道炎。(女性N：安慰劑=677，Forxiga 5mg=581，Forxiga 10mg=598)。
† 尿路感染包括以下不良反應，按通報頻率順序列出：尿路感染、膀胱炎、大腸桿菌尿路感染、生殖泌尿道感染、腎盂腎炎、膀胱三角炎、尿道炎、腎感染、前列腺炎。
‡ 增加排尿包括以下不良反應，按通報頻率順序列出：尿頻、多尿、尿量增加。
§ 生殖器黴菌感染包括下列不良反應，按通報頻率順序列出，男性：龜頭炎、黴菌生殖器感染、念珠菌性龜頭炎、生殖器念珠菌病、男性生殖器感染、陰莖感染、龜頭包皮炎、傳染性龜頭包皮炎、生殖器感染、包皮炎。(男性N：安慰劑=716，Forxiga 5mg=564，Forxiga 10mg=595)。

13項Forxiga 10mg安慰劑對照研究的合併
在一個較大型安慰劑對照研究的合併中，也評估了Forxiga 10mg的安全性和耐受性。這個合併結合13項安慰劑對照研究，包括3項單一治療研究、9項附加於背景降血糖治療研究，和一項與metformin初始合併研究。跨越這些13項研究，2360名患者每天服用1次Forxiga 10mg，平均暴露時間22週。群體平均年齡59歲，4%大於75歲。群體的58%是男性；84%為白種人，9%為亞裔，和3%為黑人或非裔美國人。在基線時，群體罹患糖尿病平均9年，平均HbA1c為8.2%，30%有確定的小血管疾病。88%患者基線腎功能正常或輕度受損，11%患者中度受損(平均eGFR 82mL/min/1.73m²)。

血容量不足
Forxiga引起滲透性利尿，可能導致血管內容積減低。表2顯示12項和13項安慰劑對照研究合併中與血容量不足相關的不良反應(包括脫水，低血容量，姿勢性低血壓，或低血壓的報告)【見警語和注意事項(5.1)】。

〔表2〕Forxiga臨床研究中血容量不足*的不良反應

	12項安慰劑對照研究的合併			13項安慰劑對照研究的合併	
	安慰劑	Forxiga 5mg	Forxiga 10mg	安慰劑	Forxiga 10mg
總族群N (%)	N=1393 5(0.4%)	N=1145 7(0.6%)	N=1193 9(0.8%)	N=2295 17(0.7%)	N=2360 27(1.1%)
患者子群數n (%)					
使用環利尿劑患者	n=55 1(1.8%)	n=40 0	n=31 3(9.7%)	n=267 4(1.5%)	n=236 6(2.5%)
中度腎功能不全患者eGFR≥30和<60mL/min/1.73m²	n=107 2(1.9%)	n=107 1(0.9%)	n=89 1(1.1%)	n=268 4(1.5%)	n=265 5(1.9%)
≥65歲患者	n=276 1(0.4%)	n=216 1(0.5%)	n=204 3(1.5%)	n=711 6(0.8%)	n=665 11(1.7%)

* 血容量不足包括脫水、低血容量、姿勢性低血壓、或低血壓報導。

腎功能受損
使用Forxiga伴隨血清肌酸酐增加和eGFR減低(見表3)。在基線時腎功能正常或輕度受損的患者，在24週時血清肌酸酐和eGFR回到基線值。腎臟相關不良反應，包括腎衰竭和血中肌酸酐增高，在使用Forxiga治療患者更常見(見表4)。老年患者和腎功能不全患者對這些不良反應較為敏感(見表4)。在中度腎功能不全患者(eGFR 30至低於60mL/min/1.73m²)中見到eGFR持續減低。

〔表3〕在12安慰劑對照研究的合併和中度腎功能不全研究中，伴隨Forxiga的血清肌酸酐和eGFR變化

		12項安慰劑對照研究的合併		
		安慰劑 N=1393	Forxiga 5mg N=1145	Forxiga 10mg N=1193
基線平均值	血清肌酸酐(mg/dL)	0.853	0.860	0.847
	eGFR (mL/min/1.73m²)	86.0	85.3	86.7
第1週變化	血清肌酸酐(mg/dL)	−0.003	0.029	0.041
	eGFR (mL/min/1.73m²)	0.4	−2.9	−4.1
第24週變化	血清肌酸酐(mg/dL)	−0.005	−0.001	0.001
	eGFR (mL/min/1.73m²)	0.8	0.8	0.3
		中度腎功能不全研究		
		安慰劑 N=84	Forxiga 5mg N=83	Forxiga 10mg N=85
基線平均值	血清肌酸酐(mg/dL)	1.46	1.53	1.52
	eGFR (mL/min/1.73m²)	45.6	44.2	43.9
第1週變化	血清肌酸酐(mg/dL)	0.01	0.13	0.18
	eGFR (mL/min/1.73m²)	0.5	−3.8	−5.5
第24週變化	血清肌酸酐(mg/dL)	0.02	0.08	0.16
	eGFR (mL/min/1.73m²)	0.03	−4.0	−7.4
第52週變化	血清肌酸酐(mg/dL)	0.10	0.06	0.15
	eGFR (mL/min/1.73m²)	−2.6	−4.2	−7.3

〔表4〕有至少一次腎功能不全相關不良反應的患者比例

	6項安慰劑對照研究的合併(直至104週)*			9項安慰劑對照研究的合併(直至104週)†	
基線特徵	安慰劑	Forxiga 5mg	Forxiga 10mg	安慰劑	Forxiga 10mg
總族群 有至少1事件之患者(%)	n=785 13(1.7%)	n=767 14(1.8%)	n=859 16(1.9%)	n=1956 82(4.2%)	n=2026 136(6.7%)
65歲或以上 有至少1事件之患者(%)	n=190 4(2.1%)	n=162 5(3.1%)	n=159 6(3.8%)	n=655 52(7.9%)	n=620 87(14.0%)
eGFR≥30和<60mL/min/1.73m² 有至少1事件之患者(%)	n=77 5(6.5%)	n=88 7(8.0%)	n=75 9(12.0%)	n=249 40(16.1%)	n=251 71(28.3%)
65歲或以上和eGFR≥30和<60mL/min/1.73m² 有至少1事件之患者(%)	n=41 2(4.9%)	n=43 3(7.0%)	n=35 4(11.4%)	n=141 27(19.1%)	n=134 47(35.1%)

* 患者子集來自12項有長期延伸之安慰劑對照研究的合併。
† 患者子集來自13項有長期延伸之安慰劑對照研究的合併。

在一項中度腎功能不全患者的研究(eGFR 30至低於60mL/min/1.73m²)評估Forxiga的安全性【見臨床研究(14)】。在這項研究中，13名患者在直至104週的治療期間發生骨折：安慰劑組未發生骨折，Forxiga 5mg組有5例，Forxiga 10mg組有8例。這13例骨折有8例發生在基線eGFR 30至45mL/min/1.73m²的患者。這13例骨折有11例在頭52週內通報。關於骨折的解剖部位沒有明顯的模式。

低血糖
表5按研究顯示低血糖的頻率【見臨床研究(14)】。當Forxiga附加於磺醯尿素類(sulfonylurea)或胰島素時，低血糖較常發生【見警語和注意事項(5.4)】。

〔表5〕在對照臨床研究中重大*和輕微†低血糖的發生率

	安慰劑/活性對照	Forxiga 5mg	Forxiga 10mg
單一治療*(24週)	N=75	N=64	N=70
重大【n(%)】	0	0	0
輕微【n(%)】	0	0	0
附加於Metformin*(24週)	N=137	N=137	N=135
重大【n(%)】	0	0	0
輕微【n(%)】	0	2(1.5)	1(0.7)
活性對照附加於Metformin相較於Glipizide (52週)	N=408	–	N=406
重大【n(%)】	3(0.7)	–	0
輕微【n(%)】	147(36.0)	–	7(1.7)
附加於Glimepiride*(24週)	N=146	N=145	N=151
重大【n(%)】	0	0	0
輕微【n(%)】	3(2.1)	8(5.5)	9(6.0)
附加於Metformin與一種Sulfonylurea (24週)	N=109	–	N=109
重大【n(%)】	0	–	0
輕微【n(%)】	4(3.7)	–	14(12.8)
附加於Pioglitazone*(24週)	N=139	N=141	N=140
重大【n(%)】	0	0	0
輕微【n(%)】	0	3(2.1)	0
附加於DPP4抑制劑(24週)	N=226	–	N=225
重大【n(%)】	0	–	1(0.4)
輕微【n(%)】	3(1.3)	–	4(1.8)
附加於胰島素Insulin有或無其他OADs‡(24週)	N=197	N=212	N=196
重大【n(%)】	1(0.5)	1(0.5)	1(0.5)
輕微【n(%)】	67(34.0)	92(43.4)	79(40.3)

* 低血糖的重大發作被定義為由於微血管或血漿血糖值< 54 mg/dL的意識或行為嚴重受損症狀發作，需要外界(第三方)幫助，並在給予葡萄糖或升糖素(glucagon)後迅速恢復。
† 低血糖的輕微發作被定義為微血管或血漿血糖值< 63 mg/dL的症狀性發作，無論是否需要外界幫助，或一種無症狀的微血管或血漿血糖值< 63 mg/dL，不認為是重大發作者。
‡ OAD=口服降血糖治療。

生殖器黴菌感染
使用Forxiga治療的生殖器黴菌感染較常發生。在12項研究安慰劑對照試驗之合併用中，0.9%使用安慰劑者報告生殖器黴菌感染，使用Forxiga 5mg者為5.7%，使用Forxiga 10mg者為4.8%。由於發生生殖器感染終止研究的比率，在使用安慰劑治療者為0%，在使用Forxiga 10mg治療者為0.2%。女性比男性更常通報感染(見表1)。最常通報的生殖器黴菌感染在女性是外陰陰道黴菌感染，男性是龜頭炎。有生殖器黴菌感染病史的患者比無既往史的患者更容易在研究期間發生生殖器黴菌感染(使用安慰劑、Forxiga 5mg、和Forxiga 10mg的患者分別是10.0%、23.1%、和25.0%比0.8%、5.9%、和5.0%)。

過敏反應
使用Forxiga治療曾報導過敏反應(例如血管水腫，蕁麻疹，過敏)。跨越臨床計畫，嚴重過敏反應和嚴重皮膚不良反應和血管水腫鑑於0.2%使用對照品治療的患者和0.3%使用Forxiga治療的患者。如果發生過敏反應，停止使用Forxiga；按照照護標準治療並監測直到徵象和症狀消失。

實驗室檢驗
血比容增加
在13項安慰劑對照研究的合併中，在Forxiga治療組患者觀察到平均血比容值在第1週開始從基線增加，並且持續到第16週，這時觀察到與基線的最大平均差。在24週時，血比容從基線的平均變化在安慰劑組是−0.33%，Forxiga 10mg組是2.30%。至第24週，血比容值> 55%的患者在安慰劑治療組有0.4%，Forxiga 10mg治療組有1.3%。

血清無機磷增加
在13項安慰劑對照研究的合併中，在24週時Forxiga治療組患者與安慰劑治療組患者比較，平均血清磷濃度從基線增加(分別平均增加0.13比−0.04 mg/dL)。在24週時，使用Forxiga的患者有明顯高磷血症(17-65歲：≥ 5.6mg/dL或≥ 66歲：≥ 5.1 mg/dL)實驗室異常的患者比例較高(安慰劑0.9%比Forxiga 10mg 1.7%)。

低密度脂蛋白膽固醇增加
在13項安慰劑對照研究的合併中，報導了Forxiga治療組患者與安慰劑組治療患者比較，其平均脂質從基線的變化。在24週時安慰劑組和Forxiga 10mg組的總膽固醇從基線的平均變化是0.0%比2.5%，LDL膽固醇從基線的平均變化是−1.0%比2.9%。

7 藥物交互作用

7.1 尿糖檢測試驗陽性反應
SGLT2抑制劑會促進葡萄糖由尿液排泄，而造成尿糖檢測試驗結果呈陽性。不建議服用SGLT2抑制劑的病患以尿糖檢測試驗做為監測血糖控制的方法，應使用其他方式監測血糖控制情形。

7.2 干擾1,5−無水葡萄糖醇(1,5-anhydroglucitol(1,5-AG))檢驗
SGLT2抑制劑會影響1, 5-AG檢驗之數據。不建議服用SGLT2抑制劑的病患以1,5-AG檢驗作為監測血糖控制的方法，應使用其他方式監測血糖控制情形。

8 在特殊族群中使用

8.1 懷孕
懷孕用藥分類C
Forxiga在孕婦族群並無適當且具有良好對照的研究。根據動物生殖和發育毒性研究，dapagliflozin可能影響腎臟的發育和成熟。在幼年大鼠研究中，在最低測試劑量(此劑量約為10mg劑量臨床暴露的15倍)，腎盂和腎小管擴張的發生率和/或嚴重程度明顯增加。
這些結果的發生乃因在動物發育期間藥物暴露，而此發育期與人類妊娠第二期和第三期相關。懷孕期間應考慮適當的替代治療，尤其是在妊娠第二期和第三期。懷孕期間只有潛在利益超過對胎兒的潛在風險時，才可使用Forxiga。
在一項幼年動物毒性研究中，從幼年大鼠出生後(PND)21天直到PND 90天直接給予dapagliflozin 1、15、或75mg/kg/天的劑量，各劑量組都有腎臟重量增加和腎盂、腎小管擴張之報告。根據AUC，最低測試劑量的暴露量是最大臨床劑量的15倍。在幼年動物觀察到的腎盂和腎小管擴張在約1個月恢復期內無完全恢復。
在一項產前和產後發育研究中，雌性大鼠從妊娠第6天至哺乳第21天接受1、15、或75mg/kg/天之劑量，而幼鼠在子宮內直到哺乳期都間接暴露於此藥。在接受75mg/kg/天劑量之母大鼠的成年子代觀察到腎盂和腎小管擴張的發生率或嚴重程度增加(母體和幼鼠的dapagliflozin暴露分別是臨床劑量時人類暴露的1415倍和137倍)。
在劑量≥ 1 mg/kg/天(約≥ 19倍臨床劑量)觀察到幼鼠呈現劑量相關的體重減輕。在1 mg/kg/天，或約臨床劑量的19倍，注意到對發育指標無不良影響。在大鼠和兔子胚胎胎兒發育研究中，於相當於人類妊娠頭三個月的器官形成期給予dapagliflozin。在兔子，任何測試劑量都沒有觀察到發育毒性。在大鼠，dapagliflozin最高劑量達75mg/kg/天或最大臨床劑量10mg的1441倍劑量下，無造成胚胎死亡，也無致畸胎性。大鼠在較高劑量≥ 150mg/kg或10mg臨床劑量之2344倍時，觀察到胎兒血管、肋骨、脊椎、胸骨柄畸形和骨骼變異。

8.3 授乳婦女
不知道Forxiga是否分泌至人類乳汁中。Dapagliflozin分泌至大鼠乳汁中，為達到母體血漿濃度的0.49倍。幼年大鼠直接暴露於dapagliflozin的數據顯示在成熟期間對腎臟發育具危險性(腎盂和腎小管擴張)。因為人類腎臟在子宮內和生命頭2年期間發育成熟，這段時間哺乳暴露可能對發育中的人類腎臟有危險。因為許多藥物會分泌至人類乳汁中，又因Forxiga可能對喝母奶的嬰兒造成嚴重不良反應，故應考慮藥物對母親的重要性，來決定停止授乳或停用Forxiga。

8.4 兒童使用
尚未確定Forxiga在18歲以下兒童患者的安全性和療效。

8.5 老年人使用
建議Forxiga無須根據年齡改變劑量。在一項21項Forxiga的雙盲對照臨床安全性和療效研究的合併中，5936名使用Forxiga治療的患者中共有1424人(24%)年齡在65歲以上，207人(3.5%)是75歲以上。控制腎功能(eGFR)水平後，對年齡小於65歲和65歲以上患者的療效相似。在≥ 65歲的患者，使用Forxiga治療的患者與使用安慰劑治療的患者比較，發生血容量不足相關不良反應和腎功能不全或腎衰竭的比例較高【見警語和注意事項(5.1)和不良反應(6.1)】。

8.6 腎功能不全
在一項包括中度腎功能不全患者(eGFR 30至低於60mL/min/1.73m²)的研究中評估Forxiga的安全性和療效。與使用安慰劑治療的患者比較，有中度腎功能不全的患者使用Forxiga治療，血糖控制沒有改善【見臨床研究(14.7)】，而且有更多腎臟相關不良反應和更多骨折【見劑量和給藥方法(2.2)，警語和注意事項(5.3)，和不良反應(6.1)】；因此，在此族群中不應開始Forxiga。
根據其作用機制，預計Forxiga對有嚴重腎功能不全(eGFR低於30 mL/min/1.73m²)或末期腎病(ESRD)的患者無效【見禁忌(4)】。

8.7 肝功能不全
對有輕度、中度、或嚴重肝功能不全患者並無調整劑量之建議。但是，在有嚴重肝功能不全患者中，應個別評估使用dapagliflozin的獲益−風險，因為尚未在此族群專門研究dapagliflozin的安全性和療效【見臨床藥理學(12.3)】。

10 藥物過量
在Forxiga臨床開發計畫期間沒有用藥過量報告。
倘若藥物過量，聯繫美國中毒控制中心。採取支持性措施也是合理的，由患者的臨床狀態決定。未曾研究通過血液透析去除dapagliflozin。

11 描述
Dapagliflozin化學上被描述為D-glucitol, 1, 5-anhydro-1-*C*-[4-chloro-3-[(4-ethoxyphenyl) methyl]phenyl]-, (1*S*)-, compounded with (2*S*)-1, 2-propanediol, hydrate (1:1:1)。經驗式為$C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$，分子量502.98。結構式為：

Forxiga為口服膜衣錠，含有相當於5mg dapagliflozin的dapagliflozin propanediol或相當於10mg dapagliflozin的dapagliflozin propanediol，和以下無活性成分：微晶纖維素、無水乳糖、交聯聚維酮(crospovidone)、二氧化矽、和硬脂酸鎂。此外，膜衣含下列無活性成分：聚乙烯醇、二氧化鈦、聚乙二醇、滑石、和黃色氧化鐵。

12 臨床藥理學

12.1 作用機制
在近端腎小管表現的鈉−葡萄糖共同轉運蛋白2(SGLT2)，負責從人類腎小管腔再吸收大部分被過濾的葡萄糖。Dapagliflozin是SGLT2的抑制劑。Dapagliflozin經由抑制SGLT2減少被過濾的葡萄糖再吸收，和減低腎葡萄糖閾值，因此增加葡萄糖經由尿液排泄。

12.2 藥效學
一般
對健康受試者和第二型糖尿病患者給予dapagliflozin後，觀察到尿中葡萄糖排泄量增加(見圖1)。在第二型糖尿病患者中，給予dapagliflozin每天5mg或10mg共12週導致在12週時每天尿中葡萄糖排泄約70克。在dapagliflozin每天20mg的劑量觀察到接近最大之葡萄糖排泄。這種dapagliflozin引起的尿葡萄糖排泄也導致尿量增加【見不良反應(6.1)】。

〔圖1〕在健康受試者和第二型糖尿病受試者(T2DM)中，24小時尿葡萄糖量之從基線變化相對於dapagliflozin劑量的散佈圖和配適線(Fitted Line)(半對數圖)

心臟電生理
在一項健康受試者的研究中，每日劑量高達dapagliflozin 150mg(建議最大劑量的15倍)未伴隨臨床上有意義的QTc間期延長。此外，在健康受試者中，給予單劑量達dapagliflozin 500mg(建議最大劑量的50倍)未觀察到對QTc間期臨床上有意義的影響。

12.3 藥動學
吸收
口服給予dapagliflozin後，在空腹狀態下通常2小時內達到最高血漿濃度(Cmax)。在治療劑量範圍內，Cmax和AUC值隨劑量增加之比例增加。給予10mg劑量後，dapagliflozin的絕對口服生體可用率為78%。Dapagliflozin與高脂肪餐併服，減低其Cmax達50%，延長Tmax約1小時，但與空腹狀態比較，AUC不變。不認為這些變化有臨床意義，dapagliflozin可空腹或隨餐服用。

分佈
Dapagliflozin約有91%與蛋白結合。有腎或肝功能不全的患者，蛋白結合不變。

代謝
Dapagliflozin的代謝主要藉由UGT1A9；CYP媒介代謝在人類是次要清除途徑。Dapagliflozin被廣泛代謝，主要產生dapagliflozin 3-O-glucuronide，其為無活性代謝物。Dapagliflozin 3-O-glucuronide佔50mg [14C]-dapagliflozin劑量的61%，是人類血漿中主要的藥物相關成分。

排除
Dapagliflozin和相關代謝物主要透過腎途徑排除。給予單劑量[14C]-dapagliflozin 50mg後，總放射活性的75%和21%分別被排泄到尿和糞便中。在尿中，原型藥物的排泄小於2%劑量。在糞中，約15%劑量以原型藥物排泄。單次口服Forxiga 10mg劑量後，dapagliflozin平均血漿末相半衰期($t_{½}$)約12.9小時。

特殊族群
腎功能不全
在穩定狀態(dapagliflozin 20mg每天1次共7天)，有輕度、中度、或嚴重腎功能不全(由eGFR判定)的第二型糖尿病患者，當與腎功能正常的第二型糖尿病患者比較，其幾何平均dapagliflozin全身暴露量分別增加為1.45倍、2.04倍、和3.03倍。在腎功能不全的第二型糖尿病患者，較高的dapagliflozin全身暴露量不會導致相應較高的24小時尿葡萄糖排泄。在有輕度、中度、和嚴重腎功能不全的第二型糖尿病患者，穩定狀態24小時尿葡萄糖排泄分別比腎功能正常的第二型糖尿病患者低42%、80%、和90%。不清楚血液透析對dapagliflozin暴露量的影響。【見劑量和給藥方法(2.2)，警語和注意事項(5.3)，在特殊族群中使用(8.6)，和臨床研究(14.7)】。

肝功能不全
在有輕度和中度肝功能不全的受試者(Child-Pugh分類A和B級)給予dapagliflozin 10mg單劑量後，dapagliflozin的平均Cmax和AUC分別比健康匹配對照受試者高出達12%和36%。不認為這些差別有臨床上意義。在有嚴重肝功能不全患者(Child-Pugh分類C級)，dapagliflozin的平均Cmax和AUC分別比健康匹配對照組高出至40%和67%【見在特殊族群中使用(8.7)】。

年齡、性別、種族、體重對藥動學的影響
根據群體藥動學分析，年齡、性別、種族、體重對dapagliflozin的藥動學沒有臨床上有意義的影響，因此無調整劑量之建議。

兒童
尚未在兒童族群研究藥動學。

藥物交互作用
藥物交互作用的體外評估
在體外研究中，dapagliflozin和dapagliflozin 3-O-glucuronide都不抑制CYP 1A2、2C9、2C19、2D6、或3A4，也不誘導CYP 1A2、2B6、或3A4。Dapagliflozin是P-糖蛋白(P-gp)主動轉運蛋白的弱受質，而dapagliflozin 3-O-glucuronide是OAT3主動轉運蛋白的受質。Dapagliflozin或dapagliflozin 3-O-glucuronide沒有有意義地抑制P-gp、OCT2、OAT1、或OAT3主動轉運蛋白。總之，dapagliflozin不太可能影響同時給予是P-gp、OCT2、OAT1或OAT3受質藥物的藥動學。

其他藥物對Dapagliflozin的影響
表6顯示併用藥物對dapagliflozin藥動學的影響。建議無需調整dapagliflozin的劑量。

〔表6〕併用藥物對dapagliflozin全身暴露量的影響

併用藥物(給藥法)*	Dapagliflozin(給藥法)*	對dapagliflozin全身暴露量的影響(變化%[90% CI])	
		Cmax	AUC†
以下無須調整劑量			
口服降血糖藥			
Metformin (1000mg)	20mg	↔	↔
Pioglitazone (45mg)	50mg	↔	↔
Sitagliptin (100mg)	20mg	↔	↔
Glimepiride (4mg)	20mg	↔	↔
Voglibose (0.2mg每天3次)	10mg	↔	↔
其他藥物			
Hydrochlorothiazide (25mg)	50mg	↔	↔
Bumetanide (1mg)	10mg每天1次共7天	↔	↔
Valsartan (320mg)	20mg	↓12% [↓3%, ↓20%]	↔
Simvastatin (40mg)	20mg	↔	↔
抗感染藥			
Rifampin (600mg每天1次共6天)	10mg	↓7% [↓22%, ↑11%]	↓22% [↓27%, ↓17%]
非類固醇抗發炎藥			
Mefenamic Acid (負荷劑量500mg，之後每6小時250mg共14劑)	10mg	↑13% [↑3%, ↑24%]	↑51% [↑44%, ↑58%]

* 單劑量，除非另有說明。
† 對於給予單劑量之藥物AUC=AUC(INF)，對於給予多劑量之藥物AUC=AUC(TAU)。
↔=無變化(試驗：對照的幾何平均比值在0.80至1.25範圍內)；↓或↑=同時給藥與單獨給予dapagliflozin比較，參數分別是較低或較高(試驗：對照的幾何平均比值低於0.80或高於1.25)。

Dapagliflozin對其他藥物的影響
表7顯示dapagliflozin對其他併用藥物的影響。Dapagliflozin對併用藥物的藥動學沒有有意義的影響。

〔表7〕Dapagliflozin對併用藥物全身暴露量的影響

併用藥物(給藥法)*	Dapagliflozin(給藥法)*	對併用藥物全身暴露量的影響(變化%[90% CI])	
		Cmax	AUC†
以下無須調整劑量			
口服降血糖藥			
Metformin (1000mg)	20mg	↔	↔
Pioglitazone (45mg)	50mg	↓7% [↓25%, ↑15%]	↔
Sitagliptin (100mg)	20mg	↔	↔
Glimepiride (4mg)	20mg	↔	↑13% [0%, ↑29%]
其他藥物			
Hydrochlorothiazid (25mg)	50mg	↔	↔
Bumetanide (1mg)	10mg每天1次共7天	↑13% [↓2%, ↑31%]	↑13% [↓1%, ↑30%]
Valsartan (320mg)	20mg	↓6% [↓24%, ↑16%]	↑5% [↓15%, ↑29%]
Simvastatin (40mg)	20mg	↔	↑19%
Digoxin (0.25mg)	負荷劑量20mg，之後10mg每天1次共7天	↔	↔

併用藥物（給藥法）*	Dapagliflozin（給藥法）*	對併用藥物全身暴露量的影響（變化％[90% CI]）	
		Cmax	AUC†
Warfarin（25mg）	負荷劑量20mg，之後10mg每天1次共7天	↔	↔

* 單劑量，除非另有說明。
† 對於給予單劑量之藥物AUC＝AUC（INF），對於給予多劑量之藥物AUC＝AUC（TAU）。
↔＝無變化（試驗：對照的幾何平均比值在0.80至1.25範圍內）；↓或↑＝同時給藥與單獨給予dapagliflozin比較，參數分別是較低或較高（試驗：對照的幾何平均比值低於0.80或高於1.25）。

13 非臨床毒理學

13.1 致癌性、致突變性、生育能力受損

在小鼠或大鼠執行2年致癌性研究中，dapagliflozin在任何劑量組皆無誘發腫瘤。小鼠的口服劑量為雄性：5、15、和40mg/kg/天，雌性：2、10、和20mg/kg/天；大鼠的口服劑量雄性和雌性均為0.5、2、和10mg/kg/天。根據AUC暴露，在小鼠的最高評估劑量約為臨床劑量每天10mg之暴露量的72倍（雄性）和105倍（雌性）。根據AUC暴露，在大鼠的最高劑量約為臨床劑量每天10mg之暴露量的131倍（雄性）和186倍（雌性）。

Dapagliflozin在Ames致突變性試驗是陰性，體外染色體變異試驗在加入S9活化和濃度≥ 100μg/mL時是陽性。Dapagliflozin在大鼠體內評估微核或DNA修復的研究中，在大鼠暴露倍數＞2100倍臨床劑量時，染色體變異是陰性。

在動物研究中無觀察到致癌性或致突變性信號，推測dapagliflozin對人類無顯示基因毒性風險。

Dapagliflozin在暴露倍數分別為男性和女性人類最大建議劑量≤ 1708倍和998倍時，對給藥的雄性或雌性大鼠交配、生育能力、或早期胚胎發育沒有影響。

14 臨床研究

14.1 Forxiga對第二型糖尿病的臨床研究概述

Forxiga曾作為單一治療，與metformin、pioglitazone、磺醯尿素類（glimepiride）、sitagliptin（有或無metformin）、metformin加一種sulfonylurea、或胰島素（有或無其他口服降糖藥治療）併用進行研究並與一種磺醯尿素類藥物（glipizide）比較。Forxiga也曾在有中度腎功能不全的第二型糖尿病患者中進行研究。

Forxiga用作單一治療和與metformin、glimepiride、pioglitazone、sitagliptin、或胰島素併用，與對照組比較，在24週時HbA1c從基線的平均變化產生統計上顯著的改善。在包括性別、年齡、種族、病程、和基線BMI等子群都見到HbA1c減低。

14.2 單一治療

總共840名未治療過的控制不佳第二型糖尿病患者參加2項安慰劑對照研究，評估Forxiga單一治療的安全性和療效。

在一項單一治療研究中，總共558名未治療過的控制不佳第二型糖尿病患者參加24週的研究。在2週飲食和運動安慰劑導入期後，485名HbA1c ≥ 7%和≤ 10%的患者被隨機分至Forxiga 5mg或Forxiga 10mg每天1次，在早晨（QAM，主要群組）或傍晚（QPM）服藥，或安慰劑。

在第24週，與安慰劑比較，使用Forxiga 10mg QAM治療顯著改善HbA1c和FPG（見表8）。

〔表8〕在第2型糖尿病患者中Forxiga單一治療安慰劑對照研究在第24週的結果（LOCF*）（主要群組AM劑量）

療效參數	Forxiga 10mg N=70†	Forxiga 5mg N=64†	安慰劑 N=75†
HbA1c（%）			
基線（平均值）	8.0	7.8	7.8
從基線變化（校正平均值‡）	−0.9	−0.8	−0.2
與安慰劑差異（校正平均值‡）（95% CI）	−0.7§（−1.0, −0.4）	−0.5（−0.8, −0.2）	
達到HbA1c < 7%的患者百分比以基線值校正	50.8%¶	44.2%¶	31.6%
FPG（mg/dL）			
基線（平均值）	166.6	157.2	159.9
從基線變化（校正平均值‡）	−28.8	−24.1	−4.1
與安慰劑差異（校正平均值‡）（95% CI）	−24.7§（−35.7, −13.6）	−19.9（−31.3, −8.5）	

* LOCF：採最後觀察值（對援救患者援救前）前推法。
† 所有隨機分配患者在短期雙盲期間至少使用1劑雙盲藥物。
‡ 對基線值校正的最小平方平均值。
§ 相較於安慰劑之p值< 0.0001。靈敏度分析產生與安慰劑治療差異的較小估算值。
¶ 對次要終點逐次檢定過程的結果未評估統計學意義。

14.3 與metformin XR初始合併治療

總共1241名未治療過的控制不佳第二型糖尿病患者（HbA1c ≥ 7.5%和≤ 12%）參加2項為期24週的活性藥物對照研究，評估使用Forxiga 5mg或10mg與metformin緩釋劑型（XR）合併初始治療。

在第一項研究中，638名患者在1週導入期後被隨機分至3個治療組：Forxiga 10mg加metformin XR（高達每天2000mg）、Forxiga 10mg加安慰劑、或metformin XR（高達每天2000mg）加安慰劑。Metformin XR劑量在耐受情況下，以500mg的增量每週向上調整，中位劑量達到2000mg。

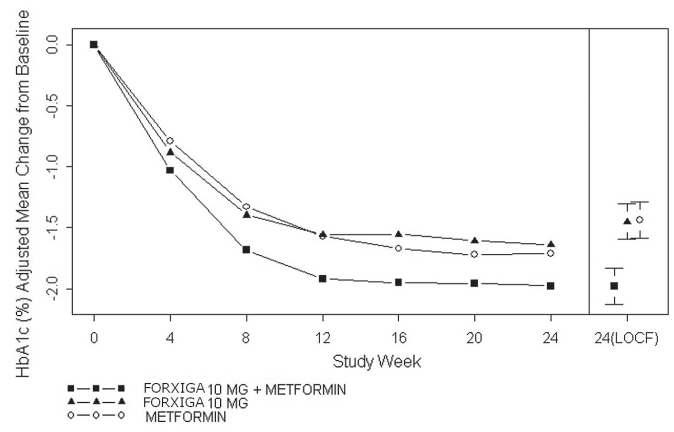
Forxiga 10mg加metformin XR的合併治療與任一種單一治療比較，HbA1c和FPG都有統計上顯著的改善；與單獨使用metformin XR比較，有統計上顯著的體重減輕（見表9和圖2）。Forxiga 10mg單一治療與單獨使用metformin比較，也有統計上顯著的FPG改善和統計上顯著的體重減輕，在降低HbA1c方面不劣於metformin XR單一治療。

〔表9〕Forxiga與metformin XR初始合併治療的活性藥物對照研究在第24週的結果（LOCF*）

療效參數	Forxiga 10mg + Metformin XR	Forxiga 10mg	Metformin XR
	N=211†	N=219†	N=208†
HbA1c（%）			
基線（平均值）	9.1	9.0	9.0
從基線變化（校正平均值‡）	−2.0	−1.5	−1.4
與Forxiga差異（校正平均值‡）（95% CI）	−0.5§（−0.7, −0.3）		
與metformin XR差異（校正平均值‡）（95% CI）	−0.5§（−0.8, −0.3）	0.0¶（−0.2, 0.2）	
達到HbA1c < 7%的患者百分比以基線值校正	46.6%#	31.7%	35.2%
FPG（mg/dL）			
基線（平均值）	189.6	197.5	189.9
從基線變化（校正平均值‡）	−60.4	−46.4	−34.8
與Forxiga差異（校正平均值‡）（95% CI）	−13.9§（−20.9, −7.0）		
與metformin XR差異（校正平均值‡）（95% CI）	−25.5§（−32.6, −18.5）	−11.6#（−18.6, −4.6）	
體重（kg）			
基線（平均值）	88.6	88.5	87.2
從基線變化（校正平均值‡）	−3.3	−2.7	−1.4
與metformin XR差異（校正平均值‡）（95% CI）	−2.0§（−2.6, −1.3）	−1.4§（−2.0, −0.7）	

* LOCF：採最後觀察值（對援救患者援救前）前推法。
† 所有隨機分配患者在短期雙盲期間至少使用1劑雙盲藥物。
‡ 對基線值校正的最小平方平均值。
§ p值 < 0.0001。
¶ 不劣於metformin XR。
# p值 < 0.05。

〔圖2〕在一項Forxiga與metformin XR初始合併治療的24週活性藥物對照研究中，HbA1c（%）隨時間從基線的校正平均變化



Left side graph: Values for adjusted mean change from baseline based on a longitudinal repeated measures model, including randomized subjects who completed the study with both baseline and Week 24 HbA1c values without rescue.
Right side graph for Week 24 (LOCF): Values for adjusted mean change from baseline and 95% CIs based on an ANCOVA model, including randomized subjects with a baseline and at least one post baseline HbA1c before rescue.

在第二項研究中，603名患者在1週導入期後被隨機分至3個治療組：Forxiga 5mg加metformin XR（高達每天2000mg）、Forxiga 5mg加安慰劑、或metformin XR（高達每天2000mg）加安慰劑。Metformin XR劑量在耐受情況下，以500mg的增量每週向上調整，中位劑量達到2000mg。

Forxiga 5mg加metforminXR的合併治療與任一種單一治療治療比較，HbA1c和FPG都有統計上顯著的改善；與單獨使用metformin XR比較，有統計上顯著的體重減輕（見表10）。

〔表10〕Forxiga與metformin XR初始合併治療的活性藥物對照研究在第24週的結果（LOCF*）

療效參數	Forxiga 5mg + Metformin XR	Forxiga 5mg	Metformin XR
	N=194†	N=203†	N=201†
HbA1c（%）			
基線（平均值）	9.2	9.1	9.1
從基線變化（校正平均值‡）	−2.1	−1.2	−1.4
與Forxiga差異（校正平均值‡）（95% CI）	−0.9§（−1.1, −0.6）		
與metformin XR差異（校正平均值‡）（95% CI）	−0.7§（−0.9, −0.5）		
達到HbA1c < 7%的患者百分比以基線值校正	52.4%¶	22.5%	34.6%
FPG（mg/dL）			
基線（平均值）	193.4	190.8	196.7
從基線變化（校正平均值‡）	−61.0	−42.0	−33.6
與Forxiga差異（校正平均值‡）（95% CI）	−19.1§（−26.7, −11.4）		
與metformin XR差異（校正平均值‡）（95% CI）	−27.5§（−35.1, −19.8）		
體重（kg）			
基線（平均值）	84.2	86.2	85.8
從基線變化（校正平均值‡）	−2.7	−2.6	−1.3
與metformin XR差異（校正平均值‡）（95% CI）	−1.4§（−2.0, −0.7）		

* LOCF：採最後觀察值（對援救患者援救前）前推法。
† 所有隨機分配患者在短期雙盲期間至少使用1劑雙盲藥物。
‡ 對基線值校正的最小平方平均值。
§ p值 < 0.0001。
¶ p值 < 0.05。

14.4 附加於metformin

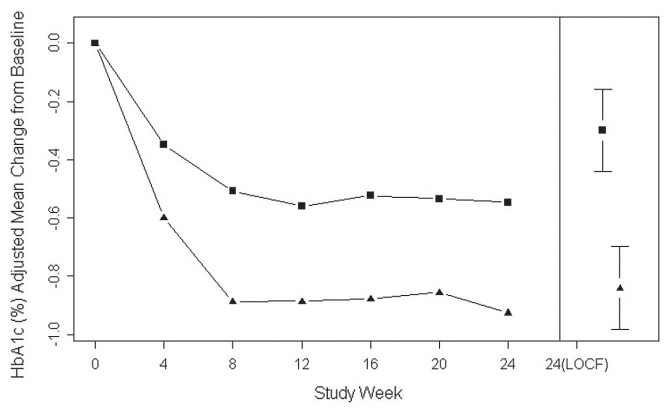
總共546名血糖控制不佳（HbA1c ≥ 7%和≤ 10%）的第二型糖尿病患者參加一項24週安慰劑對照研究，評估Forxiga與metformin合併使用。服用metformin至少每天1500mg劑量的患者，完成2週單盲安慰劑導入期後，合格的患者除了他們當時的metformin劑量之外，被隨機分至Forxiga 5mg、Forxiga 10mg、或安慰劑。作為附加於metformin的治療，Forxiga 10mg與安慰劑比較，在24週時，HbA1c和FPG有統計上顯著的改善和統計上顯著的體重減輕（見表11和圖3）。相對於安慰劑加metformin，使用Forxiga 5mg和10mg加metformin有統計上顯著的收縮壓從基線平均變化，分別為−4.5mmHg和−5.3mmHg（兩種劑量都是p < 0.05）。

〔表11〕Forxiga附加於metformin合併治療的安慰劑對照研究在第24週的結果（LOCF*）

療效參數	Forxiga 10mg + Metformin N=135†	Forxiga 5mg + Metformin N=137†	安慰劑 + Metformin N=137†
HbA1c（%）			
基線（平均值）	7.9	8.2	8.1
從基線變化（校正平均值‡）	−0.8	−0.7	−0.3
與安慰劑差異（校正平均值‡）（95% CI）	−0.5§（−0.7, −0.3）	−0.4§（−0.6, −0.2）	
達到HbA1c < 7%的患者百分比以基線值校正	40.6%¶	37.5%¶	25.9%
FPG（mg/dL）			
基線（平均值）	156.0	169.2	165.6
在第24週從基線變化（校正平均值‡）	−23.5	−21.5	−6.0
與安慰劑差異（校正平均值‡）（95% CI）	−17.5§（−25.0, −10.0）	−15.5§（−22.9, −8.1）	
在第1週從基線變化（校正平均值‡）	−16.5§（N=115）	−12.0§（N=121）	1.2（N=126）
體重（kg）			
基線（平均值）	86.3	84.7	87.7
從基線變化（校正平均值‡）	−2.9	−3.0	−0.9
與安慰劑差異（校正平均值‡）（95% CI）	−2.0§（−2.6, −1.3）	−2.2§（−2.8, −1.5）	

* LOCF：採最後觀察值（對援救患者援救前）前推法。
† 所有隨機分配患者在短期雙盲期間至少使用1劑雙盲藥物。
‡ 對基線值校正的最小平方平均值。
§ 相較於安慰劑+metformin，p值 < 0.0001。
¶ 相較於安慰劑+metformin，p值 < 0.05。

〔圖3〕在Forxiga與metformin併用的24週安慰劑對照研究中，HbA1c（%）隨時間從基線的校正平均變化



Left side graph: Values for adjusted mean change from baseline based on a longitudinal repeated measures model, including randomized subjects who completed Short-Term Period with both baseline and Week 24 HbA1c values without rescue.
Right side graph for Week 24 (LOCF): Values for adjusted mean change from baseline and 95% CIs based on an ANCOVA model, including randomized subjects with a baseline and at least one post baseline HbA1c before rescue.

14.5 附加於metformin活性的Glipizide對照研究

在一項為期52週的glipizide對照非劣效性研究中，總共816名血糖控制不佳的第二型糖尿病患者（HbA1c > 6.5%和≤ 10%）被隨機分組，評估Forxiga作為metformin的附加治療。服用metformin至少每天1500mg劑量的患者完成2週單盲安慰劑導入期後，被隨機分至glipizide組或dapagliflozin組（劑量分別是5mg或2.5mg），18週內調高劑量以達到最佳血糖作用（FPG < 110mg/dL，< 6.1mmol/L）或至患者耐受的最高劑量（直至glipizide 20mg，Forxiga 10mg）。其後，除了調降劑量防止低血糖以外，劑量保持固定。

劑量調整期結束時，87%使用Forxiga治療的患者已調整至最大研究劑量（10mg），與73%使用glipizide治療的患者相對（20mg）。第52週時（LOCF），Forxiga與glipizide比較，HbA1c從基線的平均減低相似，因此證實非劣效性（見表12）。第52週時（LOCF），Forxiga治療組有統計上顯著的體重從基線平均減低，相較之下，glipizide組體重平均增加。Forxiga加metformin相對於glipizide加metformin，有統計上顯著的（p < 0.0001）收縮壓從基線平均變化，為−5.0mmHg。

〔表12〕一項活性藥品對照研究比較Forxiga和Glipizide附加於metformin在第52週（LOCF*）的結果

療效參數	Forxiga + Metformin N=400†	Glipizide + Metformin N=401†
HbA1c（%）		
基線（平均值）	7.7	7.7
從基線變化（校正平均值‡）	−0.5	−0.5
與glipizide+metformin差異（校正平均值‡）（95% CI）	0.0§（−0.1, 0.1）	
體重（kg）		
基線（平均值）	88.4	87.6
從基線變化（校正平均值‡）	−3.2	1.4
與glipizide+metformin差異（校正平均值‡）（95% CI）	−4.7¶（−5.1, −4.2）	

* LOCF：採最後觀察值（對援救患者援救前）前推法。
† 所有隨機分配患者在短期雙盲期間至少使用1劑雙盲藥物。
‡ 對基線值校正的最小平方平均值。
§ 不劣於glipizide+metformin。
¶ p值 < 0.0001。

14.6 與其他抗糖尿病藥物附加合併治療

與磺醯尿素類藥物附加合併治療

在這項24週安慰劑對照研究中，總共597名血糖控制不佳的第二型糖尿病患者（HbA1c ≥ 7%和≤ 10%）被隨機分組，評估Forxiga與glimepiride（一種磺醯尿素類藥物）合併使用。

使用glimepiride的最大建議劑量至少一半作為單一治療（4mg）至少8週導入的患者，除了glimepiride每天4mg之外，被隨機分至Forxiga 5mg、Forxiga 10mg、或安慰劑組。治療期間允許因低血糖調降glimepiride劑量至2mg或0mg；不許調高glimepiride劑量。

與安慰劑加glimepiride比較，Forxiga 10mg與glimepiride併用時，在第24週，HbA1c、FPG和餐後2小時血糖[PPG]有統計上顯著的改善，和統計上顯著的體重減輕（見表13）。Forxiga 5mg和10mg加glimepiride相對於安慰劑加glimepiride，有統計上顯著的收縮壓從基線平均變化（兩種劑量都是p < 0.05），分別是−2.8mmHg和−3.8mmHg。

與Metformin和一種磺醯尿素類藥物附加合併治療

總共218名血糖控制不佳（HbA1c ≥ 7%和≤ 10.5%）的第二型糖尿病患者參加一項24週安慰劑對照研究，評估Forxiga與metformin和一種磺醯尿素類藥物合併使用。收案前服用metformin（立即釋放或緩釋劑型）≥每天1500mg穩定劑量加磺醯尿素類藥物最大耐受劑量（必須至少是最大劑量的一半）至少8週的患者，在8週安慰劑導入期後被隨機分至Forxiga 10mg組或安慰劑組。在24週治療期間不許調整Forxiga或metformin的劑量；允許調降磺醯尿素類藥物的劑量以預防低血糖，但不許調高。作為metformin和一種磺醯尿素類藥物的附加治療，Forxiga 10mg治療與安慰劑比較，在第24週時HbA1c和FPG有統計上顯著的改善，以及統計上顯著的體重減輕（表13）。Forxiga 10mg與metformin和一種磺醯尿素類藥物併用相對於安慰劑metformin和一種磺醯尿素類藥物併用，在第8週時有統計上顯著的（p < 0.05）收縮壓從基線平均變化−3.8mmHg。

與一種Thiazolidinedione類藥物附加合併治療

總共420名血糖控制不佳（HbA1c ≥ 7%和≤ 10.5%）的第二型糖尿病患者參加一項24週安慰劑對照研究，評估Forxiga與單獨pioglitazone（一種Thiazolidinedione類藥物[TZD]）併用。服用pioglitazone每天45mg（或每天30mg，如果不能忍受每天45mg）穩定劑量共12週的患者，在2週導入期後被隨機分組，除了他們當時的pioglitazone劑量外，添加Forxiga 5、10mg或安慰劑。研究期間不許調整Forxiga或pioglitazone的劑量。

Forxiga 10mg與pioglitazone併用治療時，與安慰劑加pioglitazone治療組比較，在第24週時HbA1c、2小時PPG、FPG、達到HbA1c < 7%的患者比例有統計上顯著的改善，和統計上顯著的體重減輕（見表13）。Forxiga 10mg與pioglitazone併用相對於安慰劑與pioglitazone併用，有統計上顯著的（p < 0.05）收縮壓從基線平均變化−4.5mmHg。

與DPP4抑制劑附加合併治療

總共452名未曾用藥治療，或在納入時單獨用或併用metformin或DPP4抑制劑治療的血糖控制不佳的第二型糖尿病患者（在隨機分組時HbA1c ≥ 7.0%和≤ 10.0%）參加一項24週安慰劑對照研究，評估Forxiga與sitagliptin（一種DPP4抑制劑）有或無metformin合併使用。

合格的患者根據有無背景metformin（≥每天1500mg）分層，在各層內被隨機分至Forxiga 10mg加sitagliptin 100mg每天1次，或安慰劑加sitagliptin 100mg每天1次。對總體研究組（sitagliptin不論有無metformin）和各分層（單獨使用sitagliptin或併用sitagliptin與metformin）測試Forxiga 10mg相較於安慰劑的療效指標。37%患者未曾用藥治療，32%單獨使用metformin，13%單獨使用DPP4抑制劑，18%使用DPP4抑制劑加metformin。研究期間不許調整Forxiga、sitagliptin、或metformin的劑量。

與安慰劑加sitagliptin（有或無metformin）組比較，Forxiga 10mg與sitagliptin（有或無metformin）併用時，在第24週時HbA1c和FPG有統計上顯著的改善，和統計上顯著的體重減輕（見表13）。這些改善也在接受Forxiga 10mg加sitagliptin的患者層見到（HbA1c安慰劑校正平均變化−0.56%；n=110），與安慰劑加sitagliptin比較（n=111）；並在接受Forxiga 10mg加sitagliptin和metformin患者層見到（HbA1c安慰劑校正平均變化−0.40；n=113），與安慰劑加sitagliptin與metformin（n=113）比較。

與胰島素附加合併治療

在一項24週安慰劑對照研究中，總共808名血糖控制不佳的第二型糖尿病患者（HbA1c ≥ 7.5%和≤ 10.5%）被隨機分組，評估Forxiga作為胰島素的附加治療。患者在納入前接受穩定胰島素療法至少8週，平均劑量至少每天30IU注射用胰島素，以及服用最多2種口服降血糖藥（OADs），包括metformin，完成2週納入期後，除了他們當時的胰島素劑量和其他OADs（如適用）以外，隨機接受Forxiga 5mg、Forxiga 10mg、或安慰劑。患者根據有無背景OADs分層。未達成特定血糖目標的患者，在治療期間只容許調高或調降胰島素劑量。除了在停止胰島素治療後因顧慮低血糖減低OAD（s）劑量以外，治療期內不許調整盲性研究藥物或OAD（s）劑量。

在這項研究中，50%患者在基線時使用胰島素單一治療，另外50%除了胰島素還使用1或2種OADs。在第24週，與安慰劑與胰島素併用，有或無最多2種OADs比較，Forxiga 10mg劑量組有統計上顯著的HbA1c改善，平均胰島素劑量減少，和統計上顯著的體重減輕（見表13）；在單獨使用胰島素治療的患者和使用胰島素加OAD治療的患者中，Forxiga對HbA1c的作用相似。Forxiga 10mg與胰島素併用相對於安慰劑與胰島素併用，有統計上顯著的（p < 0.05）收縮壓平均從基線變化−3.0mmHg。

在第24週，與安慰劑與胰島素併用比較，Forxiga 5mg（與安慰劑差值−5.7IU）和10mg（與安慰劑差值−6.2IU）每天1次有統計上顯著的平均每日胰島素劑量減低（兩種劑量都是p < 0.0001），而使用Forxiga 10mg有統計上顯著較高比例的患者（19.6%）與安慰劑比較（11.0%），其胰島素劑量減低至少10%。

〔表13〕Forxiga與降血糖藥併用的安慰劑對照研究第24週（LOCF*）的結果

療效參數	Forxiga 10mg	Forxiga 5mg	安慰劑
與磺醯尿素類併用（Glimepiride）			
意圖治療族群	N=151†	N=142†	N=145†
HbA1c（%）			
基線（平均值）	8.1	8.1	8.2
從基線變化（校正平均值‡）	−0.8	−0.6	−0.1
與安慰劑差異（校正平均值‡）（95% CI）	−0.7¶（−0.9, −0.5）	−0.5¶（−0.7, −0.3）	
達到HbA1c < 7%的患者百分比以基線值校正	31.7%¶	30.3%¶	13.0%
FPG（mg/dL）			
基線（平均值）	172.4	174.5	172.7
從基線變化（校正平均值‡）	−28.5	−21.2	−2.0
與安慰劑差異（校正平均值‡）（95% CI）	−26.5¶（−33.5, −19.5）	−19.3¶（−26.3, −12.2）	
2小時PPG#（mg/dL）			
療效參數	Forxiga 10mg	Forxiga 5mg	安慰劑
基線（平均值）	329.6	322.8	324.1
從基線變化（校正平均值‡）	−60.6	−54.5	−11.5
與安慰劑差異（校正平均值‡）（95% CI）	−49.1¶（−64.1, −34.1）	−43.0¶（−58.4, −27.5）	
Body Weight（kg）			
基線（平均值）	80.6	81.0	80.9
從基線變化（校正平均值‡）	−2.3	−1.6	−0.7
與安慰劑差異（校正平均值‡）（95% CI）	−1.5¶（−2.2, −0.9）	−0.8¶（−1.5, −0.2）	
與Metformin及一種Sulfonylurea併用			
意圖治療族群	N=108†	–	N=108†
HbA1c（%）			
基線（平均值）	8.08	–	8.24
從基線變化（校正平均值‡§）	−0.86	–	0.17
與安慰劑差異（校正平均值‡§）（95% CI）	−0.69¶（−0.89, −0.49）	–	
達到HbA1c ≥ 0.7%的患者百分比（校正百分比）	31.8%¶	–	11.1%
FPG（mg/dL）			
基線（平均值）	167.4	–	180.3
第24週時從基線變化（校正平均值‡）	−34.2	–	−0.8
與安慰劑差異（校正平均值‡）（95% CI）	−33.5¶（−43.1, −23.8）	–	
體重（kg）			
基線（平均值）	88.57	–	90.07
從基線變化（校正平均值‡）	−2.65	–	−0.58
與安慰劑差異（校正平均值‡）（95% CI）	−2.07¶（−2.79, −1.35）	–	
與Thiazolidinedione類併用（Pioglitazone）			
意圖治療族群	N=140**	N=141**	N=139**
HbA1c（%）			
基線（平均值）	8.4	8.4	8.3
從基線變化（校正平均值‡）	−1.0	−0.8	−0.4
與安慰劑差異（校正平均值‡）（95% CI）	−0.6¶（−0.8, −0.3）	−0.4¶（−0.6, −0.2）	
達到HbA1c < 7%的患者百分比以基線值校正	38.8%††	32.5%††	22.4%
FPG（mg/dL）			
基線（平均值）	164.9	168.3	160.7
從基線變化（校正平均值‡）	−29.6	−24.9	−5.5
與安慰劑差異（校正平均值‡）（95% CI）	−24.1¶（−32.2, −16.1）	−19.5¶（−27.5, −11.4）	
2小時PPG#（mg/dL）			
基線（平均值）	308.0	284.8	293.6
從基線變化（校正平均值‡）	−67.5	−65.1	−14.1
與安慰劑差異（校正平均值‡）（95% CI）	−53.3¶（−71.1, −35.6）	−51.0¶（−68.7, −33.2）	
體重（kg）			
基線（平均值）	84.8	87.8	86.4
從基線變化（校正平均值‡）	−0.1	0.1	1.6
與安慰劑差異（校正平均值‡）（95% CI）	−1.8¶（−2.6, −1.0）	−1.6¶（−2.3, −0.8）	
與DPP4抑制劑（Sitagliptin）有或無Metformin併用			
意圖治療族群	N=223†	–	N=224†
HbA1c（%）			
基線（平均值）	7.90	–	7.97
從基線變化（校正平均值‡）	−0.45	–	0.04
與安慰劑差異（校正平均值‡）（95% CI）	−0.48¶（−0.62, −0.34）	–	
達到HbA1c≥0.7%的患者百分比（校正百分比）	35.4%	–	16.6%
FPG（mg/dL）			
基線（平均值）	161.7	–	163.1
第24週時從基線變化（校正平均值‡）	−24.1	–	3.8
與安慰劑差異（校正平均值‡）（95% CI）	−27.9¶（−34.5, −21.4）	–	
體重（kg）			
基線（平均值）	91.02	–	89.23
從基線變化（校正平均值‡）	−2.14	–	−0.26
與安慰劑差異（校正平均值‡）（95% CI）	−1.89¶（−2.37, −1.40）	–	
與胰島素併用有或無最多2種口服降血糖藥			
意圖治療族群	N=194†	N=211†	N=193†
HbA1c（%）			
基線（平均值）	8.6	8.6	8.5
從基線變化（校正平均值‡）	−0.9	−0.8	−0.3
與安慰劑差異（校正平均值‡）（95% CI）	−0.6¶（−0.7, −0.5）	−0.5¶（−0.7, −0.4）	
FPG（mg/dL）			
基線（平均值）	173.7	NT‡‡	170.0
從基線變化（校正平均值‡）	−21.7	NT‡‡	3.3
與安慰劑差異（校正平均值‡）（95% CI）	−25.0¶（−34.3, −15.8）	NT‡‡	
體重（kg）			
基線（平均值）	94.6	93.2	94.2
從基線變化（校正平均值‡）	−1.7	−1.0	0.0
與安慰劑差異（校正平均值‡）（95% CI）	−1.7¶（−2.2, −1.2）	−1.0¶（−1.5, −0.5）	

* LOCF：採最後觀察值（對援救患者援救前）前推法。
† 有基線和至少1次基線後療效測定的所有隨機分配和治療患者。
‡ 對基線值校正的最小平方平均值基於共變數分析模型。
§ 對基線值校正的最小平方平均值基於長期性重複測量模型。
¶ 相較於安慰劑，p值< 0.0001。
# 餐後2小時水平作為對75克口服葡萄糖耐量試驗（OGTT）的反應。
**在短期雙盲期間至少使用1劑雙盲藥物。
†† 相較於安慰劑，p值< 0.05。
‡‡ NT：未正式測試，因為早於測試順序終點，未能達到統計上顯著的差異。

14.7 在第二型糖尿病患者和腎功能不全中使用

在一項有中度腎功能不全的糖尿病患者研究中（252名患者有平均eGFR 45mL/min/1.73m²）評估Forxiga的療效。在本研究中，Forxiga未顯示療效。在第24週Forxiga 5mg（n=83）和10mg（n=82）兩者安慰劑校正平均HbA1c變化都是−0.1%（95% CI [−0.4%, 0.2%]）。

16 包裝/儲存和處置

包裝

〔表14〕列出Forxiga（dapagliflozin）錠兩側的標記和現有含量和包裝。

錠劑單位含量	膜衣錠顏色/形狀	錠劑標記	包裝規格
5mg	黃色，雙凸，圓形	一面刻有“5” 另一面刻有“1427”	2片x14錠鋁箔盒裝
10mg	黃色，雙凸，菱形	一面刻有“10” 另一面刻有“1428”	2片x14錠鋁箔盒裝

儲存和處理

儲存於30℃以下。

17 患者用藥指導資料

指導

告知患者Forxiga的潛在風險和獲益和其他治療選項。也要告知患者關於遵守飲食指導、規律運動、定期監測血糖和HbA1c測試、識別和處理低血糖和高血糖、以及評估糖尿病併發症的重要性。建議患者在壓力期間迅速就醫，例如發熱、外傷、感染或手術，因為用藥需求可能改變。

指導患者只可遵照處方服用Forxiga。如果忘記服藥，建議患者想起來時盡快補服，若已接近下一次服藥時間，則跳過不用，於下一次服藥時間服藥。建議患者不要在同一時間服用雙倍Forxiga劑量。

告知患者使用Forxiga最常見的不良反應是生殖器黴菌感染、鼻咽炎和尿路感染。

指導患者如果懷孕了或計劃懷孕，要立即通知醫療人員。根據動物實驗數據，Forxiga在妊娠第二期和第三期可能對胎兒造成傷害。

指導患者如果正在餵母奶或打算餵母奶，要立即通知醫療人員。不知道Forxiga是否分泌至母乳中；然而，根據動物實驗數據，Forxiga可能對吃母奶的嬰兒造成傷害。

低血壓

告知患者使用Forxiga可能發生症狀性低血壓，建議他們如果遇到這種症狀要聯絡醫療人員【見警語和注意事項（5.1）】。告知患者脫水可能會增加低血壓風險，要攝取足夠的液體。

女性生殖器黴菌感染（例如外陰陰道炎）

告知女性患者可能會發生陰道酵母菌感染，提供她們陰道酵母菌感染症狀和徵象的資料。指導她們治療選項，以及何時就醫【見警語和注意事項（5.6）】。

酮酸中毒

告知患者使用Dapagliflozin有酮酸中毒的報告。若酮酸中毒的症狀發生（包括噁心、嘔吐、腹痛、全身無力、呼吸急促），指導患者檢查丙酮（當可能時）並迅速就醫，即使血糖值沒有升高【見警語和注意事項（5.2）】。

尿路感染

告知患者可能發生嚴重的尿路感染。提供他們尿路感染症狀的資料。提醒他們如果出現這種症狀要立即就醫診治【見警語和注意事項（5.5）】。

男性生殖器黴菌感染在（例如包皮龜頭炎）

告知患者男性可能發生陰莖酵母菌感染（例如龜頭炎或龜頭包皮炎），尤其是有病史的患者。提供他們龜頭炎和龜頭包皮炎（龜頭或陰莖包皮皮疹或紅腫）症狀和徵象的資料。指導他們治療選項，以及何時就醫【見警語和注意事項（5.6）】。

過敏反應

告知患者Forxiga有嚴重過敏反應（如蕁麻疹和血管性水腫）的報告。建議患者立即通報任何可能是過敏反應或血管性水腫的症狀或徵象，不要繼續服藥，直到諮詢過處方醫師。

膀胱癌

告知患者立即通報任何肉眼可見的血尿跡象或其他可能與膀胱癌有關的症狀。

實驗室檢查

由於其作用機制，服用Forxiga的患者尿液葡萄糖測試會呈陽性。

Forxiga為AstraZeneca group of companies之註冊商標
修訂日期：2016年5月

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