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New Drug Update

Dapagliflozin: a new adjunct in the treatment of Type 2 diabetes mellitus

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ABSTRACT

Diabetes mellitus (DM) Type 2 is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency. The classic symptoms are excess thirst, frequent urination, and constant hunger. Management of Type 2 diabetes focuses on lifestyle interventions, lowering other cardiovascular risk factors, and maintaining blood glucose levels in the normal range. There are several classes of anti-diabetic medications available and these include sulfonylureas, nonsulfonylurea secretagogues, alpha glucosidase inhibitors, thiazolidinediones, glucagon-like peptide-1 analog, and dipeptidyl peptidase-4 inhibitors. Recently, dapagliflozin (Farxiga™), a sodium-glucose cotransporter 2 inhibitor has been approved by Food and Drug Administration as an adjunct to diet and exercises to improve glycemic control in adults with Type 2 DM.

Keywords: Type 2 diabetes mellitus, Sodium-glucose cotransporter 2 inhibitor, Dapagliflozin

INTRODUCTION

Diabetes mellitus (DM) Type 2 is a metabolic disorder characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency.[1] The classic symptoms include excess thirst, frequent urination, and constant hunger. Treatment of Type 2 diabetes often begins with lifestyle management including diet and exercise.[2] As β-cell function declines in the presence of insulin resistance, this makes maintenance of glycemic control challenging and usually necessitates add-on therapies.[3] Inhibition of sodium-glucose cotransporter 2 (SGLT2) represents a novel approach to reduce hyperglycemia independently of insulin secretion or action.[4-7] SGLT2, located in the renal

proximal tubule, reabsorbs most of the filtered glucose[8] and its inhibition represents a new pharmacotherapy for the treatment of Type 2 diabetes. Dapagliflozin, a potent and selective SGLT2 inhibitor, has been shown to improve glycemic control in patients with Type 2 diabetes when used as monotherapy[9] or in combination with metformin,[10] sulfonylureas,[11] thiazolidinedione (TZD),[12] or insulin.[7,13] This article attempt to highlight the pharmacology, clinical studies and current regulatory status of dapagliflozin (Farxiga™) in the treatment of Type 2 DM.

PHARMACOLOGY: DAPAGLIFLOZIN

Chemical structure and description[14]

Dapagliflozin is described chemically as 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). The empirical formula is $C_{21}H_{25}ClO_6 \bullet C_3H_8O_2 \bullet H_2O$ and the molecular weight is 502.98. The structural formula is (Figure 1):

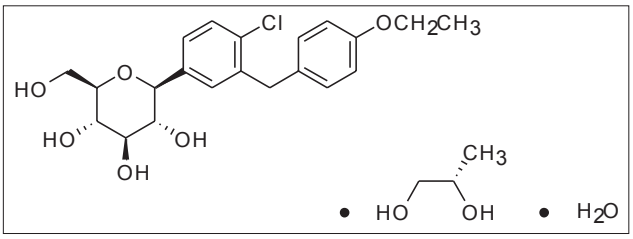

Figure 1: Chemical structure of dapagliflozin.

Dapagliflozin is available as a film-coated tablet for oral administration containing the equivalent of 5 mg dapagliflozin as dapagliflozin propanediol or the equivalent of 10 mg dapagliflozin as dapagliflozin propanediol, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, crospovidone, silicon dioxide, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and yellow iron oxide.

Mechanism of action[14]

SGLT2, expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Pharmacodynamics[15]

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with Type 2 DM following the administration of dapagliflozin. Dapagliflozin dose of 10 mg/day in patients with Type 2 DM for 12 weeks resulted in excretion of approximately 70 g of glucose in the urine per day at week 12. A near maximum glucose excretion was observed at the dapagliflozin daily dose of 20 mg. This urinary glucose excretion with dapagliflozin also results in increases in urinary volume. Dapagliflozin was not associated with clinically meaningful prolongation of corrected Q wave and the end of the T wave (QTc) interval at daily doses up to 150 mg (15 times the recommended maximum dose) in a study of healthy subjects. In addition, no clinically meaningful effect on QTc interval was observed following single doses of up to 500 mg (50 times the recommended maximum dose) of dapagliflozin in healthy subjects.

Pharmacokinetics[15]

Absorption

Following oral administration of dapagliflozin, the maximum plasma concentration (C_{max}) is usually attained within 2 hrs under fasting state. The C_{max} and area under the curve (AUC) values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Administration of dapagliflozin with a high-fat meal decreases its C_{max} by up to 50% and prolongs T_{max} by approximately 1 hr, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and dapagliflozin can be administered with or without food.

Distribution

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment.

Metabolism

The metabolism of dapagliflozin is primarily mediated by UGT1A9; cytochrome P450-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg [14C]-dapagliflozin dose and is the predominant drug-related component in human plasma.

Elimination

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [14C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, <2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life for dapagliflozin is approximately 12.9 hrs.

CLINICAL STUDIES

Overview in the treatment of Type 2 diabetes

Dapagliflozin has been studied as monotherapy and in combination with metformin, pioglitazone, glimepiride, sitagliptin (with or without metformin), or insulin (with or without other oral antidiabetic therapy). The efficacy of dapagliflozin was compared to a sulfonylurea (glipizide) added on to metformin. Dapagliflozin has also been studied in patients with Type 2 diabetes and moderate renal impairment. Treatment with dapagliflozin as monotherapy and in combination with metformin, glimepiride, pioglitazone, sitagliptin, or insulin produced statistically significant improvements in mean change from baseline at week 24 in hemoglobin A1c (HbA1c) compared to control. Reductions in HbA1c were seen across subgroups including gender, age, race, duration of disease, and baseline body mass index.

Monotherapy

In one monotherapy study, a total of 558 treatment-naive patients with inadequately controlled diabetes participated in a 24 weeks study.[9] Following a 2 weeks diet and exercise placebo lead in period, 485 patients with HbA1c ≥7% and ≤10% were randomized to dapagliflozin 5 mg or dapagliflozin 10 mg once daily in either the morning (main cohort) or evening, or placebo. At week 24, treatment with dapagliflozin 10 mg in morning provided significant improvements in HbA1c and fasting plasma glucose (FPG) compared with placebo.

Initial combination therapy with metformin

In one study, 638 patients were randomized to one of three treatment arms following a 1 week lead-in period: dapagliflozin 10 mg plus metformin extended-release (XR, up to 2000 mg/day), dapagliflozin 10 mg plus placebo, or metformin XR (up to 2000 mg/day) plus placebo. Metformin XR dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2000 mg.[10]

The combination treatment of dapagliflozin 10 mg plus metformin XR provided statistically significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and statistically significant reduction in body weight compared with metformin XR alone. Dapagliflozin 10 mg as monotherapy also provided statistically significant improvements in FPG and statistically significant reduction in body weight compared with metformin alone and was non-inferior to metformin XR monotherapy in lowering HbA1c.

In a second study, 603 patients were randomized to one of three treatment arms following a 1 week lead-in period: dapagliflozin 5 mg plus metformin XR (up to 2000 mg/day), dapagliflozin 5 mg plus placebo, or metformin XR (up to 2000 mg/day) plus placebo.[16] Metformin XR dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2000 mg. The combination treatment of dapagliflozin 5 mg plus metformin XR provided statistically significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and statistically significant reduction in body weight compared with metformin XR alone.

Add-on to metformin

A total of 546 patients with Type 2 diabetes with inadequate glycemic control (HbA1c ≥7% and ≤10%) participated in a 24 weeks, placebo-controlled study to evaluate dapagliflozin in combination with metformin.[10,17] Patients on metformin at a dose of at least 1500 mg/day were randomized after completing a 2 weeks, single-blind, placebo lead-in period. Following the lead-in period, eligible patients were randomized to dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo in addition to their current dose of metformin.

As add-on treatment to metformin, dapagliflozin 10 mg provided statistically significant improvements in HbA1c and FPG, and statistically significant reduction in body weight compared with placebo at week 24. Statistically significant ($p<0.05$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo plus metformin were −4.5 mmHg and −5.3 mmHg with dapagliflozin 5 mg and 10 mg plus metformin, respectively.

Active glipizide-controlled study add-on to metformin

A total of 816 patients with Type 2 diabetes with inadequate glycemic control (HbA1c >6.5% and ≤10%) were randomized in a 52 weeks, glipizide-controlled, noninferiority study to evaluate dapagliflozin as add-on therapy to metformin.[18] Patients on metformin at a dose of at least 1500 mg/day were randomized following a 2 weeks placebo lead-in period to glipizide or dapagliflozin (5 mg or 2.5 mg, respectively) and were up-titrated over 18 weeks to optimal glycemic effect (FPG <110 mg/dL, <6.1 mmol/L) or to the highest dose level (up to glipizide 20 mg and dapagliflozin 10 mg) as tolerated by patients. Thereafter, doses were kept constant, except for down-titration to prevent hypoglycemia.

At the end of the titration period, 87% of patients treated with dapagliflozin had been titrated to the maximum study dose (10 mg) versus 73% treated with glipizide (20 mg). Dapagliflozin led to a similar mean reduction in HbA1c from baseline at week 52 (last observation carried forward [LOCF]), compared with glipizide, thus demonstrating noninferiority. Dapagliflozin treatment led to a statistically significant mean reduction in body weight from baseline

at week 52 (LOCF) compared with a mean increase in body weight in the glipizide group. Statistically significant ($p<0.0001$) mean change from baseline in systolic blood pressure relative to glipizide plus metformin was −5.0 mmHg with dapagliflozin plus metformin.

Add-on combination therapy with a sulfonylurea

A total of 597 patients with Type 2 diabetes and inadequate glycemic control (HbA1c ≥7% and ≤10%) were randomized in this 24 weeks, placebo-controlled study to evaluate dapagliflozin in combination with glimepiride (a sulfonylurea).[11]

Patients on at least half the maximum recommended dose of glimepiride as monotherapy (4 mg) for at least 8 weeks lead-in were randomized to dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo in addition to glimepiride 4 mg/day. Down-titration of glimepiride to 2 mg or 0 mg was allowed for hypoglycemia during the treatment period; no up-titration of glimepiride was allowed.

In combination with glimepiride, dapagliflozin 10 mg provided statistically significant improvement in HbA1c, FPG, and 2 hr post-prandial plasma glucose (PPG), and statistically significant reduction in body weight compared with placebo plus glimepiride at week 24.

Statistically significant ($p<0.05$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo plus glimepiride were −2.8 mmHg and −3.8 mmHg with dapagliflozin 5 mg and 10 mg plus glimepiride, respectively.

Add-on combination therapy with a TZD

A total of 420 patients with Type 2 diabetes with inadequate glycemic control (HbA1c ≥7% and ≤10.5%) participated in a 24 weeks, placebo-controlled study to evaluate dapagliflozin in combination with pioglitazone (a TZD) alone.[12] Patients on a stable dose of pioglitazone of 45 mg/day (or 30 mg/day, if 45 mg/day was not tolerated) for 12 weeks were randomized after a 2 weeks lead-in period to 5 or 10 mg of dapagliflozin or placebo in addition to their current dose of pioglitazone. Dose titration of dapagliflozin or pioglitazone was not permitted during the study.

In combination with pioglitazone, treatment with dapagliflozin 10 mg provided statistically significant improvements in HbA1c, 2-hr PPG, FPG, the proportion of patients achieving HbA1c <7%, and a statistically significant reduction in body weight compared with the placebo plus pioglitazone treatment groups at week 24. A statistically significant ($p<0.05$) mean change from baseline in systolic blood pressure relative to placebo in combination with pioglitazone was −4.5 mmHg with dapagliflozin 10 mg in combination with pioglitazone.

Add-on combination therapy with a dipeptidyl peptidase-4 inhibitor (DPP4 inhibitor)

A total of 452 patients with Type 2 diabetes who were drug naive, or who were treated at entry with metformin or a DPP4 inhibitor alone or in combination, and had inadequate glycemic control (HbA1c ≥7.0% and ≤10.0% at randomization), participated in a 24 weeks, placebo-controlled study to evaluate dapagliflozin in combination with sitagliptin (a DPP4 inhibitor) with or without metformin.[19]

Eligible patients were stratified based on the presence or absence of background metformin (≥1500 mg/day), and within each stratum were randomized to either dapagliflozin 10 mg plus sitagliptin 100 mg once daily, or placebo plus sitagliptin 100 mg once daily. Endpoints were tested for dapagliflozin 10 mg versus placebo for the total study group (sitagliptin with and without metformin) and for each stratum (sitagliptin alone or sitagliptin with metformin). Thirty-seven percent (37%) of patients were drug naive, 32% were on metformin alone, 13% were on a DPP4 inhibitor alone, and 18% were on a DPP4 inhibitor plus metformin. Dose titration of dapagliflozin, sitagliptin, or metformin was not permitted during the study.

In combination with sitagliptin (with or without metformin), dapagliflozin 10 mg provided statistically significant improvements in HbA1c, FPG, and a statistically significant reduction in body weight compared with the placebo plus sitagliptin (with or without metformin) group at week 24. These improvements were also seen in the stratum of patients who received dapagliflozin 10 mg plus sitagliptin alone (placebo-corrected mean change for HbA1c −0.56%; n=110) compared with placebo plus sitagliptin alone (n=111), and the stratum of patients who received dapagliflozin 10 mg plus sitagliptin and metformin (placebo-corrected mean change for HbA1c −0.40; n=113) compared with placebo plus sitagliptin with metformin (n=113).

Add-on combination therapy with insulin

A total of 808 patients with Type 2 diabetes who had inadequate glycemic control (HbA1c ≥7.5% and ≤10.5%) were randomized in a 24 weeks, placebo-controlled study to evaluate dapagliflozin as add-on therapy to insulin.[7,13] Patients on a stable insulin regimen, with a mean dose of at least 30 IU of injectable insulin per day, for a period of at least 8 weeks prior to enrollment and on a maximum of 2 oral antidiabetic medications (OADs), including metformin, were randomized after completing a 2 weeks enrollment period to receive either dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo in addition to their current dose of insulin and other OADs, if applicable. Patients were stratified according to the presence or absence of background OADs. Up-or down-titration of insulin was only permitted during the treatment phase in patients who failed to meet specific glycemic goals. Dose modifications of blinded study medication or OADs

were not allowed during the treatment phase, with the exception of decreasing OADs where there were concerns over hypoglycemia after cessation of insulin therapy.

In this study, 50% of patients were on insulin monotherapy at baseline, while 50% were on one or two OADs in addition to insulin. At week 24, dapagliflozin 10 mg dose provided statistically significant improvement in HbA1c and reduction in mean insulin dose, and a statistically significant reduction in body weight compared with placebo in combination with insulin, with or without up to 2 OADs; the effect of dapagliflozin on HbA1c was similar in patients treated with insulin alone and patients treated with insulin plus OAD. Statistically significant ($p<0.05$) mean change from baseline in systolic blood pressure relative to placebo in combination with insulin was −3.0 mmHg with dapagliflozin 10 mg in combination with insulin. At week 24, dapagliflozin 5 mg (−5.7 IU, difference from placebo) and 10 mg (−6.2 IU, difference from placebo) once daily resulted in a statistically significant reduction in mean daily insulin dose ($p<0.0001$ for both doses) compared with placebo in combination with insulin, and a statistically significantly higher proportion of patients on dapagliflozin 10 mg (19.6%) reduced their insulin dose by at least 10% compared with placebo (11.0%).

Use in patients with Type 2 diabetes and renal impairment

The efficacy of dapagliflozin was assessed in a study of diabetic patients with moderate renal impairment (252 patients with mean estimated glomerular filtration rate (eGFR) 45 mL/min/1.73 m^2).[6] Dapagliflozin did not show efficacy in this study. The placebo-corrected mean HbA1c change at 24 weeks was −0.1% (95% confidence interval [−0.4%, 0.2%]) for both dapagliflozin 5 mg (n=83) and 10 mg (n=82).

REGULATORY STATUS

Dapagliflozin was granted approval by the U.S. Food and Drug Administration on January 8, 2014 to improve glycemic control, along with diet and exercise, in adults with Type 2 diabetes.[20]

INDICATION AND LIMITATION OF USE

Dapagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 DM. Dapagliflozin is not recommended for patients with Type 1 DM or for the treatment of diabetic ketoacidosis.[20]

DOSAGE AND ADMINISTRATION

Recommended dosing

The recommended starting dose of dapagliflozin is 5 mg once daily, taken in the morning, with or without food. In patients tolerating dapagliflozin 5 mg once daily who require additional glycemic control, the dose can be increased to 10 mg once daily. In patients with volume depletion, correcting this condition prior to initiation of dapagliflozin is recommended.[20]

Patients with renal impairment

Assessment of renal function is recommended prior to initiation of dapagliflozin therapy and periodically thereafter. Dapagliflozin should not be initiated in patients with an eGFR <60 mL/min/1.73 m^2. No dose adjustment is needed in patients with mild renal impairment (eGFR of 60 mL/min/1.73 m^2 or greater). Dapagliflozin should be discontinued when eGFR is persistently <60 mL/min/1.73 m^2.[20]

ADVERSE EFFECTS

In a pool of 12 placebo-controlled studies, the most common adverse reactions (≥5%) treated with dapagliflozin 5 mg, 10 mg, and placebo respectively were female genital mycotic infections (8.4% vs. 6.9% vs. 1.5%), nasopharyngitis (6.6% vs. 6.3% vs. 6.2%), and urinary tract infections (5.7% vs. 4.3% vs. 3.7%).[20]

WARNINGS AND PRECAUTIONS[20]

Hypotension

Dapagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating dapagliflozin particularly in patients with impaired renal function (eGFR <60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics. Before initiating dapagliflozin in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms of hypotension after initiating therapy.

Impairment in renal function

Dapagliflozin increases serum creatinine and decreases eGFR. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Adverse reactions related to renal function can occur after initiating dapagliflozin. Renal function should be evaluated prior to initiation of dapagliflozin and monitored periodically thereafter.

Hypoglycemia with concomitant use with insulin and insulin secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. Dapagliflozin can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin

secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with dapagliflozin.

Genital mycotic infections

Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat appropriately.

Increases in low-density lipoprotein cholesterol (LDL-C)

Increases in LDL-C occur with dapagliflozin. Monitor LDL-C and treat per standard of care after initiating dapagliflozin.

Bladder cancer

Across 22 clinical studies, newly diagnosed cases of bladder cancer were reported in 10/6045 patients (0.17%) treated with dapagliflozin and 1/3512 patient (0.03%) treated with placebo/comparator. After excluding patients in whom exposure to study drug was <1 year at the time of diagnosis of bladder cancer, there were four cases with dapagliflozin and no cases with placebo/comparator. Bladder cancer risk factors and hematuria (a potential indicator of pre-existing tumors) were balanced between treatment arms at baseline. There were too few cases to determine whether the emergence of these events is related to dapagliflozin.

There are insufficient data to determine whether dapagliflozin has an effect on pre-existing bladder tumors. Consequently, dapagliflozin should not be used in patients with active bladder cancer. In patients with prior history of bladder cancer, the benefits of glycemic control versus unknown risks for cancer recurrence with dapagliflozin should be considered.

Macrovascular outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with dapagliflozin or any other antidiabetic drug.

SPECIAL POPULATION[20]

Pregnancy

It has been assigned Category C in pregnancy. There are no adequate and well-controlled studies of dapagliflozin in pregnant women. Based on results of reproductive and developmental toxicity studies in animals, dapagliflozin may affect renal development and maturation. In a juvenile rat study, increased incidence and/or severity of renal pelvic and tubular dilatations were evident at the lowest tested dose, which was approximately 15 times clinical exposure from a 10 mg dose. These outcomes occurred with drug exposures during periods of animal development that correlate with the late second and third trimesters of human pregnancy. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. Dapagliflozin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers

It is not known whether dapagliflozin is excreted in human milk. Dapagliflozin is excreted in rat milk reaching levels 0.49 times that found in maternal plasma. Data in juvenile rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from dapagliflozin, a decision should be made whether to discontinue nursing or to discontinue dapagliflozin, taking into account the importance of the drug to the mother.

Pediatric use

Safety and effectiveness of dapagliflozin in pediatric patients under 18 years of age have not been established.

Geriatric use

No dapagliflozin dosage change is recommended based on age.

CONCLUSIONS

Dapagliflozin, with its unique and complementary mechanism of action, appears to be an important addition to the therapeutic options for the management of Type 2 diabetes, particularly when used as add-on therapy.

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