Brand Name: Farxiga

Generic Name: dapagliflozin

Manufacturer[1]: Bristol-Myers Squibb

Drug Class[1,3,4]: Antidiabetic, sodium-glucose cotransporter 2 (SGLT2) inhibitor

Uses

Labeled Uses[1,2,3,4,5]: Adjunct treatment to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Unlabeled Uses: None

Mechanism of Action[1,2,3,4,5]

Sodium-glucose cotransporter 2 (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 (RT_G), and thereby increases urinary glucose excretion.

Pharmacokinetics[1,2,3,4,5]

T_{max}	2 hours (fasting)
V_d	Not reported
$t_{1/2}$	12.9
Clearance (CL)	Not reported
Protein binding	91%
Bioavailability (F)	78% (10mg dose)

Distribution: Protein binding is not altered in patients with renal or hepatic impairment

Metabolism: Dapagliflozin is extensively metabolized, primarily to yield the inactive metabolite dapagliflozin 3-O-glucoronide. Metabolism is mediated by UGT1A9 via O-glucoronidation with CYP3A4-mediated metabolism being a minor clearance pathway in humans. Dapagliflozin 3-O-glucoronide accounts for 61% of a 50mg dapagliflozin dose and is the predominant drug-related component in human plasma.

Elimination: Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. It has been shown that with a single dose of 50mg of dapagliflozin, 75% and 21% is excreted in the urine and feces, respectively. In the urine, less than 2% of the dose is excreted as parent drug. In the feces, approximately 15% of the dose is excreted as parent drug.

Affected Cytochrome P450 (CYPP450) enzymes and drug transporters: Dapagliflozin and dapagliflozin 3-O-glucoronide neither inhibit CYP 1A2, 2C9, 2C19, 2D6, or 3A4, nor induce CYP 1A2, 2B6, or 3A4 based on in vitro studies. Dapagliflozin is a weak substrate of the P-gp active transporter, and dapagliflozin 3-O-glucoronide is a substrate for the OAT3 active transporter.

Efficacy

Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care. 2010;33(10):2217-24

Study Design: randomized, parallel-group, double-blind, placebo-controlled phase 3 trial

Description of Study: *Methods:* Patients with an A1C between 7.0-10.0% were randomly assigned equally to one of seven arms to receive once-daily placebo or 2.5, 5, or 10mg dapagliflozin, administered once daily either in the morning (main cohort) or evening (exploratory cohort) for 24-weeks. Patients with an A1C 10.1-12.0% (high-A1C exploratory cohort) were assigned randomly in a 1:1 ratio to receive blinded treatment with a morning dose of 5 or 10mg/day dapagliflozin (a placebo group was not included because of high A1C levels). The primary efficacy endpoint was change from baseline in A1C at week 24 in the main cohort. *Outcome Results:* A total of 485 patients were assigned to the main and exploratory cohorts. In addition, 74 patients were assigned to the high A1C exploratory cohort. In the main cohort, mean A1C reductions from baseline at week 24 ranged from -0.58 to -0.89% with dapagliflozin compared to -0.23 with placebo. The 5 and 10mg dapagliflozin reductions were statistically significant ($P = 0.0005$ and $P < 0.0001$ respectively vs placebo). More patients in the dapagliflozin arm achieved A1C < 7% (41, 44, and 51% with 2.5, 5, and 10mg dapagliflozin, respectively vs 32% with placebo); however, statistical significance was not reported. The FPG reductions were statistically significant in the 5 and 10mg dapagliflozin arms at week 24. Mean body weight decreases were greater with all dapagliflozin doses vs placebo but did not reach statistical significance. In the exploratory cohort, changes from baseline A1C, FPG, and body weight were similar to those seen in the main cohort. In the high AlC exploratory cohort, treatment with dapagliflozin for 24 weeks led to greater reductions in mean A1C and FPG than other cohorts. There were no clinically relevant changes in any renal function parameter, orthostatic hypotension, hypoglycemia, or lipid profiles between groups. There was an increased incidence in signs and symptoms of UTI noted with dapagliflozin.

Limitations: The study was funded by Bristol-Myers Squibb, the manufacturer of dapagliflozin, in addition to multiple authors being employed directly by the company. There was no power reported for this study. Entry criteria for this study also excluded patients with a BMI > 45 kg/m^2 from randomization, which make the results difficult to extrapolate to a more obese population. This study investigated dapagliflozin in relatively newly diagnosed diabetics averaging from 0.20 years to 1.40 years between groups. This also makes it hard to extrapolate

this evidence to patients who have longstanding diabetes. It was not mentioned if the investigators and patients were blinded to laboratory values during the study, which could cause unblinding.

Conclusion: The results of the study showed that dapagliflozin lowered mean A1C from baseline to 24 weeks in the main cohort to a greater extent vs placebo. Signs, symptoms, and other reports suggestive of UTI and genital infections were more frequently noted in the dapagliflozin arms. There were no major differences in other adverse events between groups. Although the sample population was naïve to therapy, the insulin-independent mechanism of dapagliflozin along with proven A1C lowering effects vs placebo make it an appropriate alternative option as a monotherapy for newly diagnosed type 2 diabetes mellitus who cannot tolerate other hypoglycemic, or for those responding partially to lifestyle modification.

Baily CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomized, double-blind, placebo-controlled trial. Lancet. 2010;275(9733):2223-33.

Study Design: multicenter, double-blind, parallel-group, placebo-controlled, phase 3 trial

Description of Study: *Methods:* 546 adults with type 2 diabetes who were receiving metformin (≥ 1500mg/day) and had inadequate glycemic control (A1C 7-10%), were randomly assigned to receive 2.5, 5, or 10mg of dapagliflozin or placebo orally once daily. Patients continued to receive their pre-study metformin dosing. The primary outcome was change from baseline in A1C at 24 weeks. *Outcome Results:* 88% of randomized patients completed the study to week 24. Reductions in A1C after 24 weeks were greater in the dapagliflozin groups vs the placebo group; mean change from baseline at week 24 was -0.30% for placebo vs -0.67%, -0.70%, and -0.84% in the dapagliflozin 2.5, 5, and 10mg groups respectively ($p=0.0002$, $p<0.0001$, $p<0.0001$, respectively). Patients achieving A1C < 7.0% was significantly greater for dapagliflozin 5mg (37.5%) and 10mg (40.6%) groups. Patients with A1C ≥ 9% at baseline had greater mean reductions in A1C at week 24 vs placebo group and was significant for the dapagliflozin 5mg and 10mg groups (0.84% and 0.78%, respectively). Decreases in fasting plasma glucose concentrations by week 1 in the dapagliflozin groups were greater vs placebo group and were significant for the 5mg and 10mg groups while week 24 fasting plasma glucose concentrations were significant for all dapagliflozin groups (-0.99 to -1.30 vs -0.33 [mmol/L]). Significant weight reductions at week 24 were noted in all dapagliflozin groups vs placebo. Hypoglycemia rates were similar between groups and there were no major hypoglycemic events reported. There were more genital infections in the dapagliflozin groups vs placebo (8% to 13% vs 5%).

Limitations: Many authors were either employed or had other affiliations with Bristol-Myers Squibb. Specific A1C inclusion cutoffs for the trial were 7% to 10% and those above this range were excluded from the study. This makes it difficult to extrapolate this data, or justify the use of dapagliflozin add-on therapy to uncontrolled patients on metformin with an A1C indicative of

extremely poor glycemic control. Pioglitazone or acarbose as open-labeled rescue medications were offered to patients with higher fasting plasma glucose concentrations at certain points during the trial; however, these rates were not reported in any group therefore assumptions cannot be made that glycemic reductions were caused solely by the addition of dapagliflozin to metformin.

Conclusion: The addition of dapagliflozin to metformin therapy in long-term type 2 diabetics can provide moderate decreases in A1C after 24 weeks of therapy. Dapagliflozin, in addition to metformin, showed a statistically significant A1C reduction compared to placebo as well as a significant percentage of patients achieving an A1C < 7%. Patients with A1Cs above 10% may need to be evaluated in further studies in order for a conclusion to be drawn for dapagliflozin's efficacy in that patient population.

Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2011;13(10):928-38.

Study Design: randomized, double-blind, placebo-controlled, parallel-group, multicenter phase-3 trial

Description of Study: *Methods:* Patients with uncontrolled type 2 diabetes with an A1C between 7to 10% who were also receiving sulfonylurea monotherapy were included in the study. Pre-study sulfonylurea therapy was required to be at a stable dose that was at least half the maximum recommended dose for at least 8-weeks prior to enrollment. 597 patients were randomly assigned to placebo or dapagliflozin 2.5, 5 or 10mg per day in a 1:1:1:1 ratio added to open-label glimepiride 4mg/day for 24-weeks regardless of previous sulfonylurea therapy. Open label glimepiride could be down-titrated to 2mg or discontinued to mitigate hypoglycemic events at the discretion of the investigator. Patients with inadequate glycemic control during the treatment received open-label metformin or pioglitazone. Patients with an A1C > 8% for a continuous 12-week period, despite maximum dose of rescue therapy, discontinued the trial. The primary outcome measure was change in A1C from baseline to week 24. *Outcome Results:* Dapagliflozin 2.5, 5, and 10mg groups met the primary endpoint of change in A1C from baseline to week 24 vs placebo (-0.58, -0.63, -0.82 vs -0.13 respectively, p <0.0001 for all groups). Dapagliflozin 5 and 10mg produced significant sustained mean reductions in total body weight from baseline. The proportion of patients achieving A1C < 7% at week 24 was significantly increased with dapagliflozin 5 and 10mg vs placebo (30.3% and 31.7% vs 13.0%; p=0.0001 and p < 0.0001 respectively). No hypoglycemic events led to study discontinuation.

Limitations: Multiple authors were employees or had affiliations with Bristol-Myers Squibb. Similar to previous studies, this trial randomized patients with an A1C between 7% and 10%, which makes it difficult to extrapolate this data to patients with extremely poor glycemic control

with concurrent glimepiride. Also, patients taking any form of sulfonylurea for more than 8 weeks prior to the study could be included. All patients were switched to a standard dose of glimepiride for use in the study. This fails to mimic the real life comparative efficacy of dapagliflozin in add-on use with a sulfonylurea besides glimepiride. Finally, the authors offer supplementary data in another section that was not included within the original article that included the percentage of patients requiring rescue medications. This makes it difficult to assume that glimepiride and dapagliflozin alone were the only contributors to changes in A1C. There seems to be some bias in not immediately reporting this data in the original article. Finally, baseline duration of diabetes diagnosis was not reported, which makes it difficult to apply the data to one specific population based on duration of disease.

Conclusion: The addition of dapagliflozin to glimepiride monotherapy in type 2 diabetic patients can provide a moderate decrease in A1C after 24 weeks of therapy. More patients achieved lower A1C with addition of dapagliflozin to glimepiride in all three dapagliflozin groups, however, with the 5 and 10mg dapagliflozin group showed a statistically significant proportion of patients achieving an A1C < 7%. Patients with an A1C above 10% may need to be evaluated in additional studies before a definitive conclusion can be made of dapagliflozin's efficacy in that patient population.

Contraindications

Hypersensitivity reactions[1,2,3,4,5]

Patients with a history of serious hypersensitivity to dapagliflozin or any component of the formulation should avoid use.

Organ Impairment[1,2,3,4,5]

Patients with severe renal impairment (eGFR < 30mL/min/1.73m^2), end-stage renal disease (ESRD), or patients on dialysis should avoid use of dapagliflozin due to its ineffectiveness and danger in these patient populations. Dapagliflozin should be discontinued when eGFR is persistently < 60mL/min/1.73m^2).

Precautions[1,2,3,4,5]

Hypotension

Dapagliflozin causes intravascular volume contraction in which symptomatic hypotension can occur after initiation particularly in patients with impaired renal function (eGFR < 60mL/min/1.73m^2), elderly patients, patients on other antihypertensives (eg, diuretics [particularly loop diuretics], ACE inhibitors, or angiotensin receptor blockers [ARBs]), or those with low systolic blood pressure. Prior to initiation in these patient populations, volume status should be assessed and corrected as well as monitoring for hypotension signs and symptoms.

Impaired Renal Function
Dapagliflozin can increase serum creatinine and decrease eGFR in which elderly patients and those with preexisting renal impairment may be more susceptible. Renal function should be evaluated prior to initiation and monitored periodically thereafter.

Hypoglycemia with Concomitant Use Hypoglycemic Agents
Insulin and insulin secretagogues (eg sulfonylureas and thiazolidinediones) are known to cause hypoglycemia. Dapagliflozin can increase the risk of hypoglycemia when combined with these agents. A lower dose of these agents may be required to minimize the risk of hypoglycemia when used in combination with dapagliflozin. More frequent blood glucose monitoring may be necessary in patients predisposed to hypoglycemic events.

Genital Mycotic Infections
Dapagliflozin increases the risk of genital mycotic infections (eg. vulvovaginal mycotic infection, vulvovaginal candidiasis, vulvovaginitis, candida balanitis, balanoposthitis). Those with a history of mycotic infections, or males that are uncircumcised, are more likely to develop recurrent infections while taking dapagliflozin.

Lipid Abnormalities
Dose-related increases in low-density lipoprotein cholesterol (LDL-C) can occur with dapagliflozin. LDL-C should be monitored and treated per standard of care while 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 patients (0.03%) treated with placebo/comparator. There were 4 cases of bladder cancer in which exposure to dapagliflozin was greater than 1 year compared to no cases with placebo/comparator with cancer and hematuria risk equal at baseline. There were too few cases to determine whether the emergence of bladder cancer is related to dapagliflozin. There is also insufficient data to determine whether dapagliflozin has an effect on pre-existing bladder tumors. Therefore, dapagliflozin should not be used in patients with active bladder cancer. Risk to benefit analysis should be considered for patients with a prior history of bladder cancer.

Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with dapagliflozin.

Specific Patient Populations[1,2,3,4,5]

Pregnancy (Category C)

There is currently no adequate and well-controlled studies of dapagliflozin in pregnant women. Based on current animal studies on reproductive and developmental toxicity, dapagliflozin may affect renal development and maturation. These outcomes occurred with drug exposures during developmental periods corresponding to the late second and third trimesters of human pregnancy. Consider appropriate alternative therapies while pregnant, especially during these developmental periods or weigh risk versus benefit if considering use in pregnant women.

Breastfeeding

It is not known if dapagliflozin is excreted in human milk. Dapagliflozin is excreted in rat milk reaching levels 0.49 times that found in maternal plasma. Since human kidney maturation continues after birth for the first 2 years of life, there may be risk to the developing human kidney. Due to the potential for serious adverse reactions in the nursing infant, a decision must be made whether to discontinue nursing or discontinue the drug.

Pediatrics

Safety and effectiveness in pediatric patients under 18 years of age have not been established. There is no role of dapagliflozin in the treatment of infants or neonates.

Geriatrics

There is no recommended dosage change based on age. In patients $\geq$ 65 years of age, a higher proportion of patients treated with dapagliflozin had adverse reactions related to volume depletion (eg hypotension, orthostatic hypotension, dizziness, syncope, and dehydration) and renal impairment or failure.

Renal Impairment

Compared to placebo-treated patients, patients with moderate renal impairment did not have improvement in glycemic control and had more renal-related adverse reactions and bone fractures. Based on the mechanism of action of dapagliflozin, it is not expected to be effective in patients with severe renal impairment (eGFR < 60mL/min/1.73m^2). Therefore, dapagliflozin should not be initiated in this population of patients. Treatment with dapagliflozin is contraindicated in patients with severe renal impairment (eGFR < 30mL/min/1.73m^2) and ESRD.

Hepatic Impairment

No dose adjustment is recommended for patients with mild, moderate, or severe hepatic impairment. However, the benefit-risk for the use of dapagliflozin in patients with severe hepatic impairment should be individually assessed since the safety and efficacy have not been studied in this population of patients.

Adverse Effects[1,2,3,4,5] (dapagliflozin % vs placebo %)

Common (> 10% of patients)
- Endocrine/Metabolic
  - Mild Hypoglycemia (40% to 43% vs 34%)

Less Common (> 1% to < 10% of patients)
- Endocrine/Metabolic
  - Dyslipidemia (2% to 3% vs 2%)
  - Hypovolemia (1% vs < 1%)
  - Increased Serum Phosphate (2% vs 1%)
- Gastrointestinal
  - Constipation (2% vs 2%)
  - Nausea (3% vs 2%)
- Genitourinary
  - Dysuria (2% vs 1%)
  - Fungal Vaginosis (7% to 8% vs 2%)
  - Genitourinary Fungal Infection (3% vs 1%)
  - Increased Urine Output (3% to 4% vs 2%)
  - Urinary Tract Infection (4% to 6% vs 4%)
- Hematologic/Oncologic
  - Increased Hematocrit (> 55%) (1% vs 1%)
- Infection
  - Influenza (2% to 3% vs 2%)
- Neuromuscular/Skeletal
  - Back Pain (3% to 4% vs 3%)
  - Limb Pain (2% vs 1%)
- Respiratory
  - Nasopharyngitis (6% to 7% vs 6%)

Drug Interactions[1,2,3,4,5]

Category C Risk Drug Interactions (Monitor Therapy)

Corticosteroids (Inhaled/Systemic)
May diminish the hypoglycemic effect of antidiabetic agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use.

Duloxetine
Hypotensive agents may enhance the orthostatic hypotensive effect of duloxetine

Hypoglycemic Agents
May enhance the adverse/toxic effect of other hypoglycemic agents

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May enhance the adverse/toxic effect of other hypotensive agents

Loop Diuretics
May diminish the hypoglycemic effect of hypoglycemic agents

Lutenizing Hormone-Releasing Hormone Analogues
May diminish the hypoglycemic effect of hypoglycemic agents

MAO Inhibitors
May enhance the hypoglycemic effect of hypoglycemic agents

Pegvisomant
May enhance the hypoglycemic effect of hypoglycemic agents

Salicylates
May enhance the hypoglycemic effect of hypoglycemic agents

Selective Serotonin Reuptake Inhibitors
May enhance the hypoglycemic effect of hypoglycemic agents. Selective serotonin reuptake inhibitors may increase the serum concentration of hypoglycemic agents. Consider increasing monitoring of glycemic control with concomitant use of a hypoglycemic agent and an SSRI. Dosage adjustments of the hypoglycemic agent may be necessary upon SSRI initiation or discontinuation.

Thiazide Diuretics
May diminish the therapeutic effect of antidiabetic agents

Category D Risk Drug Interactions (Consider Therapy Modification)

Somatropin
May diminish the hypoglycemic effect of antidiabetic agents

Dosing/Administration[1,2,3,4,5]

Adult Dosing
Starting dose: 5mg by mouth once daily, taken in the morning with or without food. May escalate therapy to 10mg by mouth once daily in patients tolerating 5mg once daily who require additional glycemic control

Geriatric
Refer to adult dosing

Pediatric
Safety and efficacy not established in pediatric patients

Patients with Renal Impairment
Assessment of renal function is recommended prior to initiation of dapagliflozin and periodically thereafter
Dapagliflozin should not be initiated in patients with an eGFR < 60mL/min/1.73m^2
No dosage adjustment is needed in patients with mild renal impairment (eGFR ≥ 60mL/min/1.73m^2)
Dapagliflozin should be discontinued when eGFR is persistently < 60mL/min/1.73m^2
Use is contraindicated in patients with ESRD and/or those on hemodialysis

Patients with Hepatic Impairment
Mild to moderate hepatic impairment (Child-Pugh class A, B): No dosage adjustment necessary
Severe hepatic impairment (Child-Pugh class C): No dosage adjustment recommendations provided

Conclusion:

Dapagliflozin has evidence of effectiveness in type 2 diabetic patients as monotherapy, and who are uncontrolled despite pharmacologic doses of first-line antihyperglycemic agents. More studies must be conducted in order to evaluate dapagliflozin's efficacy in patients with extremely poor glycemic control, particularly those with an A1C > 10%. Dapagliflozin is a safe and tolerable medication for most patients that causes little hypoglycemia, hypotension, and renal insufficiencies; however, there is a substantial risk for genital and urinary mycotic infections compared to placebo therapies. Dapagliflozin is an attractive agent for patients with mild-to-moderate hepatic insufficiency and for those with a mild renal insufficiency. Minimal drug interactions and hypoglycemic potential make it a good option in patients on multiple medications as well. Currently, dapagliflozin seems to have a role as a monotherapy agent in patients that cannot tolerate other hypoglycemic agents, or in those that have partially responded to lifestyle modification. With further studies in poorly controlled individuals, children, and comparative studies with first line antihyperglycemic agents, dapagliflozin can become a useful adjuvant therapy for type 2 diabetics uncontrolled on first-line agents.

Recommended References:

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8. Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled tril. Diabetes Obes Metab. 2011;13(10):928-38.

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