Dapagliflozin: A Novel Sodium-Glucose Cotransporter Type 2 Inhibitor for the Treatment of Type 2 Diabetes Mellitus

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The prevalence of diabetes mellitus has grown to staggering numbers, and its incidence is expected to rise in the next 2 decades. The need for novel approaches to treat hyperglycemia cannot be ignored. Current agents have been shown to modestly improve glycemia and in some cases prevent complications of diabetes, but they become less effective over time and are often accompanied by undesirable adverse effects. Dapagliflozin is the lead agent in a new class of oral antidiabetic agents known as sodium-glucose cotransporter type 2 (SGLT2) inhibitors, which represent a novel approach to the management of type 2 diabetes mellitus. By selectively and reversibly blocking the SGLT2 receptor, dapagliflozin prevents the reabsorption of glucose at the renal proximal tubule. Phase II and III clinical trials have demonstrated that dapagliflozin is a safe and effective method for treating type 2 diabetes. Dapagliflozin produces a sustained, dose-dependent reduction in plasma glucose levels while simultaneously improving insulin secretion and sensitivity. Over 12–24 weeks, reductions in hemoglobin A_{1c} ranged from 0.54–0.89% when dapagliflozin was administered once/day (either as monotherapy or add-on therapy to oral antidiabetic drugs with or without insulin) to patients with type 2 diabetes. Therapy with dapagliflozin also results in a mild osmotic-diuretic effect that may account for decreases in total body weight (~2–3 kg) and blood pressure (systolic 2–5 mm Hg, diastolic 1.5–3 mm Hg), and increases in hematocrit (1–2%). Dapagliflozin has a favorable safety profile, with the rates of hypoglycemia similar to those of placebo. Genital and urinary tract infections were more commonly reported in patients taking dapagliflozin (2–13%) than those taking placebo (0–8%). Dapagliflozin does not appear to cause electrolyte disturbances, hepatotoxicity, or nephrotoxicity. Results from clinical trials have been promising, and well-designed clinical programs that address the long-term safety and efficacy of dapagliflozin are under way.

Key Words: dapagliflozin, BMS-512148, sodium-glucose cotransporter type 2, SGLT2 inhibition, type 2 diabetes mellitus.

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OUTLINE

There are an estimated 285 million adults with diabetes mellitus and impaired glucose tolerance worldwide, and the prevalence is expected to increase to 438 million by 2030.[1, 2] In just 3 years (2007–2010), there was a 5.5% increase in the number of deaths attributable to diabetes.[1] Diabetes is quickly becoming a leading cause of death and disability globally. Type 2 diabetes mellitus, which accounts for more than 90% of all cases of diabetes, is defined as a defect in glucose homeostasis resulting from improper insulin secretion and insulin action.[3] Chronic elevations in plasma glucose levels lead to a debilitating menu of microvascular and macrovascular complications, including retinopathy, neuropathy, nephropathy, and vascular disease.[4–8] As a result, hyperglycemia has become a prime therapeutic target in the management of type 2 diabetes; yet, there remains a considerable proportion of patients with unmet glycemic control despite a full range of oral antidiabetic drugs (OADs).

Although OADs promote a modest improvement in glycemic control, they often lose effectiveness over time, leading to the progression of type 2 diabetes and its complications.[9, 10] As insulin resistance worsens, the body signals additional insulin secretion from pancreatic β cells.[10] The burden that is placed on pancreatic β cells causes them to progressively lose function and mass until they fail to meet the body's insulin demands, yielding overt hyperglycemia, which further damages insulin secretion and insulin sensitivity (i.e., glucotoxicity).[11] Other theories suggest that prolonged hyperglycemia impairs insulin gene expression secondary to a reduction in the activity of pancreatic-duodenum homeobox-1 and the activator of insulin promoter element 3b1.[12] Consequently, OADs that primarily function through an insulin-dependent mechanism eventually lose their ability to maintain glycemic control.

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The United Kindgdom Prospective Diabetes Study (UKPDS) found that only 50% of patients receiving monotherapy with a baseline hemoglobin A_{1c} (A1C) of less than 7.0% were able to maintain control over 3 years, and only 25% of patients were able to maintain control over 9 years.[13] This may be explained by findings from the Belfast Diabetes Study, which demonstrated that up to 40–50% of β-cell function is lost approximately 15 years before the diagnosis of type 2 diabetes and continues to progressively deteriorate.[14] Conversely, thiazolidinediones, which promote insulin sensitivity through a β-cell–independent mechanism, have been shown to improve insulin resistance and β-cell function.[15] These agents were not included in the UKPDS protocol; however, results from A Diabetes Outcome Progression Trial (ADOPT) showed that initial treatment with rosiglitazone was associated with a more durable monotherapy response than either metformin or glyburide; although even the insulin sensitizer was subject to loss of efficacy over time.[16]

Furthermore, current OAD therapy is often complicated by weight gain, hypoglycemia, edema, and gastrointestinal adverse effects.[17–20] More recently, the cardiovascular safety of several classes of agents, including the thiazolidinediones, have been called into question. Agents that are able to overcome these limitations have continued to generate much interest in the management of type 2 diabetes.

Dapagliflozin (BMS-512148) is one such agent. It inhibits the sodium-glucose cotransporter type 2 (SGLT2) receptor and is being investigated by AstraZeneca and Bristol-Myers Squibb (Princeton, NJ) for the treatment of type 2 diabetes. Inhibition of SGLT2 promotes the excretion of glucose at the renal proximal tubule, thereby lowering plasma glucose levels in an insulin-independent manner. To date, there are no OADs that address glucose transport as a molecular target; however, several drugs that target the SGLT2 receptor are being investigated, including canagliflozin, remogliflozin, and sergliflozin. The emerging class of SGLT2 inhibitors represents a promising addition to existing treatments and harbors numerous possible advantages over current OADs such as weight loss and a reduction in serum uric acid, blood pressure, and lipid levels.

In this comprehensive review of dapagliflozin, we outline the phase II clinical trials and international phase III studies that investigated the

utility of dapagliflozin. Based on the available data reviewed in this article, we attempt to forecast the potential role of dapagliflozin in the management of type 2 diabetes by spotlighting its efficacy, safety, tolerability, pharmacology, and pharmacokinetic profile.

Literature Search

We conducted a comprehensive literature search of the MEDLINE database to identify all relevant studies published in English between 1959 and February 2011. The following medical subject heading terms and key words were used: dapagliflozin, SGLT2 inhibition, BMS-512148, type 2 diabetes mellitus, oral antidiabetic agents, hyperglycemia, and renal glucose reabsorption. All pertinent reviews and research reports were evaluated, and studies performed in both humans and animals were included. Other articles with information relevant to SGLT2 inhibition were also included. Because of the limited information available, abstracts and scientific presentations of phase III clinical studies not yet published were incorporated for completeness.

Kidney Sodium-Glucose Cotransporters and Glucose Homeostasis

Glucose homeostasis is generally characterized by three processes: glucose absorption through the small intestine, glucose production in the liver, and glucose consumption by tissue.[21] However, it has recently been shown that the kidney also plays a pivotal role in regulating plasma glucose through filtration and reabsorption of glucose.[22–24] Under normal physiologic conditions, the glomeruli filter approximately 180 g/day of glucose. Virtually all of this glucose is reabsorbed in the renal proximal tubule, and only a minimal amount of glucose is lost in urine (<0.5 g/day).[25, 26] The reabsorption of glucose is mediated by SGLT type 1 (SGLT1) and SGLT2, which are two highly specialized proteins that traffic glucose in the kidney.[26] These transporters couple the transfer of glucose (against a concentration gradient) and sodium (down a concentration gradient) from the proximal tubule into epithelial cells found on the luminal membrane.[27] Once glucose enters and concentrates within the epithelial cell, facilitative diffusion transporters (GLUTs) found on the basolateral membrane reabsorb glucose into the interstitial fluid (Figure 1).[27]

The SGLT1 is a high-affinity, low-capacity transporter of glucose (K_m=0.4 mM) that plays only a minor role in the kidney. It is predominantly expressed in the late segment (S3) of the renal proximal tubule and is responsible for approximately 10% of glucose that is reabsorbed in the kidney.[28–30] The SGLT1 is largely found in the small intestinal cells, where it actively transports glucose and galactose across the intestinal brush border.[25, 31] Patients with SGLT1 genetic mutations often experience glucose and galactose malabsorption, which results in watery diarrhea and dehydration; owing to why selective SGLT1

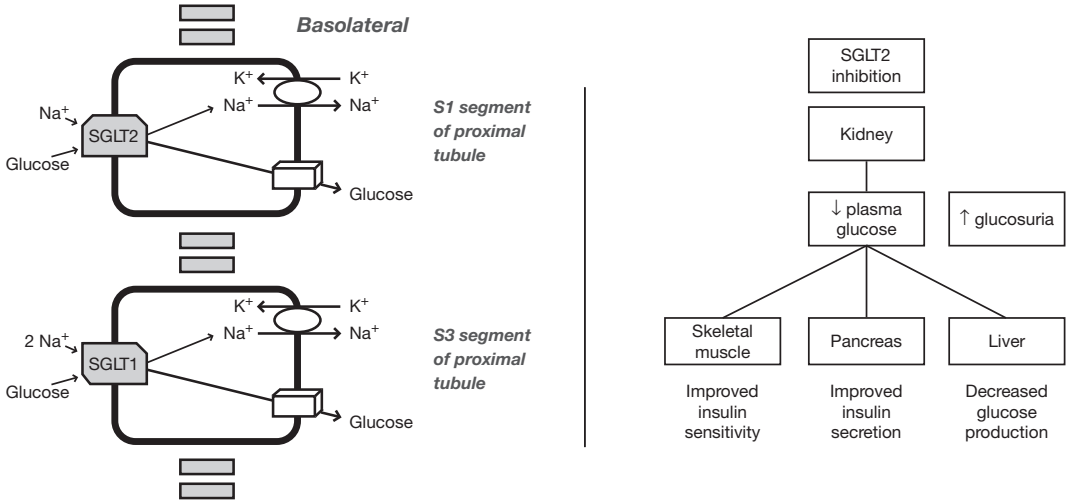

Figure 1. Sodium-glucose cotransporter types 1 (SGLT1) and 2 (SGLT2) receptors and epithelial transport of sodium and glucose. The SGLT receptors couple the transport of sodium and glucose across epithelial cells found on the luminal membrane of the renal proximal tubule, allowing for reabsorption of glucose. Inhibiting SGLT2 receptors results in an increase in glucosuria and subsequent reductions in plasma glucose concentrations. K^+ = potassium; Na^+ = sodium.

inhibitors will not likely serve as a therapeutic modality for patients with type 2 diabetes.[32, 33]

The SGLT2 is the most salient kidney glucose transporter and is the therapeutic target for agents emerging in this class. Contrary to SGLT1, SGLT2 is a low-affinity, high-capacity transporter of glucose (K_m=2 mM) found mainly at the apical domain of epithelial cells in the early segment (S1) of the renal proximal tubule (and to a lesser extent in mammary glands, liver, lung, intestine, skeletal muscle, and spleen).[34–36] Approximately 90% of glucose that is filtered by the glomeruli is reabsorbed at S1 by SGLT2,[37] suggesting that selectively inhibiting the SGLT2 receptor may be a hopeful option to treat hyperglycemia.

Table 1. Pharmacokinetic Parameters of Dapagliflozin

Parameter[a]	Value
	Mean
Bioavailability (%)	≥ 75
Protein binding (%)	91
K_i (μM)	
SGLT1	0.6
SGLT2	0.0002
	Mean ± SD
Half-life (hrs)	13.8 ± 9.4
Maximum plasma concentration (μg/ml)	0.55 ± 0.02
Area under concentration-time curve (μg•hr/ml)	2.43 ± 0.03
	Median (range)
Time to maximum concentration (hrs)	0.5 (0.5–0.75)

K_i = dissociation constant for dapagliflozin at the SGLT receptors; SGLT = sodium-glucose cotransporter types 1 and 2.
[a]After a single oral dose of dapagliflozin 50 mg.

Pharmacology and Pharmacokinetics

Dapagliflozin is a potent, highly selective, reversible, and orally active inhibitor of the SGLT2 receptor.[38] Based on in vitro studies, dapagliflozin exhibits a mean inhibitory potential (EC_{50}) of 1.12 nmol/L against human SGLT2 and an EC_{50} of 1391.00 nmol/L against human SGLT1, representing a highly selective profile for SGLT2 versus SGLT1 (~1200-fold).[39, 40] Dapagliflozin minimally inhibits the facilitative glucose transporters GLUT1 and GLUT2, and modestly inhibits GLUT4.

As a result of this mechanism profile, dapagliflozin produces dose-dependent and sustained plasma glucose lowering by promoting urinary glucose excretion.[39] A reduction in both fasting and postprandial glucose concentrations results in the consumption of fat as an energy source.[41–43] Chronic SGLT2 inhibition with dapagliflozin results in reduced hepatic glucose production, increased insulin sensitivity, enhanced glucose influx into the liver, and improvements in islet morphology without reductions in β-cell mass, although these mechanisms have not been fully elucidated. Dapagliflozin also shows dose-dependent decreases in body weight, proposed to be secondary to caloric loss as a result of glucosuria and an osmotic-diuretic effect.[44, 45]

Table 1 lists the pharmacokinetic parameters of dapagliflozin. Dapagliflozin demonstrates linear pharmacokinetics and is rapidly absorbed after oral administration.[46] It is highly protein bound in plasma (91%) and has limited distribution into human erythrocytes (blood:plasma ratio 0.88).[46] Because of its C-glucoside chemical structure, dapagliflozin is metabolically stable and exhibits a long half-life (13.8 ± 9.4 hrs), allowing for once-daily dosing.[46] Dapagliflozin is predominantly metabolized by uridine diphosphate–glucuronosyltransferase 1A9 into non–pharmacologically active glucuronides in human hepatocytes.[38, 46] In vitro studies have identified an *O*-deethylated active metabolite (BMS-511926) of dapagliflozin, which has similar SGLT2 inhibitory values as dapagliflozin.[38] However, BMS-511926 is only present with dapagliflozin doses greater than 50 mg secondary to its low area under the concentration-time curve (AUC).

There were no relevant interactions noted between dapagliflozin and substrates of cytochrome P450 (CYP) isoenzymes and P-glycoprotein (P-gp), or due to plasma protein binding.[38, 46] It is expected that drugs interacting with CYP isoenzymes or P-gp transporters will not interfere with dapagliflozin activity, and no dosage adjustment of either drug will be necessary. A recent study showed that coadministration of dapagliflozin with pioglitazone, metformin, glimepiride, or sitagliptin did not affect AUC or the maximum plasma concentrations of either drug.[47]

Renal excretion is a minor elimination pathway for dapagliflozin and its metabolites.[38] In healthy subjects, food has only a modest effect on the pharmacokinetic profile of dapagliflozin. A high-fat meal did not produce meaningful changes in urinary glucose excretion.[38]

Clinical Studies

Monotherapy

Table 2 summarizes the clinical efficacy of dapagliflozin. The safety and efficacy of dapagliflozin was evaluated in a multicenter, prospective,

Table 2. Randomized Controlled Trials of Clinical Efficacy of Dapagliflozin in Patients with Type 2 Diabetes Mellitus

Study Design and Duration	Intervention	No. of Subjects	Study Population	Reductions in Outcome Variables		
				A1C (%)	FPG (mg/dl)	TBW (kg)
Multicenter, double-blind, placebo-controlled, parallel-group; 12 wks[48]	Dapagliflozin 2.5–50 mg/day	389	Treatment-naïve	0.55–0.90	16–31	2.5–3.4[a]
Double-blind, placebo-controlled, parallel-group; 24 wks[49]	Dapagliflozin 2.5–10 mg/day	485	Treatment-naïve	0.58–0.89	15–29	3.3–3.8
Double-blind, placebo-controlled, parallel-group; 2 wks[50]	Dapagliflozin 5–100 mg/day ± metformin	47	Treatment-naïve or previously taking metformin	—	19–39	—
Multicenter, double-blind, placebo-controlled, parallel-group; 24 wks[51]	Dapagliflozin 2.5–10 mg/day + continue metformin	546	Previously taking metformin (≥ 1500 mg/day)	0.67–0.84	18–23	2.2–2.9
Single- and double-blind, placebo-controlled, parallel-group; 12 wks[54]	Dapagliflozin 10–20 mg/day + continue 50% baseline insulin dose + OAD	71	Previously taking OAD and insulin	0.61–0.69	2.4[b]–9.6	4.3–4.5
Multicenter, double-blind, active-controlled, parallel-group; 52 wks[52]	Dapagliflozin starting dose 2.5 mg/day, titrated up to 10 mg/day, + continue metformin	814	Previously taking metformin (≥ 1500 mg/day)	0.52	—	3.22
	Glipizide starting dose 5 mg/day, titrated up to 20 mg/day, + continue metformin			0.52	—	1.44[b]
Multicenter, double-blind, placebo-controlled, parallel-group; 24 wks[53]	Dapagliflozin 2.5–10 mg/day + continue glimepiride	597	Previously taking glimepiride	0.58–0.82	16.8–28.5	1.18–2.26
Placebo-controlled; 48 wks[55]	Dapagliflozin 2.5–10 mg/day	808	Previously taking insulin ± OAD	0.74–0.94	—	0.83–1.45

A1C = hemoglobin A_{1c}; FPG = fasting plasma glucose; TBW = total body weight; OAD = oral antidiabetic drug.
[a]Values are percent decrease from baseline.
[b]Value is an increase from baseline.

12-week, randomized, parallel-group, double-blind, placebo-controlled, clinical trial.[48] A total of 389 treatment-naïve patients with type 2 diabetes, aged 18–79 years, with an A1C of 7–10% were randomly assigned to dapagliflozin 2.5, 5, 10, 20, or 50 mg once/day, metformin extended-release 750 mg/day force-titrated at week 2 to 1500 mg/day, or placebo. Patient inclusion criteria were fasting C-peptide greater than 1.0 ng/ml, body mass index (BMI) of 40 kg/m^2 or less, glomerular filtration rate greater than 60 ml/minute/1.73 m^2, and urine microalbumin:creatinine ratio of 300 mg/g or less. The primary outcome was a comparison of the mean A1C reduction from baseline for each dapagliflozin group versus placebo after 12 weeks of therapy. Secondary outcomes included changes from baseline in fasting plasma glucose (FPG) level, total body weight, and urinary glucose excretion.

Baseline demographics were similar for all patient subgroups. A total of 41 patients discontinued the trial; the most common cause was withdrawal of consent. The number of patients who discontinued because of adverse events was one for dapagliflozin 2.5 mg, zero for dapagliflozin 5 mg, three for dapagliflozin 10 mg, two for dapagliflozin 20 mg, two for dapagliflozin 50 mg, one for placebo, and one for metformin. At week 12, the change in mean A1C value from

baseline was −0.55% to −0.90% for all dapagliflozin groups, −0.18% for placebo, and −0.73% for metformin ($p<0.05$ for all dapagliflozin groups vs placebo). Mean changes from baseline in FPG level were −16 to −31 mg/dl for all dapagliflozin groups, −6 mg/dl for placebo, and −18 mg/dl for metformin ($p<0.05$ for all dapagliflozin groups vs placebo). As anticipated, all dapagliflozin groups displayed an increase in urinary glucose excretion ($p<0.001$ for all dapagliflozin groups vs placebo). Mean changes in total body weight were −2.5% to −3.4% for dapagliflozin, −1.2% for placebo, and −1.7% for metformin.

Overall, dapagliflozin was well tolerated, with no deaths or serious adverse events reported. Hypoglycemia occurred in 6–10% of patients assigned to dapagliflozin, 4% assigned to placebo, and 9% assigned to metformin. Infections of the urinary tract (cystitis and urinary tract infections [UTIs]) were observed in 5–12%, 6%, and 9% of patients taking dapagliflozin, placebo, and metformin, respectively. Signs and symptoms suggestive of genital infections, but not UTIs, were reported in 2–7% of patients taking dapagliflozin, 0% taking placebo, and 2% taking metformin.

This trial demonstrated that dapagliflozin, across many dosing schemes, is effective in reducing total body weight, A1C, and FPG values. Furthermore, the adverse-effect profile of dapagliflozin was acceptable compared with those of metformin or placebo. Compared with metformin, dapagliflozin demonstrated a comparable safety and efficacy profile. Future trials need to be conducted in a similar manner and must address some of the limitations of this study such as a suboptimal metformin dose, short duration, and small sample size.

The safety and efficacy of dapagliflozin in treatment-naïve patients with type 2 diabetes who were inadequately controlled with diet and exercise alone were explored in an additional study.[49] This 24-week, randomized, parallel-group, double-blind, placebo-controlled, phase III study assessed patients with an A1C of 7–10%, BMI less than 45 kg/m^2, and a fasting C-peptide level of 1 ng/ml or greater. Patients were unable to participate if they had impaired renal or hepatic function, a cardiovascular event within 6 months, heart failure (New York Heart Association classes III–IV), or elevated blood pressure (systolic >180 mm Hg or diastolic >110 mm Hg). Patients were equally and randomly assigned to placebo or dapagliflozin 2.5, 5, or 10 mg once/day. The primary outcome of this study was a change from baseline in A1C at week 24. Additional outcomes included changes from baseline in FPG level and total body weight.

In total, 485 patients were randomly assigned to treatment. Patient demographics were similar in all study groups. The number of patients who discontinued because of adverse events was 1 (1.3%), 2 (3.1%), 3 (4.7%), and 5 (7.1%) in the placebo, dapagliflozin 2.5-mg, dapagliflozin 5-mg, and dapagliflozin 10-mg groups, respectively. Changes in A1C ranged from −0.58% to −0.89% with dapagliflozin compared with −0.23% with placebo; the reduction in A1C afforded by dapagliflozin therapy was statistically significant for the 5- and 10-mg dose groups. Dapagliflozin 5- and 10-mg doses were also associated with significant reductions in FPG compared with placebo (−15 to −29 mg/dl vs 4.1 mg/dl, respectively). Although all dapagliflozin groups had reductions in total body weight (−3.3 kg to −3.8 kg) compared with placebo (−2.2 kg), the difference in these changes was not statistically significant. Furthermore, this trial also demonstrated large A1C reductions in an additional cohort of 74 patients with baseline A1C values ranging from 10.1–12% who were treated with dapagliflozin (−2.88% and −2.66% in the dapagliflozin 5- and 10-mg groups, respectively).

Dapagliflozin was generally safe in patients with type 2 diabetes, with no discontinuations due to hypoglycemia. Consistent with other trials, dapagliflozin-treated patients experienced a higher frequency of adverse events that were suggestive for possible genital infections (7.7–12.9% with dapagliflozin vs 1.3% with placebo) and UTIs (4.6–12.5% with dapagliflozin vs 4.0% with placebo). Mean seated blood pressure values declined with dapagliflozin therapy (systolic −2.3 mm Hg to −4.6 mm Hg; diastolic −1.7 mm Hg to −2.8 mm Hg) with no notable increases in orthostatic hypotension, although these reductions were not statistically significantly different from baseline. The reduction in blood pressure observed in dapaglifozin studies has been ascribed to the drug's mild osmotic-diuretic effect. Increments in fractional renal glucose loss were directly related to reductions in body weight ($r=-0.13$, $p=0.008$).

The authors were able to conclude that treatment-naïve patients randomly assigned to dapagliflozin experienced reductions in A1C, FPG, total body weight, and blood pressure. It is encouraging to note that the reduction in total

body weight did not plateau by the end of the study, indicating that the full potential of dapagliflozin may not have been realized and underscoring the importance of longer term studies with extended follow-up. This was also the first study to explore the efficacy of dapagliflozin in patients with an A1C greater than 10%. The findings signify that numerically greater reductions are expected in patients who have a higher baseline A1C.

Combination Therapy

Dapagliflozin with Oral Antidiabetic Drugs

The efficacy of dapagliflozin in addition to metformin was first evaluated in a double-blind, placebo-controlled, randomized, parallel-group, multiple-dose, phase IIa study.[50] Inclusion criteria were age 18–70 years, treatment-naïve or receiving a stable metformin dose, BMI less than 42 kg/m^2, FPG level of 240 mg/dl or less, A1C of 6–10%, and normal renal function. Patients were not allowed to participate if they had a history of cardiovascular, renal, hepatic, neurologic, or gastrointestinal disease. Those receiving a stable dose of metformin (>4 wks) before randomization were given dapagliflozin as add-on therapy. A total of 47 patients (19 men, 28 women) were randomly assigned in a ratio of 1:1:1:2 to placebo or dapaglliflozin 5, 25, or 100 mg once/day, respectively. Baseline demographics were well balanced. Eighteen patients continued taking their maintenance dose of metformin (six, five, and seven patients in the 5-, 25-, and 100-mg dapagliflozin groups, respectively).

On day 13, treatment with dapagliflozin resulted in dose-dependent reductions in FPG of −11.7% ($p<0.05$), −13.3% ($p<0.05$), and −21.8% ($p<0.0001$) in the 5-, 25-, and 100-mg groups, respectively. After an oral glucose tolerance test (OGTT), dapagliflozin was associated with a reduction in glucose excursion on day 2 (range −9.6% to −13.7%, $p<0.001$) and on day 13 (range −17.6% to −22.6%, $p<0.001$). Increases in urinary glucose excretion were also dose dependent, resulting in losses of 36.6, 70.1, and 69.9 g/day after 2 weeks of therapy with the 5-, 25-, and 100-mg doses of dapagliflozin, respectively.

Dapagliflozin, either alone or in combination with metformin, was well tolerated with no deaths, serious adverse events, or withdrawals reported over 14 days. Two episodes of hypoglycemia were reported with dapagliflozin use; however, these were mild and self-limiting. Two female patients experienced vulvovaginal mycotic infections that were mild in nature and resolved with miconazole therapy. This study was the first to show that dapagliflozin, with or without metformin, results in clinically significant dose-dependent increases in glucosuria and improvements in FPG and OGTT results. It was noted that on day 14, a similar level of SGLT2 inhibition resulted in lower cumulative amounts of glucose excretion, indicating that the amount of glucose filtered by the glomeruli might diminish over time as plasma glucose levels stabilize. However, because of the short duration of this trial, long-term estimates are unable to be calculated from the results of this study.

In the first large-scale phase III clinical trial, the safety and efficacy of dapagliflozin in patients with type 2 diabetes who demonstrated inadequate control with metformin monotherapy were investigated.[51] This study was a 24-week, multicenter, double-blind, parallel-group, placebo-controlled trial in which 546 patients were randomly assigned to receive dapagliflozin 2.5, 5, or 10 mg once/day or matching placebo in a 1:1:1:1 ratio. Patients were eligible to participate if they were aged 18–77 years and met the following criteria: A1C of 7–10%, C-peptide concentration greater than 0.34 nmol/L (1.0 ng/ml), BMI less than 45 kg/m^2, and were taking a stable dose of metformin ($\geq$ 1500 mg/day) for at least 8 weeks before enrollment. Patients continued taking metformin during the trial. Those who had impaired renal or hepatic function, a cardiovascular event within the past 6 months, heart failure (New York Heart Association classes III –IV), or elevated blood pressure (systolic > 180 mm Hg or diastolic > 110 mm Hg) were not permitted to participate. The predefined primary end point was a change from baseline in A1C at week 24. Predefined secondary end points included a change in FPG level (assessed at wk 1 and wk 24) and total body weight.

A total of 483 patients (88%) completed the trial. The primary reason for discontinuation was withdrawal of consent (17 patients) or loss to follow-up (18 patients). Baseline demographics were well matched in each treatment group for age, sex, BMI, A1C, FPG level, blood pressure, and baseline metformin dose (1792 –1861 mg). After 24 weeks of therapy, mean change from baseline in A1C was significantly reduced in the dapagliflozin 2.5-, 5-, and 10-mg groups (−0.67%, −0.70%, and −0.84%,

respectively) compared with placebo (−0.30%, p<0.0005). At week 1, FPG level was significantly reduced in the dapagliflozin 5- and 10-mg groups compared with placebo. By week 24, however, reductions in FPG were statistically significant in all dapagliflozin dosing groups (−18 mg/dl to −23 mg/dl) compared with placebo (−6 mg/dl). Mean total body weight decreased in a similar fashion, with reductions in mean total body weight ranging from 2.2−2.9 kg with dapagliflozin versus 0.9 kg with placebo (p<0.0001 for all dapagliflozin groups vs placebo). The authors suggested that dapagliflozin may induce weight loss partly through a mild osmotic diuresis.

Although dapagliflozin was generally well tolerated, a larger proportion of patients experienced signs and symptoms suggestive of genital infections compared with the placebo group (8–13% vs 5%). The percentage of patients experiencing a UTI was 4–8% with dapagliflozin and 8% with placebo. Dapagliflozin was not associated with an increased risk of hypoglycemia compared with placebo. This trial was the largest to date showing that dapagliflozin is safe and effective when added to metformin. Several findings from this study (i.e., small increases in hematocrit and small decreases in uric acid level and blood pressure) indicate that dapagliflozin may harbor ancillary or pleiotropic properties that could confer long-term benefits not yet fully appreciated in shorter clinical trials. Furthermore, this is the first trial to demonstrate a greater reduction in A1C in patients with a higher baseline A1C value.

A 52-week, multicenter, randomized, parallel-group, double-blind, active-controlled phase III study assessed the noninferiority of dapagliflozin compared with glipizide in patients inadequately controlled with at least 1500 mg/day of metformin.[52] In total, 814 patients with type 2 diabetes aged 18 years or older with an A1C of 6.5–10% were randomly assigned to either dapagliflozin, starting at 2.5 mg/day, plus metformin, or glipizide, starting at 5 mg/day, plus metformin. Dose titration up to dapagliflozin 10 mg/day or glipizide 20 mg/day was allowed as necessary up to week 18. Noninferiority was defined as a difference in change in A1C of less than 0.35% for the comparison of dapagliflozin and glipizide. Secondary end points included the change from baseline in body weight and self-reported hypoglycemia events at week 52. These results have been published only in abstract form.

After 52 weeks of therapy, both the dapagliflozin-based regimen and glipizide-based regimen reduced A1C levels by 0.52% (difference in adjusted mean change from baseline for dapagliflozin added to metformin vs glipizide added to metformin was 0.00%, 95% confidence interval [CI] −0.11–11, indicating noninferiority).[52] Patients treated with the dapagliflozin-based regimen had significantly greater reductions in mean total body weight compared with those treated with a glipizide-based regimen (−3.22 vs + 1.44 kg, p<0.0001 for the comparison between groups). A significant difference was noted between the percentage of patients who experienced a hypoglycemic event in the dapagliflozin-based groups (3.5%) versus those in the glipizide-based groups (40.8%, p<0.0001). No baseline demographics were presented for this unpublished study at the time of writing.

Discontinuations due to an adverse event were 9.1% for the dapagliflozin-based regimen versus 5.9% for the glipizide-based regimen. Signs and symptoms suggestive of UTIs were more frequent in patients taking a dapagliflozin-based regimen (10.8%) compared with the glipizide-based regimen (6.4%). Similarly, genital infections were more frequent with the dapagliflozin-based regimen (12.3%) than the glipizide-based regimen (2.7%). The dapagliflozin-based regimen was associated with reductions in both systolic and diastolic blood pressure (4.3 mm Hg and 1.6 mm Hg, respectively), whereas the glipizide-based regimen was not (+0.8 mm Hg and +0.4 mm Hg, respectively).

This was the first study conducted to assess the noninferiority of dapagliflozin versus other agents in the antidiabetic drug arena. The results of this study indicate that dapagliflozin compares favorably with glipizide in patients who are inadequately treated with metformin, with a lower frequency of hypoglycemia but increased occurrence of UTI and genital infections.

The efficacy of dapagliflozin added to glimepiride in patients with type 2 diabetes was studied in a 24-week, multicenter, international, randomized, parallel-group, double-blind, placebo-controlled, phase III clinical trial.[53] This study randomly assigned 597 patients aged 18 years or older with an A1C of 7–10% to one of four treatment groups: dapagliflozin 2.5, 5, or 10 mg/day plus glimepiride, or placebo plus glimepiride. To be eligible, patients had to be receiving at least half the recommended maximal dose of glimepiride. The primary end point of this study assessed the change from baseline in A1C at

week 24. Additional end points included change from baseline in total body weight, OGTT, and FPG. The results from this study have been presented in abstract form and are unavailable in a peer-reviewed format; thus, no baseline demographics have been reported yet.

Reductions in A1C levels ranged from −0.58% to −0.82% with dapagliflozin compared with −0.13% with placebo when either was added to glimepiride ($p<0.0001$ for all dapagliflozin groups vs placebo). A dose-dependent reduction in total body weight was also noted, ranging from −1.18 kg to −2.26 kg with dapagliflozin compared with −0.72 kg with placebo ($p>0.05$, $p<0.01$, $p<0.0001$ for dapagliflozin 2.5, 5, and 10 mg, respectively, vs placebo). The change in OGTT results from baseline was −37.5, −32.0, −34.9 mg/dl in the dapagliflozin 2.5-, 5-, and 10-mg groups, respectively, compared with −6.0 mg/dl in the glimepiride group. Patients in the dapagliflozin 5- and 10-mg groups had significant reductions in FPG (−21.2 and −28.5 mg/dl, respectively) compared with those in the placebo group (−2.0 mg/dl, $p<0.0001$ for both dapagliflozin groups vs placebo). Patients in the dapagliflozin 2.5-mg group had a reduction in FPG of −16.8 mg/dl.

More patients allocated to dapagliflozin experienced the following adverse events compared with placebo: back pain (1.9–4.6% vs 2.7%), upper respiratory tract infection (3.2–4.6% vs 2.7%), and bronchitis (1.3–3.3% vs 0.7%). The rates of UTI were similar among all groups: 3.9%, 6.9%, and 5.3% of patients in the dapagliflozin 2.5-, 5-, and 10-mg groups, respectively, compared with 6.2% of patients taking placebo. Genital infections were reported more frequently in patients taking dapagliflozin (3.9–6.6%) than in those taking placebo (0.7%). Serious adverse events were also more common with dapagliflozin (6.0–7.1%) than with placebo (4.8%). There appeared to be an increased risk for hypoglycemia when dapagliflozin was added to glimepiride (6.9–7.9%) compared with placebo plus glimepiride (4.8%). Mean reductions in seated systolic and diastolic blood pressure in the dapagliflozin groups and placebo group were −4.0 mm Hg to −5.0 mm Hg and −1.1 mm Hg to −2.8 mm Hg, respectively.

This trial was the first to demonstrate that dapagliflozin produces significant reductions in A1C in patients with type 2 diabetes when added to glimepiride. The frequency of adverse events was similar between both treatment groups, although the rates of gential infection and hypoglycemia were numerically higher in patients taking dapagliflozin plus glimepiride. Trials that are longer in duration would be helpful to assess whether the reductions in A1C, FPG, OGTT, and blood pressure with dapagliflozin added to glimepiride result in a favorable risk-benefit profile compared with other strategies.

Dapagliflozin with Insulin, with or without Oral Antidiabetic Drugs

The safety and efficacy of dapagliflozin added to insulin and OADs have been evaluated in a 12-week, randomized, single- and double-blind, three-arm parallel group, placebo-controlled trial.[54] A total of 71 patients were randomly and equally assigned to placebo or dapagliflozin 10 mg/day or 20 mg/day, in addition to their previous OAD(s) and 50% of their current daily insulin dose. Down-titration of insulin doses occurred when patients were at risk for hypoglycemic events (plasma glucose level <54 mg/dl), and up-titration occurred when patients experienced elevated FPG values (>240 mg/dl at wks 4 and 6, >220 mg/dl at wk 8, and >200 mg/dl at wk 10). No dosage adjustments were allowed with dapagliflozin or OAD(s).

Inclusion criteria were type 2 diabetes, age 18–75 years, BMI of 45 kg/m^2 or less, A1C of 7.5–10%, stable insulin sensitizer dose for 6 weeks or longer (metformin $\geq$ 1000 mg/day and/or pioglitazone $\geq$ 30 mg/day or rosiglitazone 4 mg/day), stable insulin dose for 12 weeks or longer, fasting C-peptide level of 0.8 ng/ml or greater, serum creatinine level less than 1.5 mg/dl (men) and less than 1.4 mg/dl (women), urine microalbumin:creatinine ratio less than 300 mg/g, and total urinary protein less than 3 g/24 hours.[54] Patients were excluded if they had type 1 diabetes mellitus or any severe cardiovascular, renal, or hepatic disease. The primary outcome was a change from baseline in A1C values at week 12. Additional outcomes included change from baseline in FPG, total daily dose of insulin, and total body weight.

Most patients were taking combination metformin and insulin (74.7%) before randomization, and participants tended to be male (59.3%) and Caucasian (94.4%). Other baseline demographics were well matched. At the end of 12 weeks, the difference in mean change from baseline in A1C was −0.70% and −0.78% for dapagliflozin 10 mg and 20 mg, respectively, versus placebo. Changes in FPG levels were 17.8 mg/dl for placebo, 2.4 mg/dl for dapagliflozin 10 mg, and

−9.6 mg/dl for dapagliflozin 20 mg. Patients receiving dapagliflozin tended to have greater reductions in total body weight compared with those receiving placebo (−4.3 kg to −4.5 kg vs −1.9 kg). After the 50% dose reduction, changes in total daily dose of insulin were not different from baseline in any treatment group. Dapagliflozin reduced mean systolic blood pressure (−6.1 mm Hg to −7.2 mm Hg) and diastolic blood pressure (−1.2 mm Hg to −3.9 mm Hg) as well as mean serum uric acid levels (−0.30 mg/dl).

This study is the first to confirm the utility of combining dapagliflozin with insulin and other OADs in patients with type 2 diabetes. This initial trial experience with dapagliflozin added to insulin and OADs provides evidence of reductions in A1C and FPG with a favorable safety profile in patients not controlled with two therapies. Despite the short duration and small sample size, this trial represents the impetus for future long-term trials in this population.

Dapagliflozin was evaluated in a 48-week clinical trial in patients with type 2 diabetes who were inadequately controlled with insulin therapy (with or without up to two OADs).[55] A total of 808 patients with an A1C of 7.5–10.5% and receiving a mean insulin dose of 30 or more international units/day for at least 8 weeks were randomly assigned to dapagliflozin 2.5, 5, or 10 mg/day or placebo. Baseline demographics were not reported at the time of this writing. Down-titration of insulin was permitted when patients were at risk for hypoglycemic events (defined as a plasma glucose $\leq$ 70 mg/dl on $\geq$ 2 occasions), and up-titration was permitted if patients had three or more fasting serum glucose levels over the past 7 days that were greater than 240 mg/dl during weeks 1–12, greater than 220 mg/dl during weeks 13–24, and greater than 180 mg/dl during weeks 25–48. The primary end point was a change from baseline in A1C values at week 48. Additional end points included a change from baseline in total body weight and total daily dose of insulin at 48 weeks.

At 48 weeks, changes in A1C from baseline were −0.74% (95% CI −0.48% to −0.13%), −0.94% (95% CI −0.69% to −0.33%), and −0.93% (95% CI −0.67% to −0.32%) in the dapagliflozin 2.5-, 5-, and 10-mg groups, respectively. Placebo was associated with a −0.43% change in A1C from baseline at 48 weeks. Patients taking dapagliflozin had dose-dependent reductions in total body weight ranging from 0.83 kg to 1.45 kg, whereas placebo increased total body weight by 0.85 kg. Placebo-treated patients tended to require more up-titration of insulin throughout the study, requiring a mean increase of 10.54 IU/day. Conversely, total daily dose of insulin did not change from baseline in patients taking dapagliflozin (ranging from −0.92–0.30 IU/day), suggesting that dapagliflozin afforded patients an insulin-sparing effect. Similar to other trials, mean seated systolic blood pressure decreased from baseline with dapagliflozin (−3.8 mm Hg to −5.4 mm Hg), as well as mean seated diastolic blood pressure (−2.3 mm Hg to −3.1 mm Hg). Slight reductions in serum uric acid levels were also observed during the trial.

Dapagliflozin was generally well tolerated, and adverse events were reported in similar proportions of placebo-treated patients (73.1%) and dapagliflozin-treated patients (72.2–75.7%). More patients had a hypoglycemic event with dapagliflozin (53.6–60.4%) than with placebo (51.8%). A larger number of patients experienced genital infections in the dapagliflozin groups (13–21 patients) compared with placebo (five patients). Urinary tract infection was also reported more frequently in the dapagliflozin groups (11–16 patients) than with placebo (eight patients).

This was the second trial that assessed the efficacy and safety of adding dapagliflozin to an inadequate insulin regimen with or without OADs. Dapagliflozin produced sustained reductions in plasma glucose levels after 48 weeks of treatment and demonstrated its ability to reduce the total daily dose of insulin in patients already taking insulin. The reduction in total daily dose of insulin may likely be due to the sustained plasma glucose lowering and reduction in weight. Although it was already shown that dapagliflozin produces reductions in both A1C and total body weight in another trial,[54] this study provided evidence that dapagliflozin's effects are durable and persisted over 48 weeks. However, future trials will need to assess the long-term safety and tolerability of dapagliflozin in conjunction with insulin and other OADs.

Safety and Tolerability

The clinical trial experience with dapagliflozin has demonstrated a favorable safety profile (Table 3). In phase III clinical trials, the rate of hypoglycemia with dapaglifozin was similar to that with placebo, and no major hypoglycemic events were reported.[49, 50] This is consistent with the mechanism of action of dapagliflozin,

Table 3. Adverse Events Occurring in Two Phase III Clinical Trials in Patients with Type 2 Diabetes Mellitus Treated with Dapagliflozin

Adverse Event	Dapagliflozin[a] vs Placebo (%)[49]	Dapagliflozin[a] vs Placebo (%)[51]
Common adverse events		
Headache	4.7–7.7 vs 6.7	3–8 vs 4
Back pain	—	2–7 vs 5
Diarrhea	1.4–6.2 vs 1.3	2–7 vs 5
Influenza	—	6–9 vs 7
Nasopharyngitis	2.9–10.8 vs 5.3	3–9 vs 8
Hypertension	—	3–7 vs 4
Upper respiratory tract infection	—	2–4 vs 7
Cough	—	<1–3 vs 5
Adverse events of special interest		
Hypoglycemia	0–2.9 vs 2.7	2–4 vs 3
Urinary tract infection[b]	4.6–12.5 vs 4	4–8 vs 8
Genital tract infection[b]	7.7–12.9 vs 1.3	8–13 vs 5
Hypotension	0–1.4 vs 1.3	0–1 vs <1

[a]Data are for three dapagliflozin treatment groups: 2.5, 5, and 10 mg/day.
[b]Signs and symptoms were suggestive of possible urinary or genital tract infections.

which promotes glucosuria in a glucose-dependent fashion while sparing insulin secretion and function. Overall, there was an increased frequency of genital infections in both men and women treated with dapagliflozin (2–13% of patients) compared with placebo (0–5%) and metformin (2%).[48, 49, 51] The frequency of UTI varied largely (4.6–12.5% with dapagliflozin, 4–8% with placebo, and 9% with metformin) and was more marked in female subjects.[48, 49, 51] No deaths were related to the use of dapagliflozin. The most common adverse events ($\geq$ 5% of patients) were UTIs, genital infections, back pain, influenza, upper respiratory tract infections, cough, nasopharyngitis, diarrhea, hypertension, and headache.[51] The overall occurrence of adverse events was similar among patients treated with dapagliflozin (63.1–68.6%) and those treated with placebo (60%) and was generally consistent when dapagliflozin was given as monotherapy or add-on therapy.[49]

There were no relevant changes in renal function or serum electrolyte levels in phase II or III studies. Compared with placebo, dapagliflozin produces a significant increase in glucose excretion ranging from 20.4–53.3 g/day, but this is to be expected given the mechanism of SGLT2 inhibitors. No apparent changes were noted in renal tubular markers (*N*-acetyl-β-d-glucosaminidase and β_2-microglubulin), concentrations of serum creatinine, magnesium, sodium, potassium, phosphate, chloride, oxalate, citrate, or albumin, urinary calcium, total protein, or osmolality.[38]

An osmotic-diuretic effect was noted after 12 weeks of therapy (107–470-ml increase),[48] but such an effect does not appear to result in significant hypotension or orthostatic hypotension.[49] Furthermore, clinical trials demonstrated that dapagliflozin reduces mean seated systolic blood pressure (−2.1 mm Hg to −5.1 mm Hg) and diastolic blood pressure (−1.7 mm Hg to −2.8 mm Hg). Increases in hematocrit (1.5–3.0%) were likely due to hemoconcentration and glucose-induced osmotic diuresis, and appeared to be a dose-related effect.[38, 54] Serum uric acid levels decreased after 24 weeks of therapy, with reductions ranging from 0.35−0.54 mg/dl and also appeared to be dose related. Reductions in serum uric acid levels have been consistent across trials and have been suggested to arise from inhibition of sodium-coupled uric acid reabsorption in the renal proximal tubule.[56] No changes in fasting lipid profiles were seen, with the exception of increased high-density lipoprotein cholesterol (HDL) values (+1.8–4.4%) and decreased triglyceride values (−2.4% to −6.2%).[38]

Ongoing clinical trials, including long-term studies and studies in vulnerable populations (e.g., patients with established cardiovascular disease), will help to fully characterize the safety profile of dapagliflozin and give insight into why serious adverse events were more common in a recent trial.[53]

Controversies and Therapeutic Concerns

Diabetes is associated with a 1.21–2.2 increase in the relative risk for UTI, and it has been suggested that glucosuria is responsible for increasing UTI risk.[57–61] However, the mechanism by which patients with diabetes experience a greater frequency of urogenital infections has yet to be fully elucidated. In fact, no direct relationship linking urinary glucose and UTI frequency has been identified. A prospective trial conducted in 636 women with diabetes found that glucosuria was not associated with a risk of developing asymptomatic bacteriuria or UTI.[62] Similarly, another study assessed 528 women with type 1 diabetes and found no correlation between A1C values and prevalence of cystitis.[63] The occurrence of UTI and genital fungal infections in dapagliflozin studies has been variable, highlighting the urgency for long-term studies that address UTI and genital fungal infection

frequency in both male and female subjects treated with various antidiabetic regimens.

Long-term safety and efficacy data for dapagliflozin are still lacking. However, SGLT2 inhibition is not a novel concept and previous investigations may forecast the dapagliflozin experience. Perhaps the best insight into the long-term safety profile of SGLT2 inhibition comes from examining patients with familial renal glycosuria. These patients lose approximately 50–100 g/day of glucose in urine due to a genetic mutation on the *SLC5A2* gene that encodes for SGLT2; yet, no increased risk of urogenital infections can be ascribed to the mutation.[64, 65] Furthermore, it is anticipated that patients with this mutation are expected to have normal life expectancies and are not expected to manifest renal dysfunction, increased liver glucose production, or electrolyte disturbances.[28, 66]

The efficacy profile of SGLT2 inhibition may be best described by the use of a substance isolated from the bark of fruit trees called phlorizin.[67] When studied in the 19th century, phlorizin was noted to produce glucosuria, polyuria, and weight loss in an animal model, but was associated with a high frequency of diarrhea. In the late 20th century, it was discovered that phlorizin inhibits the active transport of glucose reabsorption at the renal proximal tubule by blocking the activity of SGLT1 and SGLT2, and at the mucosa of the small intestine.[68] When given to partially pancreatectomized diabetic rats, phlorizin resulted in normoglycemia, improved insulin sensitivity, and improved residual pancreatic β-cell functioning without affecting insulin concentrations.[69] The results are consistent with a short-term study (24 days), which showed that dapagliflozin therapy results in improved insulin sensitivity and improvements in islet cell morphology in female Zucker diabetic fatty rats.[44] Although these results are promising, their clinical significance in type 2 diabetes remains to be explored.

Both contemporary and historical studies have illuminated a possible increase in the risk of cardiovascular disease with OADs.[70, 71] Most recently, rosiglitazone was shown to increase the risk of myocardial infarction and death from other cardiovascular causes in patients with type 2 diabetes.[72, 73] As a consequence, the United States Food and Drug Administration has mandated that robust cardiovascular studies be undertaken for new OADs approaching the market, in order to demonstrate that they do not result in an increased risk of cardiovascular events. Clinical data with dapagliflozin have not revealed any evidence of an increased risk of cardiovascular events. However, given that dapagliflozin exerts a favorable effect on blood pressure, body weight, and the metabolic milieu (i.e., serum uric acid, triglyceride, and HDL levels), it is possible that dapagliflozin might emerge as a preferred agent for patients at high risk for cardiovascular events, and long-term clinical data are under way to assess its cardiovascular effects.

Dosing and Administration

Dapagliflozin is under investigation in several phase III trials. Ongoing and published phase III clinical trials have used the following dapagliflozin dosing schemes: 1, 2.5, 5, and 10 mg once/day. Dose-dependent decreases in adverse effects, FPG, and A1C are witnessed with higher dosing schemes, although clinical trials have focused on the 1–10 mg/day range based on near maximal blood glucose effects and acceptable tolerability. Dapagliflozin will likely be dosed once/day without regard to meals, given its relatively long half-life and insulin-independent mechanism of action. Future clinical trials will need to assess the use of dapagliflozin in geriatric and pediatric patients and in pregnant or nursing women. Dosage adjustments in renally impaired patients will likely be unnecessary, as renal excretion is not a major elimination pathway for dapagliflozin. Studies have not been published to categorize the impact of hepatic impairment on dapagliflozin pharmacokinetics.

Place in Therapy

Dapagliflozin is the most widely studied agent in a new class of drugs that have the ability to lower plasma glucose by promoting glucosuria. With this distinctive mechanism of action, dapagliflozin provides sustained glucose lowering and addresses the shortcomings of many currently available OADs: weight gain, fluid retention, gastrointestinal effects, and hypoglycemia. More important, dapagliflozin might interfere with the pathogenic defects of type 2 diabetes (i.e., β-cell apoptosis and insulin insensitivity), an effect that some other OADs may accelerate.[16, 74] Drugs are often underutilized in prediabetic and glucose-tolerant patients with a family history of diabetes, where it is said that deleterious effects on β-cell functioning are present.[75, 76] Dapagliflozin may serve as a useful drug in these subsets of patients given that it has an insulin-independent mechanism of action, although

clinical studies are needed to validate dapagliflozin's ability to reduce the progression to diabetes.

Dapagliflozin also provides reductions in total body weight and blood pressure. These differentiating features may render it beneficial in patients with cardiovascular disease; however, long-term clinical trials and postmarketing experience are under way and will assess dapagliflozin's cardiovascular profile. Current literature in both treatment-naïve and -experienced patients suggests that clinicians will likely be able to use dapagliflozin as monotherapy or add-on therapy. Strong clinical programs that assess the long-term safety and efficacy of dapagliflozin are ongoing and will attempt to resolve the following important therapeutic issues: its adverse-effect profile (particularly urogenital infections), antiobesity and blood pressure-lowering effects, and reversibility of β-cell dysfunction.

Conclusion

In spite of a reasonable complement of OADs and clear recommendations from guidelines and other authorities on the importance of blood glucose level control, diabetes remains a growing global health threat. Many patients with diabetes languish with poorly controlled blood glucose levels for many years, increasing the risk of micro- and macrovascular disease. Reasons for this disconnect are multifactorial but include underutilization and inadequacy of pharmacotherapy. Consequently, drugs being developed as treatment for type 2 diabetes, including SGLT2 inhibitors such as dapagliflozin, will be important for assuaging the future cost and health implications of diabetes.

Given dapagliflozin's distinctive mechanism of action, formidable efficacy, and acceptable safety profile, it will likely be a welcomed addition to the current antidiabetic drug portfolio. Dapagliflozin could afford clinicians an alternative to other agents that can cause hypoglycemia, weight gain, and edema, given that it has been shown to be associated with a low rate of hypoglycemia and promotes mild weight loss and diuresis. Its hypotensive actions might also compliment the actions of antihypertensive drugs in patients with coexisting diabetes and hypertension.

Additional studies are warranted to better characterize dapagliflozin's effects on urogenital infections and cardiovascular disease. Such studies will help clinicians better evaluate the risk-benefit profile of this new therapy. In the meantime, dapagliflozin will remain a tantalizing future option for treating the growing number of patients with diabetes destined to exhaust the currently available drugs.

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