

## Formulary Drug Reviews

### Dapagliflozin

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Generic Name:	Dapagliflozin
Proprietary Name:	Farxiga (Bristol-Myers Squibb/ AstraZeneca)
Approval Rating:	1S
Therapeutic Class:	Sodium-glucose cotransporter 2 inhibitors
Similar Drugs:	Canagliflozin
Sound- or Look-Alike Names:	Canagliflozin

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#### INDICATIONS

Dapagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.<sup>1</sup> It has been studied as monotherapy and in conjunction with oral antidiabetic agents and insulin. Canagliflozin was approved with the same indication.<sup>2</sup> Neither drug is approved

for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.<sup>1,2</sup>

#### CLINICAL PHARMACOLOGY

Dapagliflozin is a potent and selective renal sodium glucose cotransporter 2 (SGLT2) inhibitor.<sup>1,3,4</sup>

In healthy individuals, more than 99% of the plasma glucose that is filtered in the kidneys is reabsorbed. The reabsorption process is mediated by 2 sodium-dependent glucose cotransporters: sodium glucose cotransporter 1 (SGLT1), which is expressed in the gut, heart, and kidney; and SGLT2, which is expressed primarily in the kidney. Approximately 90% of renal glucose reabsorption is facilitated by SGLT2 in the S1 segment of the proximal tubule, with the other 10% facilitated by SGLT1 in the distal S3 segment of the proximal tubule.<sup>3</sup> Inhibition of SGLT2 has been proposed as a therapy for diabetes by preventing renal glucose reabsorption and promoting glucose excretion in the urine.<sup>3</sup> Its effects are independent of insulin activity. Administration of dapagliflozin in patients with type 2 diabetes resulted in up to 40% inhibition of reabsorption of filtered glucose.<sup>5</sup>

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Dapagliflozin has also been associated with diuretic-like effects, including reductions in blood pressure, body weight, glomerular filtration rate (GFR), and plasma volume.<sup>6</sup>

### PHARMACOKINETICS

Peak plasma concentrations ( $C_{max}$ ) are reached within 1 to 2 hours of dapagliflozin oral administration.<sup>1,4,5,7,8</sup> Absolute oral bioavailability following the 10 mg dose is 78%.<sup>1</sup>  $C_{max}$  and overall exposure increase proportionally with the dose over the therapeutic range.<sup>1</sup> Administration with high-fat food reduces the  $C_{max}$  by up to 50% and prolongs the time to peak concentration ( $T_{max}$ ) by about 1 hour, but it does not alter overall exposure.<sup>1,4</sup> Dapagliflozin is 91% plasma protein bound.<sup>1,7</sup>

The mean half-life is 10 to 17 hours.<sup>1,4,5,7,8</sup> Dapagliflozin is primarily metabolized via UGT1A9, with several cytochrome P450 (CYP-450) pathways serving as minor clearance pathways.<sup>1</sup> Active and inactive metabolites have been identified.<sup>4,5,7</sup> It is primarily metabolized via glucuronidation to the inactive metabolite dapagliflozin 3-O-glucuronide.<sup>1,8,9</sup>

Dapagliflozin metabolites are primarily renally eliminated.<sup>1,8</sup> Less than 4% of the dose is excreted unchanged in the urine, whereas 15% is excreted unchanged in the feces.<sup>1,4,5,7,8</sup>

Dapagliflozin pharmacokinetics have not been observed to differ with race, gender, age, or body weight.<sup>1,8</sup> Dapagliflozin exposure is increased in subjects with severe hepatic impairment and in subjects with impaired renal function; however, pharmacodynamic effects are reduced with decreasing kidney function because of the accompanying reduction in renal glucose clearance.<sup>1,9</sup> In patients with severe renal impairment, dapagliflozin exposure was increased 3-fold compared with patients with normal renal function; however, urinary glucose excretion was 90% lower in patients with severe renal impairment than in those with normal renal function.<sup>1,10</sup>

The pharmacokinetics of canagliflozin and dapagliflozin are compared in Table 1.

### COMPARATIVE EFFICACY

**Indication: Initial Treatment of Type 2 Diabetes Mellitus in Patients Not Optimally Controlled With Diet and Exercise**

#### Guidelines

**Guideline:** Standards of Medical Care in Diabetes

**Reference:** American Diabetes Association, 2014<sup>11</sup>

**Table 1.** Comparative pharmacokinetics of the SGLT2 inhibitors<sup>1,2</sup>

Pharmacokinetics	Canagliflozin	Dapagliflozin
$T_{max}$	1 to 2 hours	1 to 2 hours
Oral bioavailability	65%	78%
Half-life	10.6 to 13.1 hours	12.9 hours
Primary route of metabolism	UGT1A9 and UGT2B4	UGT1A9
Primary route of excretion	Feces and urine	Urine

**Comments:** Unless contraindicated, metformin is recommended as first-line therapy at the time of diagnosis in patients with type 2 diabetes mellitus. If metformin, at maximal tolerated doses, does not achieve or maintain the target hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) over 3 months, a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin should be added. SGLT2 inhibitors were not specifically addressed in the guidelines.

### Studies

**Drug:** Dapagliflozin vs Placebo

**Reference:** Ferrannini E, et al, 2010<sup>12</sup>

**Study Design:** Randomized, double-blind, multicenter, phase 3 study

**Study Funding:** Bristol-Myers Squibb/AstraZeneca

**Patients:** 485 treatment-naïve adult patients 18 to 77 years of age with type 2 diabetes inadequately controlled with diet and exercise, HbA<sub>1c</sub> of 7% to 10%, fasting C-peptide of 1 ng/mL or greater, and body mass index (BMI) no greater than 45 kg/m<sup>2</sup>. An additional exploratory cohort included 73 patients with HbA<sub>1c</sub> of 10.1% to 12% at baseline.

**Intervention:** Dapagliflozin 2.5, 5, or 10 mg once daily in the morning (main cohort); dapagliflozin 2.5, 5, or 10 mg once daily in the evening (evening exploratory cohort); or placebo once daily in the morning or evening for 24 weeks. Patients whose baseline HbA<sub>1c</sub> was 10.1% to 12% were randomly assigned dapagliflozin 5 or 10 mg each morning. Open-label metformin therapy was initiated in patients with fasting plasma glucose greater than 270 mg/dL at week 4, 240 mg/dL at week 8, or 200 mg/dL at week 12.

**Results:****Primary Endpoint(s)**

- In the main cohort, mean HbA<sub>1c</sub> change from baseline at week 24 was -0.58% with dapagliflozin 2.5 mg, -0.77% with dapagliflozin 5 mg ( $P < .001$  vs placebo), and -0.89% with dapagliflozin 10 mg ( $P < .001$  vs placebo), compared with -0.23% with placebo. Results in the evening exploratory cohort were similar; reductions of 2.66% to 2.88% were observed in the cohort with a baseline HbA<sub>1c</sub> of 10.1% to 12%.

**Secondary Endpoint(s)**

- In the main cohort, HbA<sub>1c</sub> less than 7% was achieved in 41% of patients on dapagliflozin 2.5 mg, 44% of patients on dapagliflozin 5 mg, and 51% of patients on dapagliflozin 10 mg, compared with 32% on placebo. Results in the evening exploratory cohort were similar.
- Fasting plasma glucose was reduced as early as week 1. At week 24, reductions in fasting plasma glucose with dapagliflozin 5 and 10 mg were greater than with placebo: -15.2 mg/dL with dapagliflozin 2.5 mg, -24.1 mg/dL with dapagliflozin 5 mg ( $P < .001$  vs placebo), and -28.8 mg/dL with dapagliflozin 10 mg ( $P < .001$  vs placebo), compared with -4.1 mg/dL with placebo.
- Weight loss was observed in all of the dapagliflozin groups, although the difference compared with placebo was not statistically significant (-2.8 to -3.3 kg with dapagliflozin vs -2.2 kg with placebo).

**Limitations:** No active comparator. The proportion of patients receiving open-label metformin in addition to dapagliflozin was not specified.

**Reference:** List JF, et al, 2009<sup>13</sup>

**Study Design:** Randomized, double-blind, multicenter study

**Study Funding:** Bristol-Myers Squibb/AstraZeneca

**Patients:** 389 treatment-naive adult patients 18 to 79 years of age with type 2 diabetes, HbA<sub>1c</sub> of 7% to 10%, fasting C-peptide greater than 1 ng/mL, and BMI no greater than 40 kg/m<sup>2</sup>.

**Intervention:** Dapagliflozin 2.5, 5, 10, 20, or 50 mg; metformin extended release titrated to 1,500 mg (used as a therapeutic benchmark); or placebo once daily for 12 weeks. Patients with fasting plasma glucose greater than 240 mg/dL at weeks 4 and 6, greater than 220 mg/dL at week 8, or greater than 200 mg/dL at week 10 were discontinued from the study.

**Results:****Primary Endpoint(s)**

- At 12 weeks, HbA<sub>1c</sub> was reduced 0.55% to 0.9% with dapagliflozin, compared with a 0.18% reduction with placebo and 0.73% reduction with metformin. The reduction was significant compared with placebo at each dapagliflozin dose ( $P < .05$ ), but no dose relationship was observed.

**Secondary Endpoint(s)**

- HbA<sub>1c</sub> less than 7% was achieved in 40% to 59% of patients treated with dapagliflozin, 54% treated with metformin, and 32% treated with placebo ( $P < .01$  only for the dapagliflozin 50 mg dose relative to placebo).
- Fasting plasma glucose was reduced within 1 week in all dapagliflozin groups, with significant reductions at all doses compared with placebo (-16 mg/dL with dapagliflozin 2.5 mg, -19 mg/dL with dapagliflozin 5 mg, -21 mg/dL with dapagliflozin 10 mg, -24 mg/dL with dapagliflozin 20 mg, and -31 mg/dL with dapagliflozin 50 mg, compared with -6 mg/dL with placebo and -18 mg/dL with metformin).
- Total body weight was reduced 2.5% to 3.4% with dapagliflozin, 1.7% with metformin, and 1.2% with placebo.

**Limitations:** 12-week study; not powered for comparison with active comparator.

**Reference:** Ji L, et al, 2014<sup>14</sup>

**Study Design:** Randomized, double-blind, multicenter, phase 3 study

**Study Funding:** Bristol-Myers Squibb/AstraZeneca

**Patients:** Drug-naive Asian patients with type 2 diabetes, HbA<sub>1c</sub> of 7% to 10.5%, C-peptide level of at least 1 ng/mL, and a BMI no greater than 45 kg/m<sup>2</sup>. Open-label metformin therapy was initiated in patients if necessary.

**Intervention:** Dapagliflozin 5 or 10 mg, or placebo once daily for 24 weeks.

**Results:****Primary Endpoint(s)**

- The mean change in HbA<sub>1c</sub> from baseline to week 24 was -1.04% with dapagliflozin 5 mg and -1.11% with dapagliflozin 10 mg, compared with -0.29% with placebo ( $P < .001$  for both doses vs placebo).

**Secondary Endpoint(s)**

- HbA<sub>1c</sub> less than 7% was achieved in 42.5% of patients treated with dapagliflozin 5 mg and 49.8% treated with dapagliflozin 10 mg, compared with 21.3% treated with placebo ( $P < .001$ ).

- Fasting plasma glucose was reduced by a mean of 25.1 mg/dL with dapagliflozin 5 mg and 31.6 mg/dL with dapagliflozin 10 mg, compared with an increase of 2.5 mg/dL with placebo.
- Two-hour postprandial glucose was reduced by a mean of 46.8 mg/dL with dapagliflozin 5 mg and 54.9 mg/dL with dapagliflozin 10 mg, compared with an increase of 1.1 mg/dL with placebo.
- Body weight was reduced 1.64 kg with dapagliflozin 5 mg and 2.25 kg with dapagliflozin 10 mg, compared with a reduction of 0.27 kg with placebo.

**Comments:** Results were comparable with those observed in studies enrolling primarily a Western population. Dapagliflozin also exhibited greater activity than placebo as assessed by changes in HbA<sub>1c</sub> and fasting plasma glucose in a 12-week phase 2 monotherapy study enrolling Japanese patients.<sup>15</sup>

**Limitations:** No active control.

**Reference:** Bailey CJ, et al, 2012<sup>16</sup>

**Study Design:** Randomized, double-blind, placebo-controlled, multicenter, phase 3 study

**Study Funding:** Bristol-Myers Squibb and AstraZeneca

**Patients:** 282 drug-naive adult patients 18 to 77 years of age with inadequately controlled type 2 diabetes, HbA<sub>1c</sub> of 7% to 10%, C-peptide of at least 1 ng/mL, and BMI no greater than 45 kg/m<sup>2</sup>.

**Intervention:** Dapagliflozin 1, 2.5, or 5 mg, or placebo once daily with the morning meal for 24 weeks. Patients with fasting plasma glucose greater than 270 mg/dL at weeks 4 through 7, greater than 240 mg/dL at weeks 8 through 11, or greater than 200 mg/dL at weeks 12 through 24 were eligible to receive open-label metformin as rescue medication; data after rescue were excluded from all analysis.

**Results:**

**Primary Endpoint(s)**

- HbA<sub>1c</sub> was reduced from baseline by 0.68% with dapagliflozin 1 mg, 0.72% with dapagliflozin 2.5 mg, and 0.82% with dapagliflozin 5 mg, compared with 0.02% with placebo ( $P < .001$  for all dapagliflozin doses vs placebo).

**Secondary Endpoint(s)**

- HbA<sub>1c</sub> less than 7 % was achieved in 53.6% of patients with dapagliflozin 1 mg, 43.4% with dapagliflozin 2.5 mg, and 49.1% with dapagliflozin 5 mg, compared with 34.6% with placebo ( $P < .05$  only for the dapagliflozin 1 mg dose vs placebo).

- Fasting plasma glucose was reduced 11 mg/dL with dapagliflozin 1 mg, 21.6 mg/dL with dapagliflozin 2.5 mg, and 28.5 mg/dL with dapagliflozin 5 mg, and was increased 4.1 mg/dL with placebo ( $P = .01$  for the dapagliflozin 1 mg dose and  $P < .001$  for the dapagliflozin 2.5 and 5 mg doses vs placebo).
- Two-hour post-liquid meal glucose was reduced 33.3 mg/dL with dapagliflozin 1 mg, 39.3 mg/dL with dapagliflozin 2.5 mg, and 51.7 mg/dL with dapagliflozin 5 mg, compared with an increase of 8.8 mg/dL with placebo ( $P < .001$  for all dapagliflozin doses vs placebo).
- Total body weight was reduced 2.69 kg with dapagliflozin 1 mg, 2.64 kg with dapagliflozin 2.5 mg, and 2.69 kg with dapagliflozin 5 mg, compared with 0.96 kg with placebo ( $P < .01$  for all dapagliflozin doses vs placebo). A 5% or greater reduction in body weight from baseline was achieved in 23.6% of patients with dapagliflozin 1 mg, 17.6% with dapagliflozin 2.5 mg, and 34.3% with dapagliflozin 5 mg, compared with 7.4% with placebo.
- Change in waist circumference was reduced 2.5 cm with dapagliflozin 1 mg, 2.31 cm with dapagliflozin 2.5 mg, and 3.17 cm with dapagliflozin 5 mg, compared with 1.7 cm with placebo (differences from placebo not significant).

**Limitations:** No active comparator.

**Drug:** Dapagliflozin vs Metformin vs Dapagliflozin plus Metformin

**Reference:** Henry RR, et al, 2012<sup>17</sup>

**Study Design:** Two randomized, double-blind, multicenter, phase 3 studies

**Study Funding:** Bristol-Myers Squibb/AstraZeneca

**Patients:** Adults 18 to 77 years of age with type 2 diabetes uncontrolled with diet and exercise, HbA<sub>1c</sub> of 7.5% to 12%, C-peptide concentration of at least 1 ng/mL, and BMI no greater than 45 kg/m<sup>2</sup> (598 patients in study 1 and 638 patients in study 2 were included in the modified intent-to-treat population).

**Intervention:** Patients in study 1 received dapagliflozin 5 mg, metformin extended release, or dapagliflozin 5 mg and metformin extended release; patients in study 2 received dapagliflozin 10 mg, metformin extended release, or dapagliflozin 10 mg and metformin extended release. Treatments

were administered once daily with the evening meal for 24 weeks. Metformin was force titrated in 500 mg weekly increments as tolerated up to 2,000 mg daily. Open-label rescue with pioglitazone, sitagliptin, or acarbose was permitted, in addition to double-blind treatment for patients not achieving glycemic control (fasting plasma glucose greater than 270 mg/dL at weeks 6 through 7, greater than 240 mg/dL at weeks 8 through 11, or greater than 200 mg/dL at weeks 12 through 20).

#### Results:

##### Primary Endpoint(s)

- The mean change in HbA<sub>1c</sub> from baseline to week 24 was greater with the combination than with either monotherapy in both trials (−2.05% with combination, −1.19% with dapagliflozin, and −1.35% with metformin in study 1; −1.98% with combination, −1.45% with dapagliflozin, and −1.44% with metformin in study 2;  $P < .001$  for the combinations vs either individual agent). Dapagliflozin 10 mg was noninferior to metformin monotherapy for HbA<sub>1c</sub> reduction in a prespecified analysis in study 2.

##### Secondary Endpoint(s)

- The mean change in fasting plasma glucose from baseline to week 24 was greater with the combination than with either monotherapy in both trials (−61.1 mg/dL with combination, −42 mg/dL with dapagliflozin, and −33.5 mg/dL with metformin in study 1; −60.4 mg/dL with combination, −46.5 mg/dL with dapagliflozin, and −34.8 mg/dL with metformin in study 2;  $P < .001$  for the combinations vs either individual agent). Dapagliflozin 10 mg was superior to metformin monotherapy for fasting plasma glucose reduction ( $P = .0012$ ).
- HbA<sub>1c</sub> less than 7% was achieved in more patients with the combination than with either monotherapy in both trials (52.4% with combination, 22.5% with dapagliflozin, and 34.6% with metformin in study 1; 46.6% with combination, 31.7% with dapagliflozin, and 35.2% with metformin in study 2;  $P \leq .001$  for the combinations vs either individual agent).
- Total body weight loss was greater with the combination and with dapagliflozin monotherapy than with metformin monotherapy in both trials (−2.66 kg with combination, −2.61 kg with dapagliflozin, and −1.29 kg with metformin in study 1; −3.33 kg with combination, −2.73 kg with dapagliflozin, and −1.36 kg with metformin

in study 2;  $P < .001$  for combination vs metformin and for dapagliflozin 10 mg vs metformin).

- Fewer patients treated with the combination or dapagliflozin monotherapy than treated with metformin monotherapy required rescue for not achieving fasting plasma glucose targets (0.5% with combination, 7.4% with dapagliflozin, and 12.9% with metformin in study 1; 1.4% with combination, 7.8% with dapagliflozin, and 13.5% with metformin in study 2).

##### Endpoint(s)

Adverse events were generally of mild to moderate intensity; there were no cases of major hypoglycemia or hypoglycemia resulting in discontinuation from either study. Urinary tract infections (UTIs) and genital infections were more common with dapagliflozin, whereas diarrhea was more common with metformin.

#### Indication: Treatment of Type 2 Diabetes Mellitus in Patients Not Optimally Controlled With Oral Antidiabetic Agents and/or Insulin

##### Guidelines

**Guideline:** Standards of Medical Care in Diabetes  
**Reference:** American Diabetes Association, 2014<sup>11</sup>  
**Comments:** Unless contraindicated, metformin is recommended as first-line therapy at the time of diagnosis in patients with type 2 diabetes mellitus. If metformin, at maximal tolerated doses, does not achieve or maintain the target HbA<sub>1c</sub> over 3 months, a second oral agent, a GLP-1 receptor agonist, or insulin should be added. SGLT2 inhibitors were not addressed in the guidelines.

##### Studies

**Drug:** Dapagliflozin vs Placebo

**Reference:** Zhang M, et al, 2013<sup>18</sup>

**Study Design:** Systematic review and meta-analysis of randomized controlled trials

**Study Funding:** None; the 10 studies included in the meta-analysis were funded by Bristol-Myers Squibb and AstraZeneca.

**Patients:** Adults with type 2 diabetes included in 10 randomized controlled trials (3,464 patients treated with dapagliflozin and 1,331 patients treated with placebo); baseline HbA<sub>1c</sub> ranged from 6.5% to 12%.

**Intervention:** Dapagliflozin 1 to 50 mg once daily or placebo as monotherapy (3 studies) or used in conjunction with other hypoglycemic agents

(7 studies), with treatment duration of at least 12 weeks.

#### Results:

##### Primary Endpoint(s)

- The mean HbA<sub>1c</sub> reduction from baseline was 0.39% to 2.05% with dapagliflozin (weighted mean difference [WMD] vs placebo -0.53%; 95% confidence interval [CI], -0.58% to -0.47%). In 2 of the trials also comparing dapagliflozin (*n* = 701) with metformin (*n* = 463), there was no difference in HbA<sub>1c</sub> reduction between the 2 therapies (WMD, 0.01%; 95% CI, -0.08% to 0.1%; *P* = .8).

##### Secondary Endpoint(s)

- HbA<sub>1c</sub> less than 7% was achieved in more patients treated with dapagliflozin than with placebo (relative risk [RR], 1.43; 95% CI, 1.29 to 1.58; *P* < .001).
- Fasting plasma glucose was reduced from baseline to a greater extent with dapagliflozin than with placebo (WMD, -18.9 mg/dL; 95% CI, -20.7 to -16.9 mg/dL; *P* < .001). In the 2 trials also comparing dapagliflozin with metformin, dapagliflozin reduced fasting plasma glucose to a greater extent than metformin (WMD, -6.1 mg/dL; 95% CI, -10.3 to -2 mg/dL; *P* < .001).
- Body weight was reduced from baseline to a greater extent with dapagliflozin than with placebo (WMD, -1.63 kg; 95% CI, -1.83 to -1.43 kg; *P* < .001) and to a greater extent with dapagliflozin than with metformin (WMD, -1.3 kg; 95% CI, -1.62 to -0.98 kg; *P* < .001).

##### Endpoint(s)

- Hypoglycemia risk was not increased with dapagliflozin monotherapy (RR, 1.44; 95% CI, 0.86 to 2.41; *P* = .17), but it increased when dapagliflozin was combined with other hypoglycemic drugs (RR, 1.16; 95% CI, 1.05 to 1.29; *P* = .005).
- UTIs occurred more frequently with dapagliflozin therapy (RR, 1.33; 95% CI, 1.1 to 1.6; *P* = .004).
- Genital tract infections occurred more frequently with dapagliflozin therapy (RR, 3.23; 95% CI, 2.5 to 4.18; *P* = .001).
- Systolic and diastolic blood pressure were reduced to a greater extent with dapagliflozin than with placebo (WMD, -3.57 mm Hg; 95% CI, -4.38 to -2.27; *P* < .001 for dapagliflozin; WMD -1.49 mm Hg; 95% CI, -1.98 to -0.99; *P* < .001 for placebo).

**Limitation:** Most included studies only allowed comparison of dapagliflozin with placebo. All

included studies were funded by industry. No unpublished studies were included.

**Reference:** Bailey CJ, et al, 2010<sup>19,20</sup>

**Study Design:** Randomized, double-blind, placebo-controlled, multicenter, phase 3 study

**Study Funding:** Bristol-Myers Squibb/AstraZeneca

**Patients:** 546 patients 18 to 77 years of age with type 2 diabetes who were inadequately controlled on metformin at dosages of at least 1,500 mg/day, with HbA<sub>1c</sub> of 7% to 10%, C-peptide concentration of at least 1 ng/mL, and BMI no greater than 45 kg/m<sup>2</sup>.

**Intervention:** Dapagliflozin 2.5, 5, or 10 mg, or placebo once daily before the morning meal in addition to a prestudy dose of metformin for 24 weeks. Open-label pioglitazone could be added to the drug regimen if the fasting plasma glucose concentration was inadequately controlled between weeks 4 and 24. Patients remaining in the study at week 24 were eligible for continuation in a long-term study with treatment for up to 102 weeks; 339 patients completed the 102-week study.

#### Results:

##### Primary Endpoint(s)

- At week 24, mean HbA<sub>1c</sub> was reduced 0.3% in the placebo group, compared with reductions of 0.67% in the dapagliflozin 2.5 mg group (*P* < .001), 0.7% in the dapagliflozin 5 mg group (*P* < .001), and 0.84% in the dapagliflozin 10 mg group (*P* < .001). In the double-blind extension, mean change from baseline was +0.02% in the placebo group and -0.48% in the dapagliflozin 2.5 mg group (*P* < .001), -0.58% in the dapagliflozin 5 mg group (*P* < .001), and -0.78% in the dapagliflozin 10 mg group (*P* < .001).

##### Secondary Endpoint(s)

- HbA<sub>1c</sub> less than 7% was achieved in 25.9% of patients in the placebo group, compared with 33% in the dapagliflozin 2.5 mg group, 37.5% in the dapagliflozin 5 mg group (*P* = .0275), and 40.6% in the dapagliflozin 10 mg group (*P* = .0062). At week 102, HbA<sub>1c</sub> less than 7% was achieved in 15.4% treated with placebo, compared with 20.7% in the dapagliflozin 2.5 mg group, 26.4% in the dapagliflozin 5 mg group (*P* = .0176), and 31.5% in the dapagliflozin 10 mg group (*P* = .0011).
- Fasting plasma glucose at week 24 was reduced 5.9 mg/dL with placebo, compared with reduc-

tions of 17.9 mg/dL with dapagliflozin 2.5 mg ( $P = .0019$ ), 21.4 mg/dL with dapagliflozin 5 mg ( $P < .001$ ), and 23.4 mg/dL with dapagliflozin 10 mg ( $P < .001$ ). Significant reductions were observed at week 1 in the dapagliflozin 5 and 10 mg groups.

- Reductions in body weight were observed at 24 weeks in each dapagliflozin group, compared with placebo ( $-2.2$  kg with dapagliflozin 2.5 mg,  $-3$  kg with dapagliflozin 5 mg, and  $-2.9$  kg with dapagliflozin 10 mg, compared with  $-0.9$  kg with placebo; all  $P$ s  $< .001$ ). Sustained reductions were observed in the extension phase in the dapagliflozin groups ( $-1.1$  to  $-1.74$  kg), compared with an increase of 1.36 kg in the placebo group.

**Reference:** Bolinder J, et al, 2012<sup>21-23</sup>

**Study Design:** Randomized, double-blind, placebo-controlled, multicenter, phase 3 study

**Study Funding:** Bristol-Myers Squibb/AstraZeneca

**Patients:** 180 patients (80 postmenopausal women 55 to 75 years of age and 102 men 30 to 75 years of age) with type 2 diabetes inadequately controlled on metformin (stable dose of at least 1,500 mg/day), HbA<sub>1c</sub> of 6.5% to 8.5% (mean, approximately 7.17%), fasting plasma glucose no greater than 240 mg/dL, BMI of at least 25 kg/m<sup>2</sup> (mean, approximately 31.9 kg/m<sup>2</sup>), and body weight no greater than 120 kg (mean, approximately 91.5 kg).

**Intervention:** Dapagliflozin 10 mg or placebo once daily in the morning added to open-label metformin for 24 weeks; rescue sitagliptin 100 mg daily was permitted with continued inclusion in the study.

**Results:**

**Primary Endpoint(s)**

- Total body weight was reduced 2.96 kg with dapagliflozin compared with a mean reduction of 0.88 kg with placebo (difference,  $-2.08$  kg; 95% CI,  $-2.84$  to  $-1.31$ ;  $P < .001$ ). The placebo-corrected weight loss was greater in male patients ( $-2.76$  kg; 95% CI,  $-3.78$  to  $-1.74$ ) than in female patients ( $-1.22$  kg; 95% CI,  $-2.36$  to  $-0.08$ ).

**Secondary Endpoint(s)**

- Waist circumference was reduced to a greater extent in the dapagliflozin group ( $-2.51$  cm) than the placebo group ( $-0.99$  cm; difference,  $-1.52$  cm; 95% CI,  $-2.74$  to  $-0.31$ ;  $P = .014$ ).
- Total body-fat mass was reduced to a greater extent in the dapagliflozin group ( $-2.22$  kg)

than the placebo group ( $-0.74$  kg; difference,  $-1.48$  kg; 95% CI,  $-2.22$  to  $-0.74$ ;  $P = .001$ ).

- At least a 5% reduction in total body weight was achieved in 30.5% of patients in the dapagliflozin group, compared with 4.3% of patients in the placebo group (difference, 26.2%; 95% CI, 15.5 to 36.7;  $P < .001$ ).

**Endpoint(s)**

- In a subset of patients, analysis of visceral adipose tissue and subcutaneous adipose tissue also revealed significantly greater reductions with dapagliflozin than with placebo.
- HbA<sub>1c</sub> was reduced  $-0.39\%$  in the dapagliflozin group and  $-0.1\%$  in the placebo group ( $P < .001$ ).
- Fasting plasma glucose was reduced 14.7 mg/dL in the dapagliflozin group and increased 2.4 mg/dL in the placebo group ( $P < .001$ ).
- Dapagliflozin exhibited no effect on markers of bone formation or resorption.

**Limitations:** Baseline HbA<sub>1c</sub> was low. Conducted in Bulgaria, Czech Republic, Hungary, Poland, and Sweden.

**Reference:** Strojek K, et al, 2011<sup>24</sup>

**Study Design:** Randomized, double-blind, placebo-controlled, multicenter study

**Study Funding:** Bristol-Myers Squibb/AstraZeneca

**Patients:** 597 adult patients with type 2 diabetes inadequately controlled on sulfonylurea monotherapy, with HbA<sub>1c</sub> of 7% to 10% (mean baseline HbA<sub>1c</sub>, 8.07% to 8.15%), fasting plasma glucose no greater than 270 mg/dL, and fasting C-peptide of at least 1 ng/mL.

**Intervention:** Dapagliflozin 2.5, 5, or 10 mg, or placebo once daily before the first meal of the day added to open-label glimepiride 4 mg daily for 24 weeks; patients receiving other sulfonylureas at study entry were switched to glimepiride during an 8-week lead-in period. Open-label glimepiride could be down-titrated to 2 mg or discontinued during the study at the investigator's discretion but could not be up-titrated. Open-label rescue with metformin, pioglitazone, or rosiglitazone was permitted for patients with inadequate glycemic control after week 4.

**Results:**

**Primary Endpoint(s)**

- At week 24, HbA<sub>1c</sub> was reduced 0.13% with placebo, 0.58% with dapagliflozin 2.5 mg, 0.63% with dapagliflozin 5 mg, and 0.82% with dapagliflozin 10 mg (all  $P$ s  $< .001$  vs placebo).

**Secondary Endpoint(s)**

- Body weight was reduced 0.72 kg in the placebo group, 1.18 kg in the dapagliflozin 2.5 mg group, 1.56 kg in the dapagliflozin 5 mg group ( $P < .01$ ), and 2.26 kg in the dapagliflozin 10 mg group ( $P < .001$ ).
- HbA<sub>1c</sub> of less than 7% was achieved in 13% of patients in the placebo group, 26.8% of patients in the dapagliflozin 2.5 mg group, 30.3% of patients in the dapagliflozin 5 mg group ( $P < .001$ ), and 31.7% of patients in the dapagliflozin 10 mg group ( $P < .001$ ).
- Change from baseline in 2-hour postchallenge plasma glucose was greater with dapagliflozin 5 mg ( $-32$  mg/dL;  $P < .001$ ) and dapagliflozin 10 mg ( $-35$  mg/dL;  $P < .001$ ) than with placebo ( $-6$  mg/dL).
- Change in fasting plasma glucose was greater with dapagliflozin 5 mg ( $-21$  mg/dL;  $P < .001$ ) and dapagliflozin 10 mg ( $-28$  mg/dL;  $P < .001$ ) than with placebo ( $-2$  mg/dL).
- Hypoglycemia occurred more frequently in patients treated with dapagliflozin plus glimepiride (6.9% to 7.9%) than in patients treated with placebo plus glimepiride (4.8%).

**Limitations:** Study was conducted in the Czech Republic, Hungary, Korea, Philippines, Poland, Thailand, and Ukraine.

**Reference:** Jabbour SA, et al, 2013<sup>25</sup>

**Study Design:** Randomized, double-blind, placebo-controlled, multicenter phase 3 study

**Study Funding:** Bristol-Myers Squibb/AstraZeneca

**Patients:** 451 adult patients with type 2 diabetes, with baseline HbA<sub>1c</sub> of 7.7% to 10.5% for those not receiving a dipeptidyl peptidase-4 (DPP-4) inhibitor at enrollment and 7.2% to 10% for those receiving a DPP-4 inhibitor, and fasting plasma glucose less than 270 mg/dL.

**Intervention:** All patients received sitagliptin 100 mg daily for 10 weeks; those with HbA<sub>1c</sub> of 7% to 10% at 10 weeks were randomized to dapagliflozin 10 mg or placebo once daily for 24 weeks in addition to sitagliptin. Patients receiving metformin at study entry continued on metformin. Rescue glimepiride was permitted for patients not achieving glycemic control. Patients completing the 24-week double-blind phase were eligible to continue a 24-week extension phase.

**Results:****Primary Endpoint(s)**

- HbA<sub>1c</sub> was reduced 0.5% in the dapagliflozin group and was unchanged in the placebo group at week 24 ( $P < .001$ ). The placebo-corrected change in HbA<sub>1c</sub> at week 48 was  $-0.7\%$  (95% CI,  $-0.9$  to  $-0.5$ ).

**Secondary Endpoint(s)**

- Total body weight was reduced 2.1 kg in the dapagliflozin group and 0.3 kg in the placebo group at week 24 ( $P < .001$ ). At week 48, the placebo-corrected change in total body weight was  $-2.2$  kg (95% CI,  $-3$  to  $-1.5$ ).
- Fasting plasma glucose was reduced 24.1 mg/dL in the dapagliflozin group and increased 3.8 mg/dL in the placebo group at week 24 ( $P < .001$ ). At week 48, the placebo-corrected change in fasting plasma glucose was  $-33.2$  mg/dL (95% CI,  $-41.6$  to  $-24.7$ ).
- Systolic blood pressure in patients with baseline systolic blood pressure greater than 130 mm Hg was reduced 6 mm Hg in the dapagliflozin group and 5.1 mm Hg in the placebo group at week 8 ( $P = .056$ ). By week 48, the placebo-corrected change in systolic blood pressure was  $-0.2$  mm Hg (95% CI,  $-4.8$  to  $4.4$ ).
- HbA<sub>1c</sub> reduction of at least 0.7% was achieved in 35.3% of patients treated with dapagliflozin compared with 16.6% of patients treated with placebo. At week 48, a reduction of at least 0.7% was achieved in 25.9% of patients treated with dapagliflozin, compared with 5% of patients treated with placebo.
- The 2-hour post-liquid meal glucose was reduced 47.7 mg/dL in the dapagliflozin group and 4.8 mg/dL in the placebo group. At week 48, the placebo-corrected change in 2-hour post-liquid meal glucose was  $-30.9$  mg/dL (95% CI,  $-42.5$  to  $-19.2$ ).

**Endpoint(s)**

HbA<sub>1c</sub> less than 7% was achieved in 27.8% of patients treated with dapagliflozin and 17.9% of patients treated with placebo at 24 weeks and 22.1% of patients treated with dapagliflozin and 12% of patients treated with placebo at 48 weeks.

**Comments:** Overall, the addition of dapagliflozin therapy to therapy with sitagliptin or sitagliptin plus metformin was associated with modest improvements in HbA<sub>1c</sub> and the proportion of patients achieving glycemic goals.



**Reference:** Rosenstock J, et al, 2012<sup>26</sup>

**Study Design:** Randomized, double-blind, placebo-controlled, multicenter study

**Study Funding:** Bristol-Myers Squibb/AstraZeneca

**Patients:** 420 adult patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy, with HbA<sub>1c</sub> of 7% to 10.5% on pioglitazone 30 to 45 mg daily, fasting C-peptide of at least 1 ng/mL, and BMI no greater than 45 kg/m<sup>2</sup>.

**Intervention:** Dapagliflozin 5 or 10 mg or placebo once daily for 24 weeks, in conjunction with open-label pioglitazone 30 to 45 mg daily. Rescue with metformin or sulfonylurea was permitted in patients with inadequate glycemic response; patients receiving rescue medication were excluded from the efficacy analysis. Patients completing the first 24 weeks of the study were eligible for a 24-week study extension.

Results

#### Primary Endpoint(s)

- At 24 weeks, HbA<sub>1c</sub> was reduced 0.82% with dapagliflozin 5 mg ( $P < .001$ ) and 0.97% with dapagliflozin 10 mg ( $P < .001$ ), compared with a reduction of 0.42% with placebo. At week 48, HbA<sub>1c</sub> was reduced 0.95% with dapagliflozin 5 mg and 1.21% with dapagliflozin 10 mg, compared with a reduction of 0.54% with placebo.

#### Secondary Endpoint(s)

- At 24 weeks, fasting plasma glucose was reduced 24.9 mg/dL with dapagliflozin 5 mg and 29.6 mg/dL with dapagliflozin 10 mg, compared with a reduction of 5.5 mg/dL with placebo (both  $P$ s  $< .001$  vs placebo). At 48 weeks, reductions were 22.8 mg/dL with the 5 mg dose and 33.1 mg/dL with the 10 mg dose, compared with 13.1 mg/dL with placebo.
- Postprandial glucose measured by 120-minute postchallenge response to an oral glucose tolerance test at 24 weeks was reduced 65.1 mg/dL with dapagliflozin 5 mg and 67.5 mg/dL with dapagliflozin 10 mg, compared with a reduction of 14.1 mg/dL with placebo (both  $P$ s  $< .001$  vs placebo). At 48 weeks, postprandial glucose was reduced 60.4 mg/dL with dapagliflozin 5 mg and 80.9 mg/dL with dapagliflozin 10 mg, compared with 25.4 mg/dL with placebo.
- Total body weight at 24 weeks was increased 0.09 kg with dapagliflozin 5 mg and reduced 0.14 kg with dapagliflozin 10 mg, compared with a 1.64 kg increase with placebo (both  $P$ s  $< .001$  vs placebo). At 48 weeks, body weight was

increased 1.35 kg with dapagliflozin 5 mg and 0.69 kg with dapagliflozin 10 mg, compared with a 2.99 kg increase with placebo.

**Reference:** Wilding JP, et al, 2012<sup>27,28</sup>

**Study Design:** Randomized, double-blind, placebo-controlled, multicenter study

**Study Funding:** Bristol-Myers Squibb/AstraZeneca

**Patients:** 808 patients with type 2 diabetes inadequately controlled on at least 30 units of insulin daily, with or without up to 2 oral antidiabetic drugs, with HbA<sub>1c</sub> of 7.5% to 10.5% (mean, 8.53%), and BMI no greater than 45 kg/m<sup>2</sup>.

**Intervention:** Dapagliflozin 2.5, 5, or 10 mg, or placebo once daily in addition to insulin (mean baseline dosage, 77 units/day), with or without oral antidiabetic agents for 24 weeks. At enrollment, 50% of patients were receiving oral antidiabetic agents in addition to insulin. Patients completing the initial 24-week treatment period were eligible for a 24-week extension. Those completing 48 weeks were eligible for a further 56-week study extension, with patients in the dapagliflozin 5 mg group switched to dapagliflozin 10 mg. All parties remained blinded during the extension periods. Insulin doses were not titrated to target, with doses only adjusted for poor glycemic control or hypoglycemia.

**Results:**

#### Primary Endpoint(s)

- At week 24, HbA<sub>1c</sub> was reduced by 0.79% with dapagliflozin 2.5 mg, 0.89% with dapagliflozin 5 mg, and 0.96% with dapagliflozin 10 mg, compared with 0.39% with placebo (all  $P$ s  $< .001$  vs placebo). HbA<sub>1c</sub> reductions observed at week 24 were maintained through week 48. Mean HbA<sub>1c</sub> reductions from baseline to 48 weeks were 0.79% with dapagliflozin 2.5 mg, 0.96% with dapagliflozin 5 mg, and 1.01% with dapagliflozin 10 mg, compared with 0.47% with placebo (all  $P$ s  $< .001$  vs placebo). At 104 weeks, mean HbA<sub>1c</sub> reductions from baseline were 0.64% with dapagliflozin 2.5 mg, 0.82% in the group switched from dapagliflozin 5 to 10 mg, and 0.78% with dapagliflozin 10 mg, compared with 0.43% with placebo.

#### Secondary Endpoint(s)

- At week 24, body weight was decreased 0.92 kg in the dapagliflozin 2.5 mg group, 1 kg in the dapagliflozin 5 mg group, and 1.61 kg in the dapagliflozin 10 mg group, compared with an increase of 0.43 kg in the placebo group (all  $P$ s  $< .001$  vs placebo). At week 48, body weight

decreased 0.96 kg in the dapagliflozin 2.5 mg group, 1 kg in the dapagliflozin 5 mg group, and 1.61 kg in the dapagliflozin 10 mg group, compared with an increase of 0.82 kg in the placebo group (all  $P$ s < .001 vs placebo). At week 104, body weight was decreased 0.99 kg in the dapagliflozin 2.5 mg group, 1.03 kg in the group switched from dapagliflozin 5 to 10 mg, and 1.5 kg in the dapagliflozin 10 mg group, compared with an increase of 1.83 kg in the placebo group (all  $P$ s < .001 vs placebo).

- Mean daily insulin dosages were increased in the placebo group but remained relatively constant in the dapagliflozin groups over 104 weeks. At 24 weeks, a reduction in mean insulin dose of at least 10% had occurred in 10.2% of placebo-treated patients and 19.1% of patients treated with dapagliflozin 10 mg ( $P = .013$ ). At 48 weeks, a 10% or greater reduction in mean insulin dose had occurred in 10.5% of placebo-treated patients and 17.5% to 18.6% of dapagliflozin-treated patients ( $P < .05$  for all dapagliflozin doses vs placebo). At 104 weeks, the dose reduction had still occurred in more patients in the dapagliflozin 10 mg group than the placebo group (17% vs 7%;  $P = .002$ ). After 24 weeks, an increase in insulin dose of at least 10% or discontinuation of the study due to poor glycemic control occurred in 9.7% to 11.2% of dapagliflozin-treated patients, compared with 29.2% of placebo-treated patients.
- Adjusted fasting plasma glucose was reduced 11.7 mg/dL in the dapagliflozin 2.5 mg group, 20.2 mg/dL in the dapagliflozin 5 mg group, and 19.8 mg/dL in the dapagliflozin 10 mg group (all  $P$ s < .001). At 48 weeks, adjusted fasting plasma glucose was reduced 12.4 mg/dL in the dapagliflozin 2.5 mg group, 16.2 mg/dL in the dapagliflozin 5 mg group, and 16.9 mg/dL in the dapagliflozin 10 mg group (all  $P$ s < .001).

#### Endpoint(s)

- Through 48 weeks, hypoglycemic events occurred in 60.4% of patients in the dapagliflozin 2.5 mg group, 55.7% in the dapagliflozin 5 mg group, and 53.6% in the dapagliflozin 10 mg group, compared with 51.8% of patients in the placebo group (differences not statistically significant). After 104 weeks, hypoglycemic events had occurred in 60% or more of patients in each treatment group (differences not statistically significant).

**Comments:** Dapagliflozin was also assessed in a randomized, double-blind, placebo-controlled study enrolling 71 patients inadequately controlled with high doses of insulin plus oral anti-diabetic agents (metformin and/or pioglitazone or rosiglitazone). Patients received dapagliflozin 10 or 20 mg or placebo once daily, plus oral agents and 50% of their daily insulin dose. At week 12, the mean change in HbA<sub>1c</sub> from baseline versus placebo was a 0.7% reduction in the dapagliflozin 10 mg group and 0.78% in the dapagliflozin 20 mg group. An HbA<sub>1c</sub> reduction of at least 0.5% was achieved in 65.2% of patients in the dapagliflozin groups, compared with 15.8% of patients in the placebo group. Body weight was reduced 4.5 kg in the dapagliflozin 10 mg group and 4.3 kg in the dapagliflozin 20 mg group, compared with 1.9 kg in the placebo group.<sup>29</sup>

**Limitations:** Insulin doses were not titrated to target.

**Drug:** Dapagliflozin vs Glipizide

**Reference:** Nauck MA, et al, 2011<sup>30</sup>

**Study Design:** Randomized, double-blind, multicenter, phase 3, noninferiority study

**Study Funding:** Bristol-Myers Squibb/AstraZeneca

**Patients:** 814 adult patients with type 2 diabetes inadequately controlled on metformin or other oral agents, HbA<sub>1c</sub> of 6.5% to 10% (mean HbA<sub>1c</sub>, 7.72%), fasting plasma glucose no greater than 270 mg/dL, and C-peptide of at least 1 ng/mL.

**Intervention:** Dapagliflozin 2.5 mg once daily (406 patients) or glipizide 5 mg once daily (408 patients) in addition to open-label metformin, with dosages up-titrated over the first 18 weeks to a maximum of dapagliflozin 10 mg/day or glipizide 20 mg/day and continued for a total of 52 weeks of therapy. Prior to randomization, all other oral hypoglycemic agents were discontinued and metformin dosages were up-titrated to the nearest of 1,500, 2,000, or 2,500 mg/day and maintained for 8 weeks. Patients were discontinued from the study for inadequate glycemic control (fasting plasma glucose greater than 270 mg/dL at weeks 3 through 9, greater than 240 mg/dL at weeks 12 through 18, greater than 220 mg/dL at weeks 26 through 34, or greater than 200 mg/dL at week 42) or if the calculated creatinine clearance fell below 60 mL/min.

**Results:****Primary Endpoint(s)**

- HbA<sub>1c</sub> was reduced 0.52% with dapagliflozin and 0.52% with glipizide, confirming noninferiority.

**Secondary Endpoint(s)**

- Dapagliflozin was associated with a 3.2 kg weight loss, compared with a 1.4 kg weight gain with glipizide (difference, 4.65 kg;  $P < .001$ ).
- A weight loss of at least 5% from baseline was achieved in 33.3% of patients treated with dapagliflozin, compared with 2.5% of patients in the glipizide group (number needed to treat, 3.2 with dapagliflozin).
- Hypoglycemic episodes occurred in 40.8% of patients treated with glipizide, compared with 3.5% of patients treated with dapagliflozin ( $P < .001$ ) (number needed to harm, 2.7 for glipizide).
- The proportion of patients discontinuing therapy due to inadequate glycemic control by week 52 was 0.2% in the dapagliflozin group, compared with 3.6% in the glipizide group (difference, -3.6%; 95% CI, -5.3 to -1.5).

**Comments:** The average dose of glipizide was 16.4 mg and dapagliflozin was 9.2 mg. Glipizide was associated with a more rapid reduction in HbA<sub>1c</sub> during the titration phase, followed by a gradual increase during the maintenance period, whereas dapagliflozin was associated with a more gradual reduction in HbA<sub>1c</sub>, which was maintained during the maintenance period.

**Limitations:** Conducted in Argentina, France, Germany, Italy, Mexico, the Netherlands, South Africa, Spain, and Sweden.

**CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS****Contraindications**

Patients with severe renal impairment, end-stage renal disease, on dialysis, or who have a history of serious hypersensitivity reaction to dapagliflozin should not use this medication.<sup>1</sup>

Table 2 compares the contraindications, warnings and precautions, and recommendations for use in special populations for the SGLT2 inhibitors.

**Warnings and Precautions**

Dapagliflozin causes intravascular volume contraction, which can result in symptomatic hypotension during initiation of therapy, particularly in patients with impaired renal function, elderly

patients, or patients on loop diuretics. Volume status should be assessed prior to therapy. Volume depletion should be corrected prior to initiating therapy with dapagliflozin.<sup>1</sup>

Dapagliflozin increases serum creatinine and decreases estimated GFR. Elderly patients and patients with impaired renal function may be more susceptible to these changes.<sup>1</sup> In a clinical trial enrolling patients with moderate renal impairment, dapagliflozin did not reduce HbA<sub>1c</sub> and was associated with more renal-related adverse reactions and more bone fractures. Dapagliflozin use is not recommended in patients with moderate renal impairment (estimated GFR 30 to less than 60 mL/min/1.73 m<sup>2</sup>).<sup>1,31</sup>

Hypoglycemia risk may increase when dapagliflozin is combined with insulin or an insulin secretagogue. A lower dose of insulin or insulin secretagogue may be necessary when these agents are used in combination with dapagliflozin.<sup>1</sup>

Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections are more likely to develop them.<sup>1</sup>

Low-density lipoprotein-cholesterol (LDL-C) was increased with dapagliflozin therapy; monitoring is recommended with treatment initiated as recommended in current guidelines.<sup>1</sup>

Bladder cancer occurred in a small number of patients treated with dapagliflozin in clinical trials. There is insufficient evidence to determine the effects of dapagliflozin on emergence of bladder cancer or the effects in patients with preexisting bladder tumors. Dapagliflozin should not be used in patients with active bladder cancer. Risk versus benefit should be considered in patients with a history of bladder cancer.<sup>1</sup>

Dapagliflozin is in Pregnancy Category C. Animal data suggest a potential effect on renal development and maturation. Alternative therapies are recommended during pregnancy, particularly during the second and third trimesters.<sup>1</sup>

It is not known whether dapagliflozin is excreted in human milk. In animal models, it is excreted in milk at levels approximately half those found in maternal plasma. Juvenile animals exposed directly to dapagliflozin exhibited evidence of risk to the developing kidney. Because of the risk of kidney damage in a breast-feeding infant, use in a breast-feeding mother is not recommended.<sup>1</sup>

Dapagliflozin has not been evaluated in patients younger than 18 years.<sup>1</sup>

**Table 2.** Contraindications, warnings, and precautions for the SGLT2 inhibitors<sup>1,2</sup>

	Canagliflozin	Dapagliflozin
<i>Contraindications</i>		
Severe renal impairment	X	X
End-stage renal disease or dialysis	X	X
Hypersensitivity to the agent	X	X
<i>Warnings and precautions</i>		
Volume depletion/hypotension	X	X
Impairment in renal function	X	X
Hyperkalemia	X	
Hypoglycemia	X	X
Genital mycotic infections	X	X
Hypersensitivity reactions	X	
LDL-C	X	X
Bladder cancer		X
Macrovascular outcomes not studied	X	X
<i>Special populations</i>		
Renal impairment	Reduce dose if GFR 45 to < 60 mL/min/1.73 m <sup>2</sup> Avoid if GFR is < 45 mL/min/1.73 m <sup>2</sup>	Avoid if GFR < 60 mL/min/1.73 m <sup>2</sup>
Hepatic impairment	No unique precautions in mild to moderate impairment Not studied in severe impairment; therefore, use is not recommended	No unique precautions in mild to moderate impairment Not studied in severe impairment; therefore, risk versus benefit should be considered
Elderly	Increased risk of volume depletion	Increased risk of volume depletion and renal impairment
Pediatric	Safety and efficacy not established	Safety and efficacy not established
Pregnancy	Category C; avoid use	Category C; avoid use
Lactation	Avoid use	Avoid use

Note: GFR = glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol.

## ADVERSE REACTIONS

Dapagliflozin-associated adverse effects have included an increased rate of genital infections and possibly of UTIs.<sup>12,13,19,29,30,32-34</sup> Other adverse events frequently observed in clinical trials, but at a similar frequency with placebo, have included nausea, headache, nasopharyngitis, back pain, and diarrhea.<sup>12,13,19,29</sup> **Table 3** lists the adverse effects observed in at least 3% of dapagliflozin-treated patients in placebo-controlled trials of dapagliflozin.

In a pooled analysis of data from 12 clinical trials, including 3,152 patients treated with dapagliflozin and 1,393 treated with placebo, genital infection incidence was increased with dapagliflozin therapy (4.1% with dapagliflozin 2.5 mg, 5.7% with dapagliflozin 5 mg, 4.8% with dapagliflozin 10 mg, compared with 0.9% with placebo), but the incidence of UTIs was not increased (3.6% with dapagliflozin 2.5 mg, 5.7% with dapagliflozin 5 mg, 4.3% with dapagliflozin 10 mg, compared with 3.7% with placebo).<sup>35,36</sup>

**Table 3.** Adverse effects (at least 3%) in placebo-controlled studies of dapagliflozin<sup>1</sup>

Adverse effects	Dapagliflozin 5 mg (n = 1,145)	Dapagliflozin 10 mg (n = 1,193)	Placebo (n = 1,393)
Female genital mycotic infections	8.4%	6.9%	1.5%
Nasopharyngitis	6.6%	6.3%	6.2%
UTI	5.7%	4.3%	3.7%
Back pain	3.1%	4.2%	3.2%
Increased urination	2.9%	3.8%	1.7%

Note: UTI = urinary tract infection.

Hypoglycemia occurred no more frequently than with placebo when used alone; hypoglycemia was more frequent when dapagliflozin was added to sulfonylureas or insulin.<sup>1,12,13,19,33</sup>

Consistent with a diuretic effect, dapagliflozin has been associated with reductions in systolic and diastolic blood pressure and increased or changed hematocrit, as well as nocturia with evening administration.<sup>6,12,13,19,30,32,34</sup>

### DRUG INTERACTIONS

Dapagliflozin does not appear to inhibit or induce CYP-450 enzymes, P-glycoprotein, or OCT 2, OAT1, or OAT3 active transporters.<sup>1,7</sup>

No pharmacokinetic interactions were observed with coadministration of dapagliflozin and metformin, glimepiride, pioglitazone, sitagliptin, hydrochlorothiazide, bumetanide, simvastatin, valsartan, warfarin, or digoxin.<sup>1,37-40</sup> Patients receiving loop diuretics may be at increased risk for symptomatic hypotension upon initiation of dapagliflozin therapy.<sup>1</sup>

Coadministration of rifampin, a UGT1A9 inducer, reduced dapagliflozin exposure, whereas concomitant administration of mefenamic acid, a UGT1A9 inhibitor, increased dapagliflozin exposure; however, neither change was considered clinically significant.<sup>1,41</sup>

### RECOMMENDED MONITORING

Glucose and HbA<sub>1c</sub> should be monitored periodically throughout therapy. Renal function should be assessed prior to initiating therapy and periodically thereafter.<sup>1</sup> Volume status should be assessed prior to initiating therapy, and patients should be monitored for signs and symptoms of hypotension.<sup>1</sup> LDL-C should be monitored periodically.<sup>1</sup> All patients should also be monitored for genital infections.

### DOSING

The recommended dapagliflozin starting dose is 5 mg once daily, taken in the morning, with or without food. If tolerated at 5 mg, the dose may be increased to 10 mg once daily in patients requiring additional glycemic control.<sup>1</sup>

No dosage adjustment is required in patients with mild renal impairment (estimated GFR of at least 60 mL/min/1.73 m<sup>2</sup>). Dapagliflozin therapy should not be initiated in patients with estimated GFR less than 60 mL/min/1.73 m<sup>2</sup> and should be discontinued if the estimated GFR falls persistently below 60 mL/min/1.73 m<sup>2</sup>.<sup>1</sup>

Table 4 compares the recommended dosages for the SGLT2 inhibitors.

### PRODUCT AVAILABILITY

Dapagliflozin received US Food and Drug Administration approval January 8, 2014. It is available as 5 and 10 mg film-coated tablets packaged in bottles of 30, 90, and 500 and in unit-dose cartons of 100.<sup>1</sup> Dapagliflozin tablets should be stored at controlled room temperature.<sup>1</sup>

### DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for dapagliflozin.<sup>42</sup>

### POSTMARKETING REQUIREMENTS

Studies in pediatric patients (10 to 17 years of age); a randomized, double-blind, placebo-controlled trial evaluating the effect of dapagliflozin on major adverse cardiovascular events, as well as liver toxicity, bone fractures, nephrotoxicity, breast and bladder cancer, complicated genital infections, complicated UTIs, hypovolemia, and hypersensitivity reactions; enhanced pharmacovigilance studies for serious hepatic abnormalities and pregnancy outcomes; and

**Table 4.** Comparative dosages for the SGLT2 inhibitors<sup>1,2</sup>

Comparative dosages	Canagliflozin	Dapagliflozin
Starting dose (patients with estimated GFR of 60 mL/min/1.73 m <sup>2</sup> )	100 mg once daily	5 mg once daily
Maximum dose (patients with estimated GFR of 60 mL/min/1.73 m <sup>2</sup> )	300 mg once daily	10 mg once daily
Maximum dose (estimated GFR 45 to < 60 mL/min/1.73 m <sup>2</sup> )	100 mg once daily	Use not recommended

Note: GFR = glomerular filtration rate.

a study in a rodent bladder tumor model are required postmarketing.<sup>42</sup>

## CONCLUSION

Like canagliflozin, dapagliflozin offers an oral treatment option as an adjunct to diet and exercise for patients with type 2 diabetes. HbA<sub>1c</sub> reductions appear comparable with those observed with canagliflozin and with other oral agents. Dapagliflozin appears to be well tolerated, with only an increased incidence of genital infections reported relative to comparator agents. Weight loss, once-daily oral administration, and a low incidence of hypoglycemia and gastrointestinal adverse effects are potential advantages associated with this class, which also includes canagliflozin. No head-to-head studies have been conducted comparing dapagliflozin and canagliflozin. Comparative studies or additional long-term study data will be necessary to elucidate differences in the frequency of adverse reactions between these agents.

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