Drug Monograph

Drug/Drug Class:	**Farxiga™ (dapagliflozin) tablet/ sodium-glucose cotransporter 2 (SGLT2) inhibitor**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ New Criteria ☐ Revision of Existing Criteria

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Farxiga™ is available in 5 mg and 10 mg tablets which contain 5 mg and 10 mg of dapagliflozin respectively. Bristol-Myers Squibb Company Princeton, NJ 08543 USA
Summary of Findings:	Farxiga™ is an orally administered SGLT2 inhibitor approved for the treatment of type 2 diabetes mellitus in combination with diet and exercise. Farxiga demonstrated efficacy in the treatment of type 2 diabetes when used as monotherapy and in combination with other antidiabetic agents.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Fiscal Edit ☒ PDL Edit
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction[1,3]

Type 2 diabetes is a condition that affects millions of Americans. Controlling blood sugars in diabetic patients has proven to decrease complications as well as increasing overall quality of life.

Dosage Form(s) [1]

Farxiga™ is available in 5 mg and 10 mg tablets which contain 5 mg and 10 mg of dapagliflozin respectively.

Manufacturer [1]

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Indication(s) [1]

Farxiga™ is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Clinical Efficacy [1-3] (mechanism of action/pharmacology, comparative efficacy)

Farxiga™ inhibits sodium-glucose co-transporter 2 (SGLT2) in the proximal renal tubules, thereby reducing reabsorption of filtered glucose, lowering the renal threshold for glucose, and increasing urinary glucose excretion.

Pharmacokinetics

	FARXIGA
Protein Binding	91%
Volume of Distribution	---
Metabolism	Liver, via UGT1A9
Excretion	Urine, 75% (< 2% unchanged) Feces, 21% (15% unchanged)
Half-life	12.9 hours

Farxiga demonstrated efficacy in the treatment of type 2 diabetes when used as monotherapy and in combination with various other antidiabetic agents. As monotherapy, it reduced HbA1c by an average of 0.77% with a 5 mg daily dose and by 0.89% with a 10 mg daily dose after 24 weeks in a double-blind, placebo-controlled trial in treatment-naive patients. The combination of Farxiga and extended-release metformin as initial therapy was significantly superior to either agent alone in

reducing HbA1c levels over 24 weeks in a randomized, double-blind study. In the same trial, Farxiga 10 mg daily was shown to be noninferior to extended-release metformin as initial therapy.

TYPE 2 DIABETES MELLITUS - MONOTHERAPY

STUDY DESIGN	Randomized, double-blind, placebo-controlled, 24-week, phase 3 trial (n=485).
INCLUSION CRITERIA	Treatment-naive adult patients with type 2 diabetes inadequately controlled with diet and exercise, with an HbA1c level of 7% to 10%.
EXCLUSION CRITERIA	Type 1 diabetes, renal insufficiency, and severely uncontrolled diabetes.
TREATMENT REGIMEN	Patients were randomized to receive once daily treatment with either placebo (n=75), Farxiga 2.5 mg in the morning (n=65) or evening (n=67), 5 mg in the morning (n=64) or evening (n=68), or 10 mg in the morning (n=70) or evening (n=76).
RESULTS	After 24 weeks of treatment, mean HbA1c values changed by -0.77% and -0.89% from baseline in the patients receiving morning doses of Farxiga 5 mg and 10 mg, respectively, compared with -0.23% in the placebo arm ($p < 0.001$ and $p < 0.0001$, respectively). Only 32% of placebo patients achieved an HbA1c value of < 7% compared with 44% and 51% of patients receiving morning doses of Farxiga 5 mg and 10 mg, respectively. Farxiga treatment provided decreases in FPG as early as 1 week. By week 24, FPG decreased by 24.1 mg/dL and 28.8 mg/dL from baseline among patients receiving morning doses of Farxiga 5 mg and 10 mg, respectively, compared with 4.1 mg/dL in the placebo group ($p < 0.001$ and $p < 0.0001$, respectively). Similar changes in HbA1c and FPG were observed among patients receiving evening doses of Farxiga 5 mg and 10 mg. In addition, similar results were also observed in an exploratory cohort of patients with high HbA1c values (range, 10.1% to 12%; n=73).
SAFETY	Both Farxiga and placebo were associated with similar rates of hypotension, dehydration, and hypovolemia, and no major episodes of hypoglycemia occurred during the study. The incidence of urinary tract infections and genital infections was higher in the Farxiga groups compared with placebo.

TYPE 2 DIABETES MELLITUS - METFORMIN COMBINATION

STUDY DESIGN	Two randomized, double-blind, active-controlled, 24-week trials (n=598; n=638).
INCLUSION CRITERIA	Treatment-naive adult patients with type 2 diabetes inadequately controlled with diet and exercise, with an HbA1c level of 7.5% to 12%.
EXCLUSION CRITERIA	Renal insufficiency and severely uncontrolled diabetes.
TREATMENT REGIMEN	In each study, patients were randomized to 1 of 3 treatment groups: combination Farxiga plus metformin extended-release, Farxiga plus placebo, or metformin extended-release plus placebo. Farxiga was dosed as 5 mg daily in study 1 (n=598) and 10 mg daily in study 2 (n=638). Metformin was titrated in increments of 500 mg weekly as tolerated up to 2000 mg daily. Study medication was administered once daily with the evening meal.
RESULTS	After 24 weeks of treatment, mean HbA1c values changed by -2.1%, -1.2%, and -1.4% from baseline in the combination (n=194), Farxiga 5 mg (n=203), and metformin (n=201) groups, respectively, in study 1 ($p < 0.0001$ for combination arm compared with each of the monotherapy arms). After 24 weeks of treatment, mean HbA1c values changed by -2%, -1.5%, and -1.4% in the combination (n=211), Farxiga 10 mg (n=219), and metformin (n=208) groups, respectively, in study 2 ($p < 0.0001$ for combination arm compared with each of the monotherapy arms). In study 2, monotherapy with Farxiga was noninferior to monotherapy with metformin (difference of change in HbA1c at 24 weeks, -0.01; 95% CI, -0.22 to -0.2; p=0.9144). More patients in the combination arm (52.4%) achieved an HbA1c of < 7% compared with Farxiga alone (22.5%) and metformin alone (34.6%) in study 1, as well as in study 2 (46.6%, 31.7%, and 35.2%, respectively). Treatment with the combination of Farxiga and metformin also significantly reduced FPG from baseline compared with monotherapy with either agent in both studies. Body weight changed by -2.7 kg, -2.6 kg, and -1.3 kg in the combination, Farxiga, and metformin arms ($p < 0.0001$ for combination arm versus metformin arm) in study 1, and by -3.3 kg, -2.7 kg, and -1.4 kg, respectively, in study 2 ($p < 0.0001$ for combination arm versus metformin arm; $p < 0.0001$ for Farxiga arm versus metformin arm).
SAFETY	Major hypoglycemia was not reported in either trial. Signs and symptoms suggestive of urinary tract infections were observed more frequently in Farxiga patients in study 2, while signs and symptoms of genital infections occurred more frequently in Farxiga patients in both studies. In each

	study, diarrhea occurred more often in metformin groups.

Contraindications [1]

- Dialysis
- End-stage renal disease
- Hypersensitivity to Farxiga
- Renal impairment, severe (estimated GFR less than 30 mL/min/1.73 m(2))

Warnings and Precautions [1]

- Bladder cancer, active; use not recommended.
- Bladder cancer, history of; unknown risk of cancer recurrence; weigh benefits of glycemic control versus risk of recurrence prior to treatment.
- Bladder cancer, new onset; may occur.
- Genital mycotic infection may occur; increased risk in patients with prior history of genital mycotic infections; monitoring recommended.
- Hypoglycemia; increased risk when used concomitantly with insulin or an insulin secretagogue; dose adjustments may be required.
- LDL cholesterol increases may occur; monitoring recommended.
- Renal impairment, preexisting; use not recommended in patients with moderate impairment (estimated GFR 30 to < 60 mL/min/1.73 m(2)); use contraindicated in patients with severe impairment (estimated GFR less than 30 mL/min/1.73 m(2)).
- Renal impairment; increases in serum creatinine, decreases in estimated GFR, and adverse effects related to renal function may occur; increased risk in the elderly and patients with preexisting renal dysfunction; monitoring recommended.
- Symptomatic hypotension may occur; increased risk in patients with impaired renal function (estimated GFR < 60 mL/min/1.73 m(2)), elderly patients, or those on loop diuretics; assess and correct volume status prior to treatment; monitoring recommended.

Adverse Effects [1]

Most common, >= 2%	Farxiga 5 mg (n=1145)	Placebo (n=1393)
▪ Female genital mycotic infections	8.4%	1.5%
▪ Male genital mycotic infections	2.8%	0.3%
▪ Nasopharyngitis	6.6%	6.2%
▪ Urinary tract infections	5.7%	3.7%
▪ Increased urination	2.9%	1.7%
▪ Nausea	2.8%	2.4%
▪ Influenza	2.7%	2.3%
▪ Dyslipidemia	2.1%	1.5%
▪ Constipation	2.2%	1.5%
▪ Extremity pain	2.0%	1.4%

Drug Interactions [1]

- None

Dosage and Administration [1]

The recommended dose is 5 mg orally once daily in the morning, with or without food. Increase dose to 10 mg once daily if tolerated and necessary for additional efficacy.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/ MONTH
Dapagliflozin propanediol	Farxiga	Bristol-Myers Squibb	5 mg tablets	1 tablet daily	$ 289.20
			10 mg tablets	1 tablet daily	$ 289.20

*WholesaleAcquisitionCost

Conclusion

Farxiga™ is an orally administered SGLT2 inhibitor approved for the treatment of type 2 diabetes mellitus in combination with diet and exercise. Farxiga demonstrated efficacy in the treatment of type 2 diabetes when used as monotherapy and in combination with other antidiabetic agents. When used as initial therapy, it improves HbA1c by an average of 0.77% to 0.89% after 24 weeks. It has shown noninferiority to extended-release metformin as initial therapy, and to glipizide as add-on therapy to metformin. In a trial of patients with moderate renal impairment, Farxiga was not effective in reducing HbA1c levels compared with placebo. The most common adverse effects are genital yeast infections, nasopharyngitis, and urinary tract infections. Cases of bladder cancer were reported in patients receiving dapagliflozin in clinical trials.

Recommendation

This drug is being considered for the inclusion in the state specific Preferred Drug List (PDL).

References

1. Product Information: Farxiga™, dapagliflozin. Bristol-Myers Squibb Company, Princeton, NJ, 1/2014.
2. Ferrannini E, Ramos SJ, Salsali A et al: Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care 2010; 33(10):2217-2224.
3. Henry RR, Murray AV, Marmolejo MH et al: Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. Int J Clin Pract 2012; 66(5):446-456.

Prepared by: Katie Wilbers, PharmD

Date: May 13, 2014