Drug Monograph: Dapagliflozin
Prepared by: Amber L Schilling, Pharm D
Date: September 8, 20XX
Site: [Hospital X]

Generic Name: Dapagliflozin

Trade Name: Farxiga® (far-SEE-guh)

Strengths: 5 mg, 10mg (oral tablet)

Source of Supply: Bristol-Myers Squibb, Princeton NJ (Manufacturer)
AstraZeneca (Marketing)
No generic available at this time

FDA Approval Date: January 8, 2014

Pharmacologic Category: Anti-diabetic Agent
Sodium-Glucose Co-Transporter 2 Inhibitor (SGLT-2 Inhib.)

Mechanism of Action: Dapagliflozin increases the amount of glucose that gets excreted in the urine through inhibition of the SGLT2 in the proximal tubules of the kidney. Inhibition of the SGLT-2 transporter reduces the amount of filtered glucose that gets reabsorbed through the tubular lumen. The SGLT-2 is the main mechanism by which filtered glucose gets reabsorbed in the kidney. Through this mechanism, dapagliflozin reduces plasma glucose concentrations.

FDA Approved Indications: Improvement of glycemic control in Type 2 Diabetes Mellitus, as an adjunct to diet and exercise

Non-FDA Indications: None

Pharmacy Recommendation: Adding dapagliflozin to the [Hospital X] formulary is recommended at this time. No SGLT-2 Inhibitors currently exist on [Hospital X] formulary and this class of drugs has a unique mechanism of action that is not represented by the other non-insulin anti-diabetic drugs available on formulary. This drug is relatively well tolerated. Canagliflozin would be an alternative option for formulary addition, but has higher protein binding than dapagliflozin, which increases the likelihood for drug-drug interactions (e.g., warfarin). Canagliflozin also carries a risk of hyperkalemia (>10% frequency) whereas dapagliflozin does not. Empagliflozin (the third and final drug in this class) was FDA approved in August 2014 and is not yet commercially available. Although dapagliflozin use is associated with mycotic genital infections, this appears to be a class effect and simply requires monitoring. For patients coming in to the hospital on an SGLT-2 Inhibitor, it would be advantageous to allow them to continue taking a drug in this class for continuity of care. However, it should be noted that SGLT-2 inhibitors like dapagliflozin can cause hypovolemic dehydration, a condition that has the potential to exacerbate many conditions found in the acute care hospital setting.

Current Formulary Alternatives: No SGLT-2 Inhibitors currently exist on [Hospital X] formulary. See the table below for the non-insulin anti-diabetic agents that are available on [Hospital X] formulary. According to American Association of Clinical Endocrinologists 2013 guidelines for diabetes management, metformin is the first line agent for treatment of T2DM. If there is an intolerance or contraindication to metformin, AACE suggests those agents indicated as such in the table. Beyond that, agents can be added on to metformin (or an acceptable alternative) to achieve blood glucose control. Although the AACE has an algorithm for how adjunctive agents should be added on, they also recognize that treatment decisions should be highly individualized based upon the pros and cons of each agent. As stated in the guideline, the algorithm "cannot capture many decisions that a physician must make to treat individual patients" (p.14).[4] Thus, a list of all of the non-insulin therapies available at [Hospital X] are provided here.

Non-Insulin Anti-diabetic Agent Available on [Hospital X] Formulary	***Route***	***Suggested hierarchy of usage when dual or triple therapy is needed (AACE)[4]***	***Acceptable Therapeutic Alternative to Metformin when intolerance or contraindication to metformin (AACE)[4]***	***Therapeutic Class***
metformin (Glucophage)	PO	1-first line / backbone	---	Biguanide
liraglutide (Victoza)	SQ	2	Yes	GLP-1 Receptor Agonist
linagliptin (Tradjenta)	PO	3	Yes	DPP-4 Inhibitor
pioglitazone (Actos)	PO	4	Use with caution due to propensity for causing weight gain	Thiazolidinedione (TZD)
dapagliflozin (Farxiga), canagliflozin (Invokana) *not currently on [Hospital X] formulary*	PO	5	Yes	SGLT2 Inhibitor
acarbose (Precose)	PO	6	Yes	Alpha-Glucosidase Inhibitors
repaglinide (Prandin)	PO	7	Use with caution due to propensity for causing weight gain and hypoglycemia	Meglitinide Derivatives (glinides)
tolazamide (generic only)	PO	7	Use with caution due to propensity for causing weight gain and hypoglycemia	Sulfonylurea, 1st Generation
glimepiride (generic only)	PO	7	Use with caution due to propensity for causing weight gain and hypoglycemia	Sulfonylurea, 2nd Generation
glipizide (Glucotrol XL)	PO			
glyburide (Diabeta, Micronase)	PO			

Advantages of medication over current formulary options:

Would allow continuity of care for patients coming into the hospital already on an SGLT-2 Inhibitor; lower risk of GI side effects than some of the other agents; can provide additional hemoglobin A1c lowering when metformin or other agents have allowed the patient to reached goal; may help with weight loss; has been suggested in AACE guidelines as an acceptable alternative to metformin when there is a contraindication or intolerance to metformin; unique mechanism of action is non insulin-dependent;

Disadvantages of medication over current formulary options:

New agent (still relatively unknown what adverse events are most likely, especially cardiovascular effects); contraindicated in renal failure; rather high protein binding (could compete with other highly protein bound drugs such as warfarin); increase in genital fungal infections and urinary tract infections due to dapagliflozin-induced glucosuria; hypovolemic dehydration is a risk due to its mechanism of action (this could be a problem in diabetic patients, most of whom are already on blood pressure lowering therapies in concordance with established guideline recommendations); relatively high risk of hypoglycemia when combined with other anti-diabetic agents (40%); correlation with bladder cancer remains unknown

Dosage Forms: Oral Tablet (5mg, 10mg)

Storage / Stability: Store at 20-25^{0}C (68-77^{0}F)

Dosage Regimen:

- Initial: 5 mg one daily in the morning (can be taken without regard to meals)
- Maximum: 10 mg once daily

Use in Special Populations:

Agent	*Geriatric*	*Pediatric*	*Renal Impairment (eGFR in units of mL/min/1.73m²)*	*Hepatic Impairment*
Dapagliflozin	utilize normal adult dosing	has not been studied in patients under 18 years of age	eGFR <60: Not recommended eGFR <30: Contraindicated Hemodialysis: Contraindicated	Mild-Moderate (Child-Pugh Class A/B): No adjustment necessary Severe (Child-Pugh Class C): Has not been studied
Canagliflozin			eGFR 45 to <60: Max dose 100mg daily eGFR 30-45: Not recommended eGFR <30: Contraindicated Hemodialysis: Contraindicated	

Pregnancy Category: C (Adverse events observed in animal studies)

Use During Breast-Feeding: Unknown if dapagliflozin is excreted in breast milk. Due to potential risk of causing harm to nursing infant, it is recommended to either discontinue the drug or discontinue breast-feeding.

Pharmacodynamic / Kinetic Comparisons:

Agent	*Protein Binding*	*Metabolism*	*Bioavailability*	*Half-life Elimination*	*Excretion*
dapagliflozin (Farxiga)	91%	Glucuronidation to inactive metabolite (major pathway) CYP-mediated metabolism (minor pathway	78% (PO)	13 hrs	Urine (75%) Feces (21%)
canagliflozin (Invokana)	99%	Glucuronidation to inactive metabolites (major pathway) CYP-mediated metabolism (minor pathway)	65%	10.6-13 hrs	Urine (33%) Feces (42% unchanged)
metformin (Glucophage)	Negligible	Not hepatically metabolized	Fasting: 50-60% (PO)	4-9 hrs	Urine (90% unchanged; active secretion)
liraglutide (Victoza)	>98%	Metabolized to DPP-IV enzyme	55% (SQ)	13 hrs	Urine (6%) Feces (5%)
linagliptin (Tradjenta)	70-80%	Not extensively metabolized	30%	12 hrs (terminal saturable binding >100hrs)	Urine (5% unchanged) Feces (80% unchanged)
pioglitazone (Actos)	>99% Active metabolites (>98%)	CYP2C8, 3A4 (99%) Active and inactive metabolites	---	3-7 hrs (parent) 16-24 hrs (total)	Urine (15-30%) Feces As metabolites

Major Adverse Reactions:

- Hypoglycemia (40% when combined with insulin or other oral anti-diabetic therapy)
- Mycotic genital infections (Females, 8%; Males, 3%)
- Nasopharyngitis (7%)
- UTI (5%)
- Polyuria (4%)
- Dyslipidemia (3%)
- Nausea (3%)
- Back pain (3%)
- Hypovolemia (dehydration, intravascular volume depletion) (1%)
- Bladder neoplasms (<1%)
- Bone fracture in patients with moderate renal impairment (frequency not defined)
- Decreased renal function (frequency not defined)

Contraindications:

- Severe renal impairment, ESRD, patients on dialysis
- Patients in Diabetic Ketoacidosis (DKA)
- Active bladder cancer

Warnings / Precautions:

- Those with a history of genital mycotic infections or uncircumcised males are at greater risk of developing such an infection while taking dapagliflozin.
- Hypersensitivity reactions (angioedema, urticaria) can occur in some patients; discontinue treatment if this occurs.
- Correct intravascular volume depletion prior to initiation and monitor for hypotension / dehydration while taking dapagliflozin. Elderly age, concomitant use of anti-hypertensive medications, and those with low systolic blood pressure are at increased risk.
- May cause elevations in LDL cholesterol; monitor and treat as needed.
- Elderly and patients with pre-existing renal impairment may be at increased risk of renal abnormalities while taking dapagliflozin. Monitor renal function at baseline and periodically throughout treatment; discontinue if eGFR<60 mL/min/1.73m^2.
- Although causal relationship has not been definitively established, newly diagnosed bladder cancer occurred more frequently in dapagliflozin patients. Do not use this agent in patients with active bladder CA and use caution in patients with h/o bladder CA (weigh risks / benefits).
- Dapagliflozin has not been studied in patients with Type I Diabetes Mellitus; do not use this agent.
- On ISMP's high alert mediation list (as are all oral anti-diabetic medications that have the potential lower blood sugar)

Monitoring Parameters:

- Blood glucose
- Hemoglobin A1c
- Renal function (at baseline, and then periodically during therapy)
- LDL
- Genital mycotic infections
- Blood pressure
- Hydration status

Drug Interactions:

- Substrate of P-glycoprotein, UGT-1A9
- Dapagliflozin may increase effect / levels of:
    - Duloxetine
    - Other Hypoglycemia Agents
    - Hypotensive Agents
- Dapagliflozin's effect / levels can be increased by:
    - Androgens
    - Barbiturates
    - Herbs w/ hypoglycemic properties
    - MAOI's
    - Pegvisomant
    - Salicylates

- SSRI's
- Dapagliflozin's effect / levels can be decreased by:
  - Corticosteroids (inhaled or systemic)
  - Danazol
  - Loop Diuretics
  - LHRH Analogs
  - Somatropin
  - Thiazide Diuretics

Therapeutic Comparisons:

Agent	*Expected % Decrease in A1c lowering with Monotherapy*[5]	*Advantages*[4]	*Disadvantages*[4]	*Main Adverse Effects*[5]
Biguanide				
metformin (Glucophage)	1-2	Low risk of hypoglycemia Potential for modest weight loss Robust A1c lowering Good cardiovascular safety record	GI SE (dose-related) can preclude use in 10-15% of pts) Renally eliminated → CI in renally impaired due to increased risk of Lactic Acidosis Vitamin B12 deficiency	Lactic Acidosis (Boxed Warning) GI distress (n/d) Weakness
Glucagon-like Peptide-1 Receptor Agonists (GLP-1)				
liraglutide (Victoza)	1	Robust A1c lowering Potential for 1-4kg weight loss Low hypoglycemia risk Reduce both fasting and post-prandial glucose values No adverse CVD outcomes reported as of yet Administered once daily	Injectable (requires more instruction) Hypoglycemia risk increases when combined with SU C-cell hyperplasia and pancreatitis found in rodents, but confirmatory studies still lacking Should not be used in combination with DPP-4 inhibitors	GI (n/v/d)
Sodium-Glucose Co-Transporter 2 Inhibitors (SGLT-2 Inhib)				
dapagliflozin (Farxiga)	0.8-0.9	May help with weight loss	Increased genital and urinary tract infections Increased LDL-C (unexplained) Little experience (newer agents) CVD safety studies planned, but risk currently unknown Hyperkalemia (canagliflozin)	Genital mycotic infections UTI Increased urination
canagliflozin (Invokana)	0.77-1.03			
Dipeptidyl Peptidase IV Inhibitor (DPP-4 Inhib)				
linagliptin (Tradjenta)	0.4	Low hypoglycemic risk May be cardioprotective	(Weight-neutral) Hypoglycemia risk increases when combined with SU Concerns over pancreatitis and pancreatic cancer risk remain unresolved Should not be used in combination with GLP-1 RA	Headache Nasopharyngitis Arthralgia Back pain Hypoglycemia
Alpha-Glucosidase Inhibitors				
acarbose (Precose)	0.5-0.8	Low (if any) hypoglycemia risk Cardiovascular benefit shown in clinical trials	GI SE limit use Must be dosed before each meal	GI distress Bloating Flatulence Elevated liver enzymes (rare)

Agent	*Expected % Decrease in A1c lowering with Monotherapy[5]*	*Advantages[4]*	*Disadvantages[4]*	*Main Adverse Effects[5]*
				Intestinal infections (rare)
Meglitinide Derivatives (-glinides)				
repaglinide (Prandin)	0.5-1.5	Shorter half-life than most SU's so hypoglycemia won't last as long if it occurs Main effect during postprandial period	Highest risk of hypoglycemia of any non-insulin therapy Dosed with meals Should not be used in combination with SU's	Upper Respiratory Tract Infx Flu-like syndrome Headache Hypoglycemia
Sulfonylurea, 1st Generation				
tolazamide (generic only)	1-2	Potent anti-hyperglycemic effects	Highest risk of hypoglycemia of any non-insulin therapy Modest weight gain Efficacy may plateau at doses lower than the maximal approved dose Concerns about CVD safety Should not be used in combination with meglitinides	Hypoglycemia Dizziness Headache GI distress SIADH
Sulfonylurea, 2nd Generation				
glimepiride (generic only) glipizide (Glucotrol XL) glyburide (Diabeta, Micronase)	1-2 1-2 1-2	Potent anti-hyperglycemic effects	Highest risk of hypoglycemia of any non-insulin therapy Modest weight gain Efficacy may plateau at doses lower than the maximal approved dose Concerns about CVD safety Should not be used in combination with meglitinides	Hypoglycemia Dizziness Headache GI distress SIADH
Thiazolidinedione (TZD)				
pioglitazone (Actos)	0.5-1.4	Low risk of hypoglycemia Possible CVD benefit	Weight gain Fluid retention Adverse metabolic effects on bone (increased risk of fx) Association with bladder CA is unresolved	Cause or exacerbate Heart Failure (Boxed Warning) Hepatic dysfunction Weight gain Edema, Lipid changes

Cost Comparisons:

Agent	*How supplied: Quantity (dose)*	*Price ($)*	*Price ($) / unit*	*Recommended dosing regimen*	*Cost($)/day based on Recommended dosing regimen*
dapagliflozin (Farxiga)	30 (5mg tablet) 30 (10mg tablet)	347.04 347.04	11.57/tablet	5-10mg/day	11.57
canagliflozin (Invokana)	30 (100mg tablet) 30 (300mg tablet)	346.97 346.97	11.57/tablet	100-300mg/day	11.57
metformin (Glucophage)	Generic: 100 (500mg tablet) 100 (850mg tablet) 100 (1000mg tablet) Generic XR:	 70.43 119.70 144.95	 0.70/tablet 1.20/tablet 1.45/tablet	1500-2000mg/day	2.10 (1500mg) 2.80 (2000mg)

Agent	*How supplied: Quantity (dose)*	*Price ($)*	*Price ($) / unit*	*Recommended dosing regimen*	*Cost($)/day based on Recommended dosing regimen*
	100 (500mg tablet) 100 (750mg tablet)	74.50 119.70	0.75/tablet 1.20/tablet		
liraglutide (Victoza)	Pen-injector 18mg/3mL (SQ soln)	214.27	11.90/mg	1.2mg/day	14.28
linagliptin (Tradjenta)	90 (5mg tablet)	1021.78	11.35/tablet	5 mg/day	11.35
pioglitazone (Actos)	Generic: 30 (15mg tablet) 30 (30mg tablet) 30 (45mg tablet)	 210.17 321.19 348.39	 7.00/tablet 10.71/tablet 11.61/tablet	15-45 mg/day	7.00-11.61

Review of Literature:[6,7]

Authors	*Study*	*Population*	*Study Duration*	*Doses*	*Mean Change in HbA1c from Baseline*	*Notes*
Ferrannini E et al (2010)	Dapa vs Placebo Randomized Double-blind Parallel-group Multicenter	485 • T2DM • HbA1c 7-10% (baseline) • 18-77yo	24 weeks	2.5mg 5mg 10mg (All once daily)	2.5mg:-0.58% 5mg: -0.77 (p=0.0005) 10mg: -0.89 (p<0.0001)	UTI and genital infection higher incidence in dapagliflozin group Although not statistically significant compared to placebo, weight loss was observed in all dapa groups (2.8-3.3 kg weight loss) Dapa studied as monotherapy (no active comparator) Metformin given open-label to patients whose FBG remained elevated at week 4, 8, or 12. (# of patients who received open-label metformin as rescue not specified)
Bailey CJ et al (2010)	Dapa or Placebo + Prestudy Metformin Randomized Double-blind Parallel-group Placebo-controlled Multicenter	534 • T2DM • HbA1c 7-10% (baseline) • 18-77 yo • Already receiving Metformin ≥1500mg QD	24 weeks	2.5mg 5mg 10mg (All once daily)	2.5mg: -0.67% (p=0.0002) 5mg: -0.7% (p<0.0001) 10mg: -0.48% (p<0.0001)	Genital infx more common in dapa groups Weight loss statistically more with all dapa groups (p<0.0001) (2.2-2.9kg weight loss) ITT population Last observation carried forward (all who received at least one dose of study

Authors	*Study*	*Population*	*Study Duration*	*Doses*	*Mean Change in HbA1c from Baseline*	*Notes*
						medication analyzed)
Henry RR et al (2012)	Dapa vs Metformin vs Dapa+Metformin Randomized Double-blind Multicenter	598 (Part 1) 638 (Part 2) Both Parts: • T2DM • HbA1c 7.5-12% (baseline) • 18-77yo	24 weeks	Part 1 • Dapa 5mg • Met ER (titrated to 2000 mg QD) • Dapa 5 + Met ER Part 2 • Dapa 10mg • Met ER • Dapa 10mg + Met ER	Dapa 5: -1.19% Met ER: -1.35% **Combo: -2.05% (p<0.0001)** Dapa 10: -1.45% Met ER: -1.44% **Combo: -1.98% (p<0.0001)** Dapa 10mg shown to be noninferior to metformin monotherapy	Genital infection reported in 6.7 - 12.8% of patients using dapa (alone or in combo UTI reported in 7.9-11% of patients using dapa (alone or in combo) Weight loss significantly more with dapa 10 monotherapy and combination therapy compared to metformin monotherapy (p<0.0001) No cases of hypoglycemia reported
Jabbour SA et al (2013)	Dapa or Placebo + Sitagliptin + (Metformin if pt was already on at study entry) Randomized Double-blind Placebo-controlled Parallel-group Multicenter	All patients received sitagliptin 100mg daily for 10 weeks 432 patients with A1cs of 7-10% at 10 weeks were then randomized to receive add-on of dapagliflozin or placebo	24 weeks after addition of dapa	Dapa 10mg Sitagliptin 100mg Metformin ≥1500mg	Dapa group: -0.5% (p<0.0001)	Genital infection more frequent in dapagliflozin group (9.8% vs 0.4% w/ placebo) Weight loss significantly more in dapa group (p<0.0001) (2.1 kg loss)

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