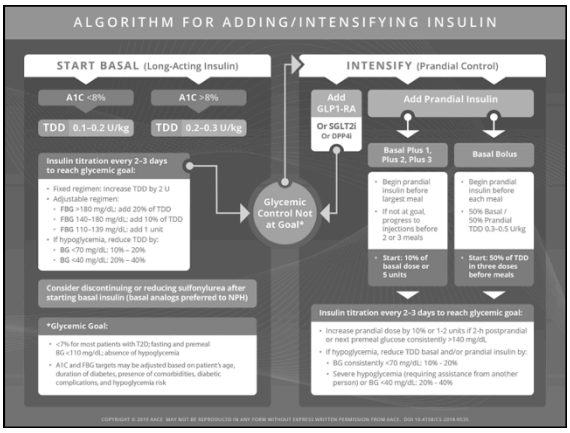
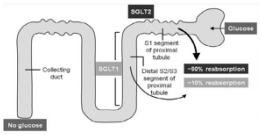
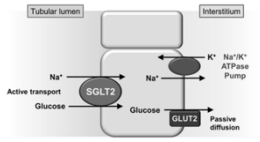


Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors

Inhibit SGLT in proximal renal tubules, reducing reabsorption of filtered glucose from tubular lumen

Lowers renal threshold for glucose → increase urinary excretion of glucose → decreased plasma glucose

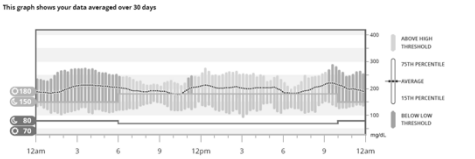




	Dapagliflozin (Farxiga®)	Canagliflozin (Invokana®)	Empagliflozin (Jardiance®)	Ertugliflozin (Steglatro®)
Dose	5 mg daily May increase to 10 mg daily	100 mg daily May increase to 300 mg daily	5 mg daily May increase to 25 mg daily	5 mg daily May increase to 15 mg daily
Administration	Take in the morning +/- food	Take before first meal of the day	Take in the morning +/- food	Take in the morning +/- food
Renal Impairment (eGFR in mL/min/ 1.73m^2)	< 45: Not recommended < 30 or dialysis: Contraindicated	45 to < 60: MDD 100 mg/day 30 to 45: Not recommended < 30 or dialysis: Contraindicated	< 45: Do not initiate; discontinue therapy Dialysis: Contraindicated	< 60: Do not initiate; discontinue therapy < 30 or dialysis: Contraindicated

Patient Case 1

MH is a 28 year-old female with history of type 1 diabetes mellitus on multiple daily injections who presents to clinic today. She notes poorly controlled blood sugars, increasing insulin requirements and weight gain. She is hoping to start a SGLT-2 inhibitor.



What do you recommend?

What concerns, if any, do you have?

Patient Case 1

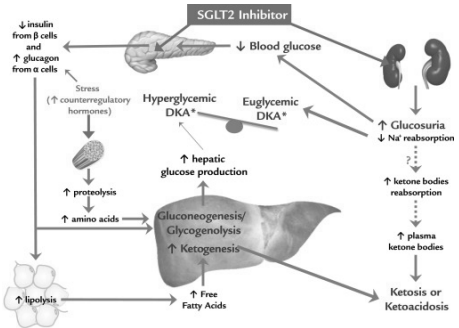
A. SGLT-2 inhibitors are not recommend or FDA approved for use in patients with type 1 diabetes

B. Any of the SGLT-2 inhibitors can be started and doses should be up-titrated based on effect

C. Any of the SGLT-2 inhibitors can be started, but would not recommend up-titrating dose

D. An SGLT-2 inhibitor should not be started until insulin doses are optimized

SGLT2 Inhibitor–associated Euglycemic Diabetic Ketoacidosis



Risk Factors for Euglycemic Ketoacidosis

- Surgery
- Inter-current illness
- Alcohol consumption
- Low carbohydrate diet
- Withdrawal of insulin or reduction of insulin dose

Minimizing Risk of Euglycemic Diabetic Ketoacidosis with SGLT2 Inhibitor Therapy

Optimize insulin prior to starting therapy

Check ketones before and after starting treatment

Hold when patient is at high risk

Do not start in high risk patients

Minimizing Risk of Euglycemic Diabetic Ketoacidosis with SGLT2 Inhibitor Therapy

Optimize insulin prior to starting therapy

- Cautious insulin reductions after starting to avoid ketosis / DKA
- Consider stopping if adequate insulin dosing cannot be achieved

Check ketones before and after starting treatment

Hold when patient is at high risk

Do not start in high risk patients

Minimizing Risk of Euglycemic Diabetic Ketoacidosis with SGLT2 Inhibitor Therapy

Optimize insulin prior to starting therapy

Check ketones before and after starting treatment

- For insulin pump patients check ketones 3-4 hours after infusion set or component changes
- Stop and seek medical attention
  - Mildly elevated ketones with clinical symptoms of ketosis / DKA
  - Moderately elevated ketones regardless of symptoms
- Consider restarting
  - Complete event resolution
  - Correction of precipitating factors

Hold when patient is at high risk

Do not start in high risk patients

Minimizing Risk of Euglycemic Diabetic Ketoacidosis with SGLT2 Inhibitor Therapy

Optimize insulin prior to starting therapy

Check ketones before and after starting treatment

Hold when patient is at high risk

- Infection or intercurrent illness
- Peri-operative period

Do not start in high risk patients

Minimizing Risk of Euglycemic Diabetic Ketoacidosis with SGLT2 Inhibitor Therapy

Optimize insulin prior to starting therapy

Check ketones before and after starting treatment

Hold when patient is at high risk

Do not start in high risk patients

- Recent or recurrent DKA
- Ketosis at baseline
- Risk for ketosis (e.g. excessive alcohol use, ketogenic diets)

Clinical Considerations

Advantages

- CV benefit
- Low risk of hypoglycemia
- Weight Loss
- Renal benefit

Disadvantages

- Expensive
- Increased urination
- Hypotension/dehydration
- Urinary tract infections, genital mycotic infections
- Fournier's gangrene
- Increased risk of amputations (canagliflozin)
- Euglycemic ketoacidosis
- Electrolyte abnormalities
- Increased risk of bladder cancer? (dapagliflozin)

Emerging Therapies: Sotigliflozin (Zynquista™)

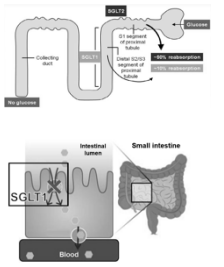
Proposed indication:

As an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus who have failed to achieve desired glycemic control despite optimal insulin therapy

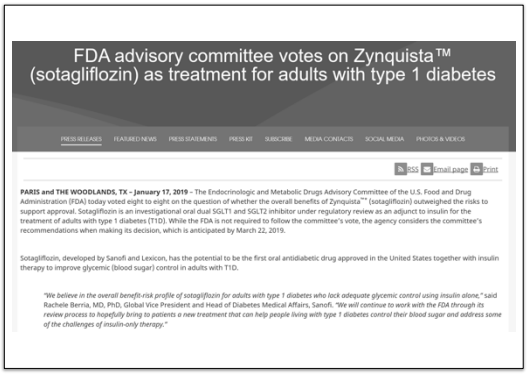
Recommended dose:

200 mg orally, once daily before first meal

Dose may be increased to 400 mg in patients who tolerate 200 mg and need additional glycemic control



SGLT1 inhibition blunts and delays glucose absorption and reduces postprandial glucose (PPG) excursions[1]



FDA advisory committee votes on Zynquista™ (sotagliflozin) as treatment for adults with type 1 diabetes

PRESS RELEASES FEATURED NEWS PRESS STATEMENTS PRESS KIT SUBSCRIBE MEDIA CONTACTS SOCIAL MEDIA PHOTOS & VIDEOS

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PARIS and THE WOODLANDS, TX – January 17, 2019 – The Endocrinologic and Metabolic Drugs Advisory Committee of the U.S. Food and Drug Administration (FDA) today voted eight to eight on the question of whether the overall benefits of Zynquista™ (sotagliflozin) outweighed the risks to support approval. Sotagliflozin is an investigational oral dual SGLT1 and SGLT2 inhibitor under regulatory review as an adjunct to insulin for the treatment of adults with type 1 diabetes (T1D). While the FDA is not required to follow the committee's vote, the agency considers the committee's recommendations when making its decision, which is anticipated by March 22, 2019.

Sotagliflozin, developed by Sanofi and Lexicon, has the potential to be the first oral antidiabetic drug approved in the United States together with insulin therapy to improve glycemic (blood sugar) control in adults with T1D.

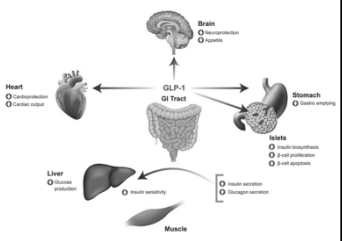
"We believe in the overall benefit-risk profile of sotagliflozin for adults with type 1 diabetes who lack adequate glycemic control using insulin alone," said Rachele Berria, MD, PhD, Global Vice President and Head of Diabetes Medical Affairs, Sanofi. *"We will continue to work with the FDA through its review process to hopefully bring to patients a new treatment that can help people living with type 1 diabetes control their blood sugar and address some of the challenges of insulin-only therapy."*

Glucagon-like peptide-1 (GLP-1) Receptor Agonists

Enhance glucose-dependent insulin secretion

Suppress inappropriately elevated glucagon levels, both in fasting and postprandial states

Slow gastric emptying and reduce postprandial glycemic excursions



Short-Acting GLP-1 Receptor Agonists

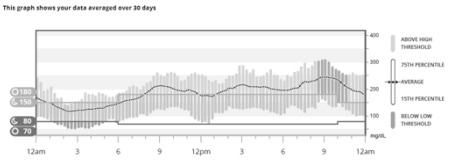
	Liraglutide (Victoza®)	Exenatide (Byetta®)	Lixisenatide (Adlyxin™)
Dose	0.6 mg daily for 7 days, then increase to 1.2 mg daily May increase to 1.8 mg daily after 7 days	5 mcg BID May increase to 10 mcg BID after 1 month	10 mcg daily for 14 days, then increase to 20 mcg daily
Administration	Anytime of day, independent of meals	Within 60 minutes prior to morning and evening meals Or before the two main meals of the day, approximately 6 hours or more apart	Within 60 minutes before the first meal of the day
Renal Impairment (eGFR in mL/min/1.73m²)	No dose adjustment recommended	ESRD receiving dialysis: Use not recommended	< 15: Use not recommended

Long-Acting GLP-1 Receptor Agonists

	Semaglutide (Ozempic®)	Exenatide Extended- Release (Bydureon®)	Dulaglitude (Trulicity®)
Dose	0.25 mg once weekly for 4 weeks, then increase to 0.5 mg one weekly May increase to 1 mg once weekly after 4 weeks	2 mg once weekly	0.75 mg once weekly May increase to 1.5 mg once weekly
Renal Impairment (eGFR in mL/min/1.73m²)	No dose adjustment recommended	< 45: Not recommended	No dose adjustment recommended

Patient Case 2

RB is a 53 year-old male with history of type 1 diabetes mellitus on insulin pump with CGM who was seen by his endocrinologist earlier today and started on dulaglutide 0.75 mg once weekly. He comes to see you for medication education. During the visit, RB asks if adjustments should be made to his pump settings with the addition of a new medication. What do you recommend?



Patient Case 2

A. Basal insulin should be reduced by 10-30%

B. Both basal and prandial insulin doses should be reduced by 10-30%

C. Prandial insulin doses should be reduced by 10-30%

D. No dose adjustments should be made at this time

Clinical Considerations

Advantages

- CV benefit
- Low risk of hypoglycemia
- Weight Loss
- Renal benefit

Disadvantages

- Expensive
- Injectable
- GI side effects (nausea, vomiting, diarrhea, constipation)
- Pancreatitis
- BBW: contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2

Emerging Therapies: Oral Semaglutide

Novo Nordisk files oral semaglutide for US regulatory approval of glycaemic control, as well as for CV risk reduction for oral semaglutide and Ozempic®

Bagsværd, Denmark, 20 March 2019 - Novo Nordisk today announced the submission of two New Drug Applications (NDAs) to the US Food and Drug Administration (FDA) for oral semaglutide, a once-daily glucagon-like peptide-1 (GLP-1) analogue in a tablet, as well as a supplemental NDA (sNDA) for once-weekly Ozempic® (semaglutide).

An NDA was submitted for oral semaglutide seeking approval for an indication for the treatment of adults with type 2 diabetes. A priority review voucher (PRV) has been applied to the NDA, leading to an anticipated review time of six months from the submission date, according to standard FDA review timelines.

The submission for oral semaglutide for the treatment of glycaemic control in adults with type 2 diabetes is based on the results from 10 PIONEER clinical trials, which included 9,543 adults with type 2 diabetes. In the PIONEER programme, people treated with oral semaglutide achieved greater blood glucose reductions compared to sitagliptin, empagliflozin, liraglutide and placebo. In addition, oral semaglutide demonstrated greater reductions in mean body weight vs most comparators. Across the PIONEER trials, oral semaglutide had a safe and well-tolerated profile, with the most common adverse event being nausea.

Emerging Therapies: ITCA 650 (Exenatide Implant)

Subdermal osmotic mini-pump that continuously delivers exenatide subcutaneously for 3–6 months

Emerging Therapies: Novel Classes

- Oxyntomodulins: Glucagon-like-peptide 1 (GLP-1) and glucagon dual agonist
- Glucose-dependent Insulinotropic Polypeptide (GIP) and GLP-1 receptor dual agonist