Advances in Antidiabetic Pharmacotherapy: Focus on SGLT2-Inhibitors

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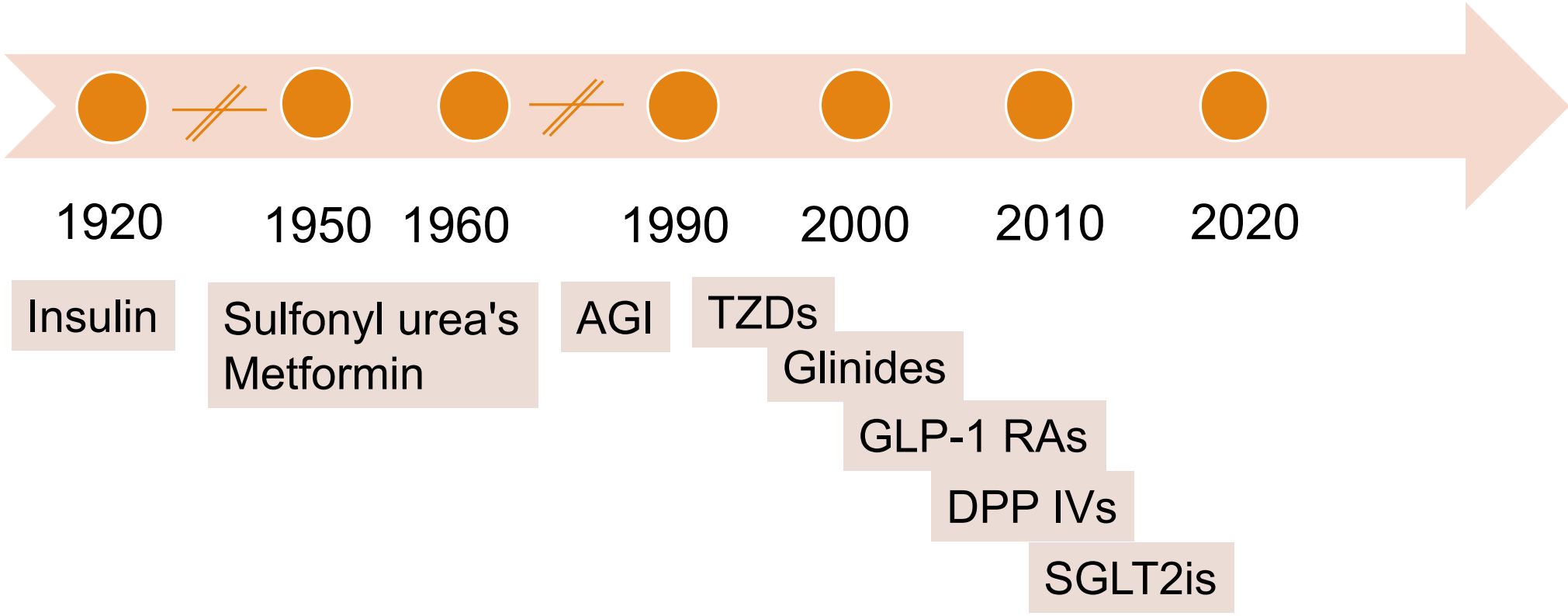
Learning Objectives

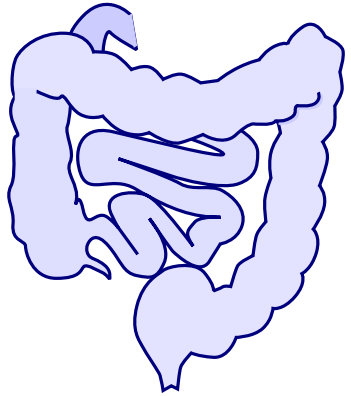
- Describe the structural aspects of SGLT inhibitors.
- Explain the mechanism of action of SGLT2 and dual SGLT1/2 inhibitors.
- Describe the adverse effects and warnings associated with SGLT inhibitors.

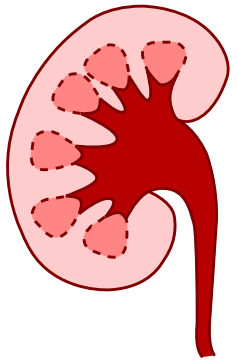
Timeline Antidiabetic Drugs



Scheen AJ. Clinical pharmacology of antidiabetic drugs: what can be expected of their use? Presse Med. 2022;52(1):104158.

What are Sodium-glucose cotransporters (SGLTs)?

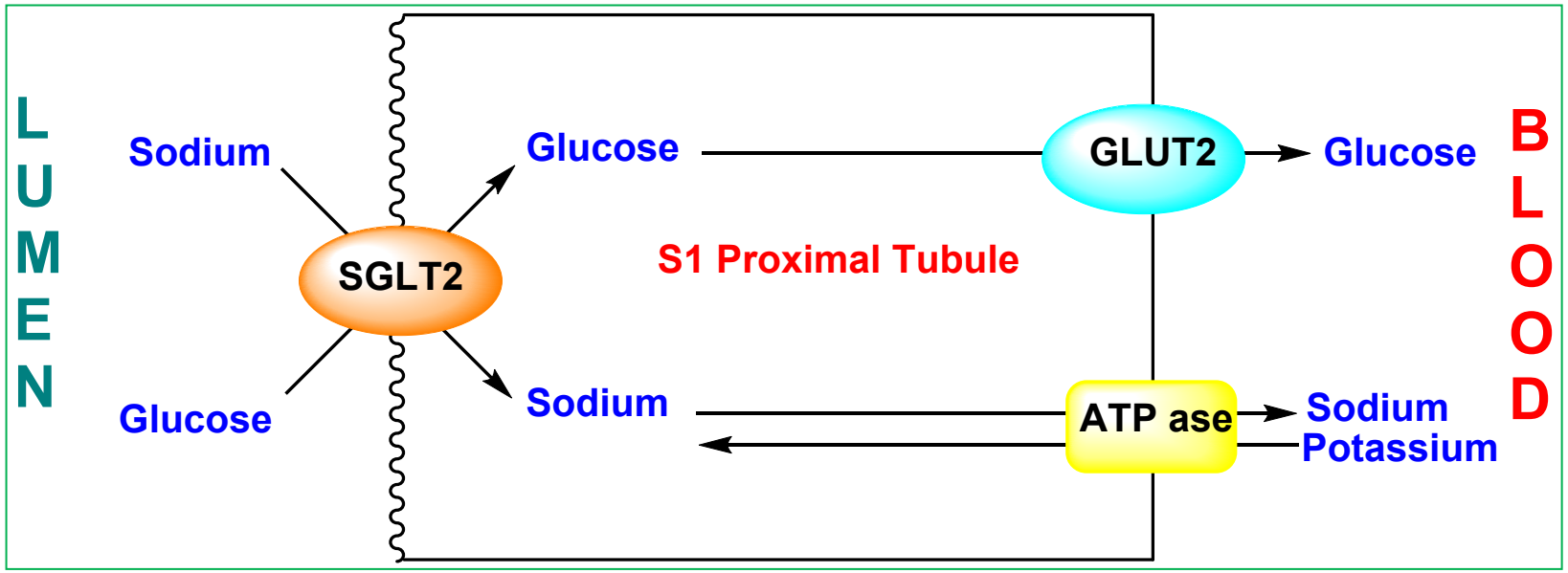




SGLT1	SGLT2
• Mostly small intestine • Some in the late proximal straight tubule (S3 segment) of kidney	• Almost in Kidneys • Early proximal convoluted tubule (S1 segment)
~10% of renal glucose reabsorption	~90% of renal glucose reabsorption

Chao, E., Henry, R. SGLT2 inhibition — a novel strategy for diabetes treatment. Nat Rev Drug Discov 9, 551–559 (2010).

What is the function of SGLT2?



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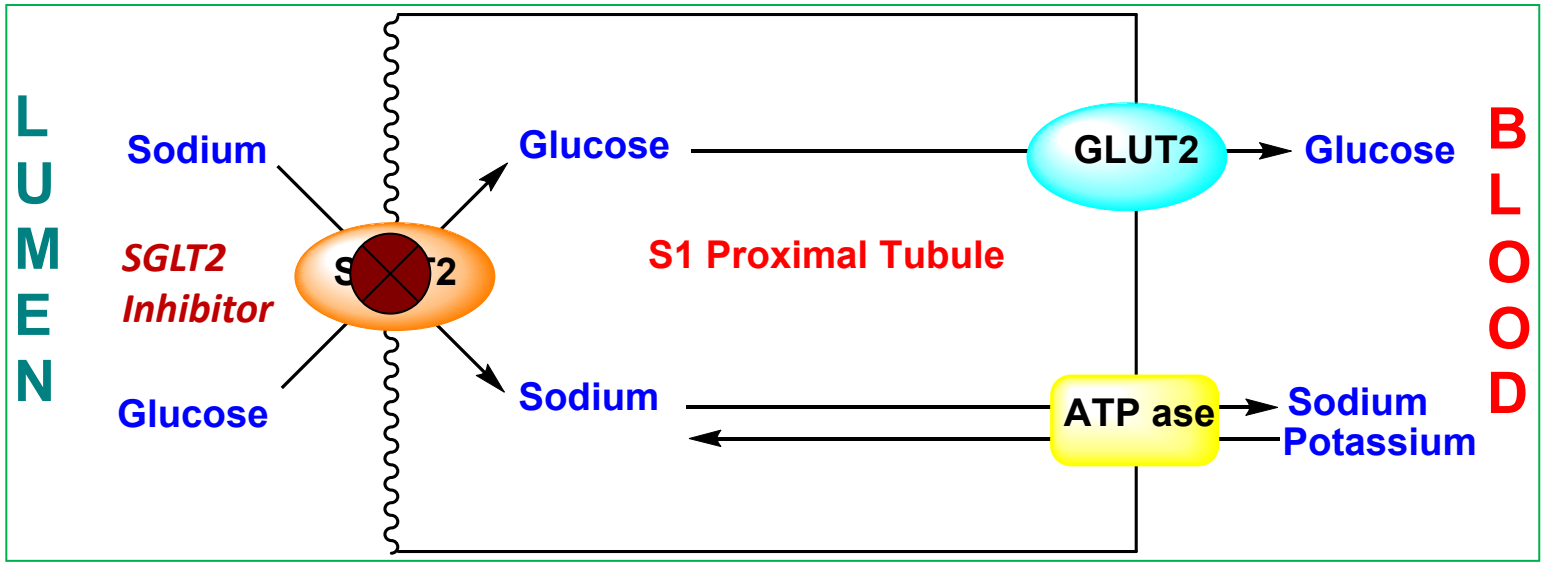
How do SGLT2-Inhibitors work? MOA

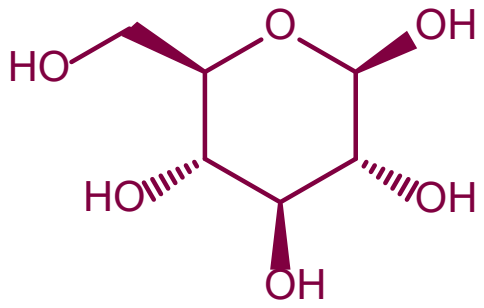
- Mechanism of Action
  - Reduces reabsorption of glucose from the tubular lumen



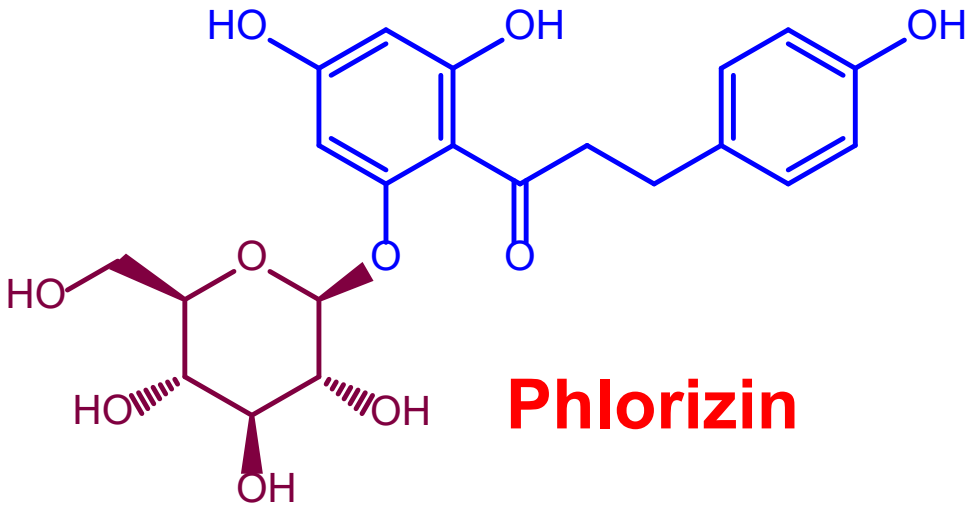
Sodium–glucose cotransporter 2 (SGLT2) inhibitors

- Referred as gliflozins
- FDA-approved drugs: Few including canagliflozin, dapagliflozin, and empagliflozin
  - Please refer to the specific drug labels at the Drugs@FDA: FDA-Approved Drugs https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- Outside the US: Many other drugs

Discovery of SGLT Inhibitors



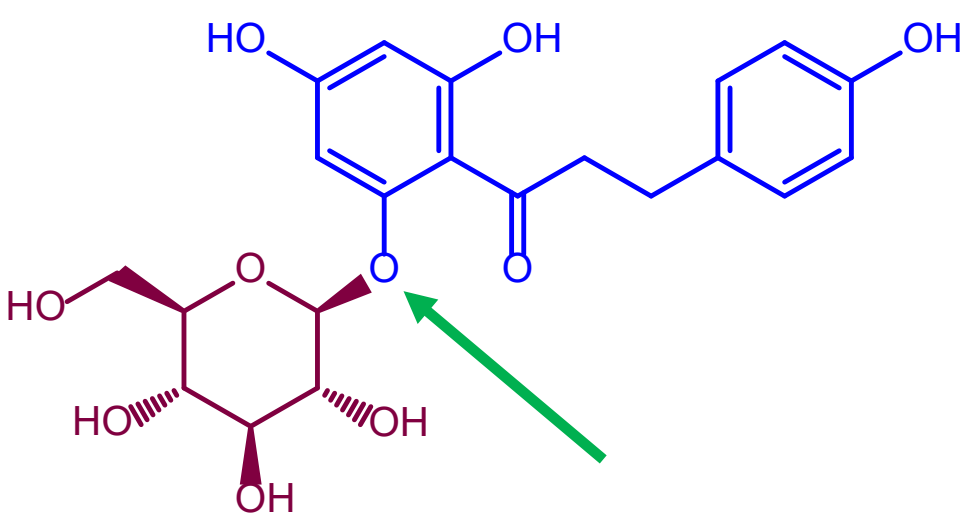
Beta-D-glucose



Phlorizin

- Chemical structure
  - consists of a glucose sugar
  - substituted group attached to the β-position of the anomeric carbon

Discovery of SGLT Inhibitors



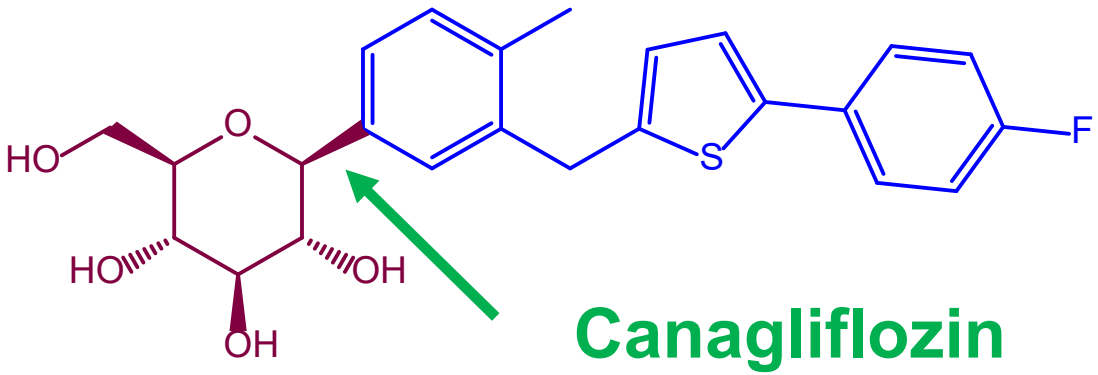
Phlorizin

- O-glucose derivative/O-glycoside
- Isolated in 1835 from apple tree bark
- Dual SGLT inhibitor

  Inhibits both SGLT1 (IC_{50} 330nm) and SGLT2 (IC_{50} 36nm)
- Produce renal glycosuria and block intestinal glucose absorption
- Poor bioavailability

  Unstable due to hydrolysis of the O glycosidic bond

Discovery of SGLT Inhibitors



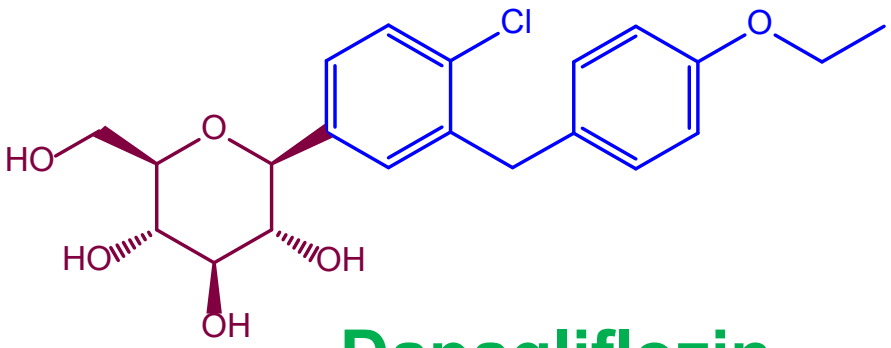
Canagliflozin

- U.S. Approval: 2013 for T2DM
- The first clinical C-glycosyl compound. Followed by several….

https://pubchem.ncbi.nlm.nih.gov/compound/Canagliflozin

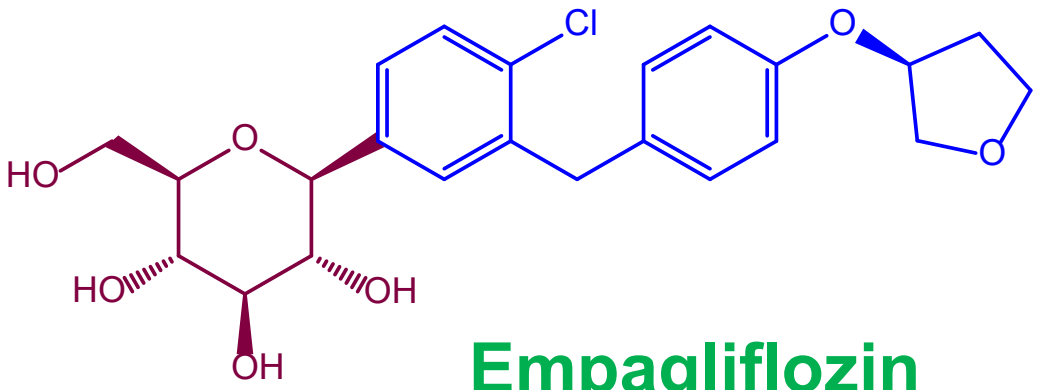
https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/204042s041s042lbl.pdf

SGLT2 Inhibitors



Dapagliflozin

- U.S. Approval: 2014 for T2DM
- US approval June 2024 for T2DM pediatric patients aged 10 years and older



Empagliflozin

- U.S. Approval: 2014 for T2DM

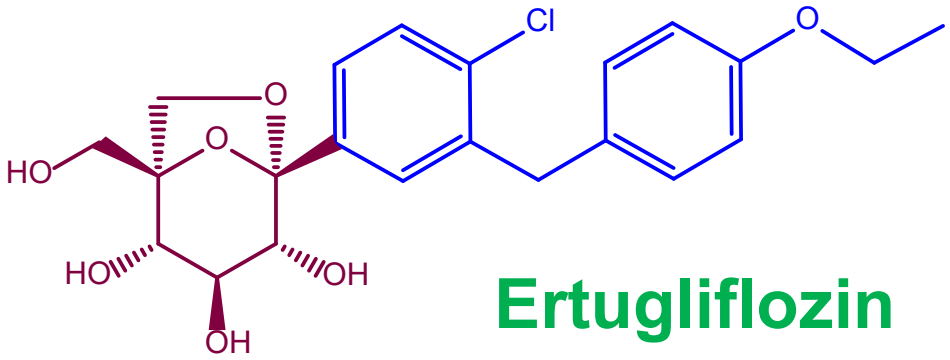
https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/202293s031lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/204629s040lbl.pdf

Pharmacokinetics

	Canagliflozin	Dapagliflozin	Empagliflozin
Bioavailability	~65%	~78%	86%
Protein binding	99%	91%	86%
Metabolism	*O*-glucuronidation	*O*-glucuronidation	*O*-glucuronidation
$t_{1/2}$ elimination	~10-13 hours	~10-13 hours	~12.4 hours

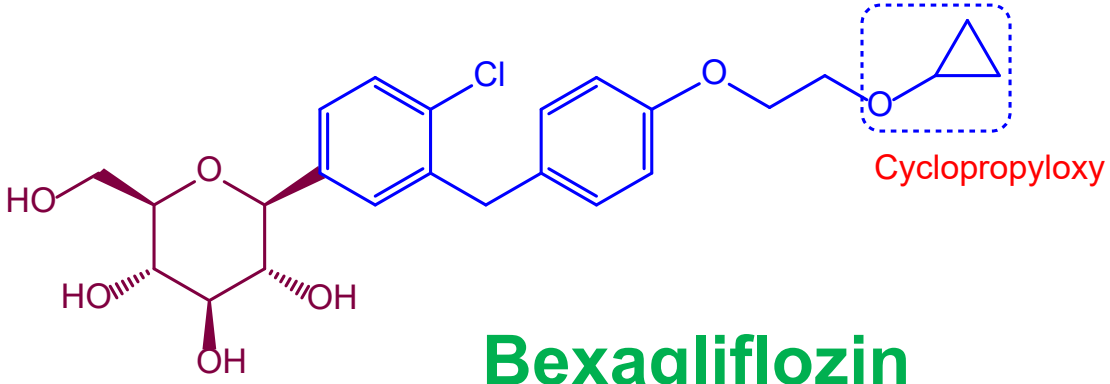
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

SGLT2 Inhibitors



Ertugliflozin

- U.S. Approval: 2017 for T2DM
- Protein binding: 93%
- Metabolism: O-glucuronide
- $t_{1/2}$ elimination: 16.6 hours

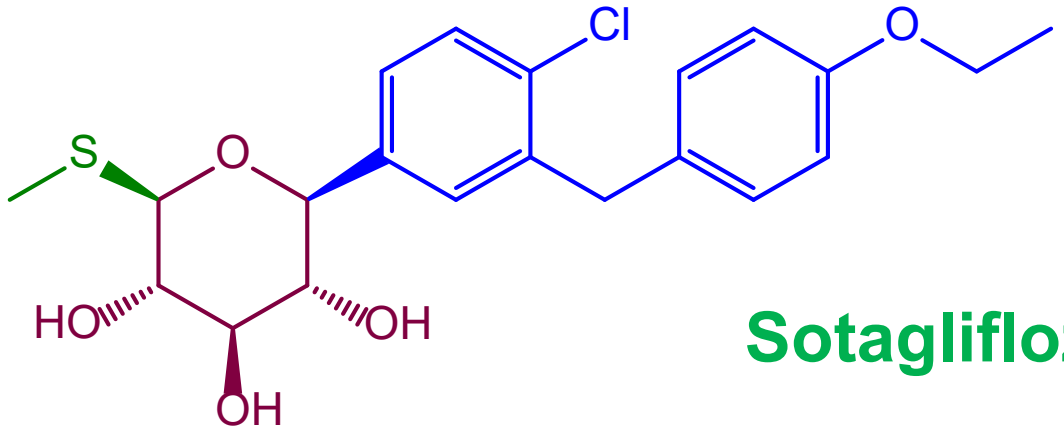


Bexagliflozin

- U.S. Approval: 2023 for T2DM
- Protein binding: 93%
- Metabolism: *O*-glucuronide
- $t_{1/2}$ elimination: 12 hours

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/209803s007lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214373s001lbl.pdf

Dual SGLT inhibitor



Sotagliflozin

- U.S. Approval: 2023 for HF
- Dual SGLT inhibitor *(intestinal SGLT-1 and renal SGLT inhibitor)*
- Protein binding: 93%
- Metabolism: *O*-glucuronide metabolite
- $t_{1/2}$ elimination: 21 to 35 hours

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216203s000lbl.pdf

Benefits of SGLT2-Inhibitors

- Oral medication
- Low risk of hypoglycemia
- Lowers blood pressure
- Weight loss
- Cardiovascular benefits

Current Status of SGLT2-Inhibitors

- Cardiovascular
  - Phase 3: Balcinrenone/dapagliflozin: heart failure with CKD
  - Phase 2: Sotagliflozin: hypertrophic cardiomyopathy
- Type 1 Diabetes: Phase 3 -Sotagliflozin: FDA declined in 2019, resubmitted 2024
- Renal - Indication CKD
  - Phase 2: aldosterone synthase inhibitor + empagliflozin ; Albuminuria reductions by up to 39.5%- Additive efficacy?

Side Effects and Precautions of SGLT2-Inhibitors

- Genital and Urinary Tract Infections
- Hypotension
- Polyuria
- Dehydration
- Renal Impairment: Monitor renal function
- Risk of DKA (FDA warning in May 2015)

Conclusions

- Novel Mechanism of Action
- SGLT inhibitors have shown good results in the treatment of type 2 diabetes and beyond
- Beneficial effects for other diseases such as heart failure
- Greater potential for this class of drugs in the future

References

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Questions?