New Drug Update 2023

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Disclosure

- I have had no financial relationship over the past 24 months with any commercial sponsor with a vested interest in this presentation

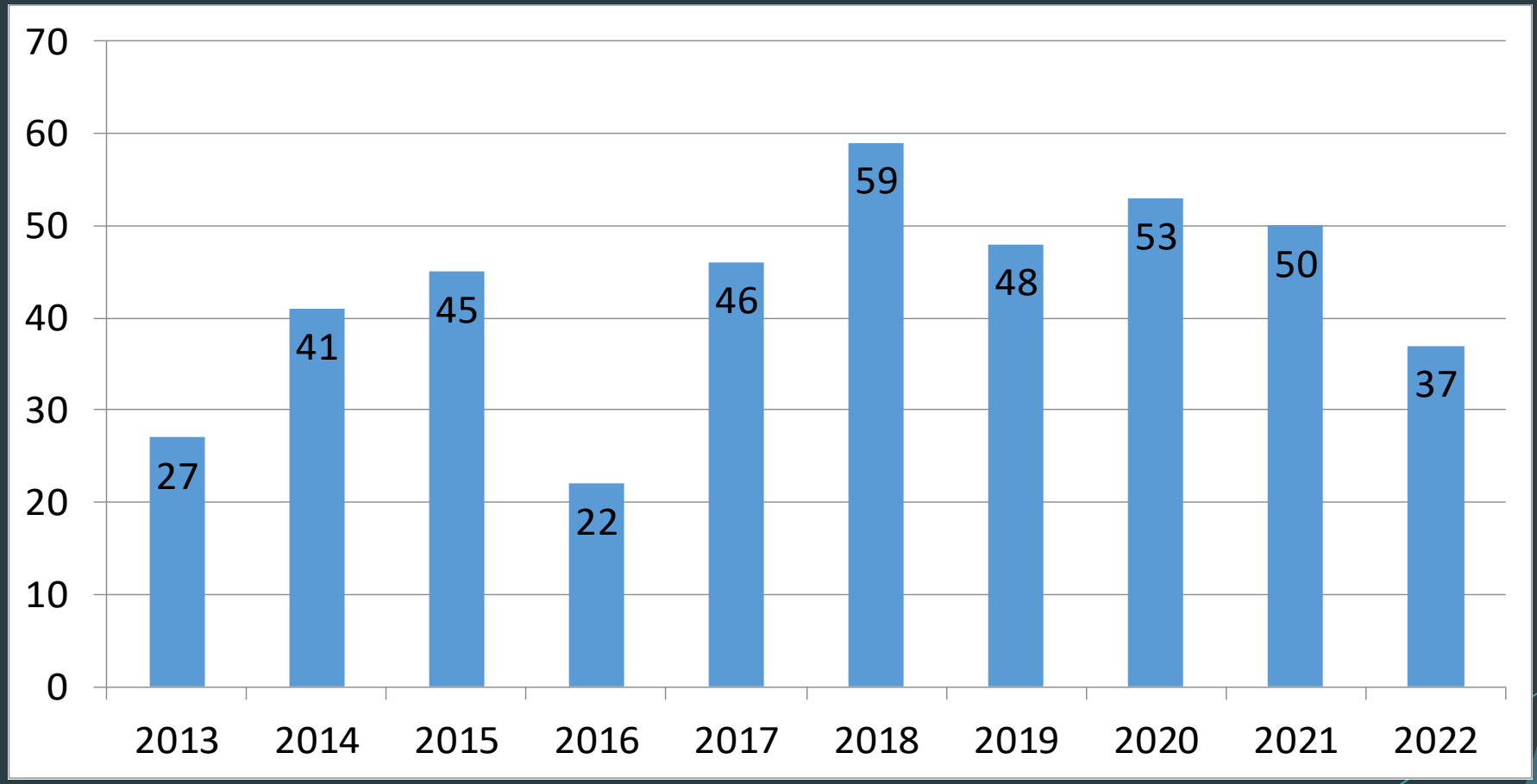
Pharmacist Learning Objectives

- Upon successful completion of this activity, pharmacists will be able to:
  - Summarize therapeutic indications of medications recently approved by the FDA.
  - Discuss pharmacological properties of the new medications
  - List side effects, warnings, precautions and significant drug interactions associated with each medication.
  - Identify the normal dose and dosage forms of the drugs presented.
  - Describe limitations to implementing the new medications into clinical practice

Pharmacy Technician Learning Objectives

- Following this presentation, pharmacy technicians will be able to:
  - Identify new medications recently approved by the FDA
  - List the classification for the new medications
  - Recall major indications for the new medications
  - Identify the usual dose and route of administration for each medication
  - Discuss the cost associated with each of the new medications

CDER's Novel Drug Approval Trends



https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2023. Accessed June 21, 2023.

Agenda

- Daprodustat (Jesduvroq®)
- Dextromethorphan/Bupropion (Auvelity™)
- Teplizumab (Tzield™)
- Sulbactam/durlobactam (Xacduro®)
- Fezolinetant (Veozah™)
- Rezafungin (Rezzayo™)
- Lecanemab (Leqembi™)
- Zavegepant (Zavzpret™)
- Sotagliflozin (Inpefa™)
- Bexaglifozin (Brenzavvy™)

The starting dose of daprodustat is based on:

A. Renal function
B. Hemoglobin
C. Weight
D. BMI

Daprodustat (Jesduvroq®)

- Indication
  - Anemia due to chronic kidney disease and on dialysis for at least 4 months
- Pharmacology
  - Reversible inhibitor of HIF-PH1, PH2 & PH3
  - Leads to stabilization and nuclear accumulation of HIF-1α and HIF-2α transcription factors
  - Leads to increased transcription of erythropoietin

Jesduvroq (daprodustat) prescribing information. Durham NC: GlaxoSmithKline; February 2023.

Daprodustat (Jesduvroq®)

- Pharmacokinetics/dynamics
  - Increase in erythropoietin in 6-8 hours
  - New Hgb steady-state levels in ~ 4 weeks (on ESA) and ~ 16-20 week (not on ESA)
  - T ½ ~ 7 hours in CKD patients
  - Metabolized by CYP2C8

Jesduvroq (daprodustat) prescribing information. Durham NC: GlaxoSmithKline; February 2023.

Daprodustat (Jesduvroq®)

- Contraindications
  - Uncontrolled hypertension
  - Strong CYP450 2C8 inhibitors
- Boxed Warning
  - Increased risk of death, MI, stroke, venous thromboembolism and thrombosis of vascular access
  - Avoid if history of MI, CV or ACS events in past 3 months
  - Hgb > 11 g/dl or increase of 1 g/dl over 2 weeks may increase risk

Jesduvroq (daprodustat) prescribing information. Durham NC: GlaxoSmithKline; February 2023.

Daprodustat (Jesduvroq®)

- Other Warnings and precautions
  - Hospitalization for heart failure
  - Hypertension
  - Gastric or esophageal erosion & GI bleed
  - Active malignancy

Jesduvroq (daprodustat) prescribing information. Durham NC: GlaxoSmithKline; February 2023.

Daprodustat (Jesduvroq®)

- Drug interactions
  - Gemfibrozil (Strong CYP2C8 inhibitor)
    - Increased daprodustat AUC 18.6X
    - Contraindicated
  - Clopidogrel (moderate CYP2C8 inhibitor)
    - Expected to increase daprodustat AUC 4X
    - Reduce starting dose by half
  - Rifampin (CYP2C8 inducer)
    - May decrease daprodustat exposure
    - Monitor Hgb and increase dose as needed

Jesduvroq (daprodustat) prescribing information. Durham NC: GlaxoSmithKline; February 2023.

Adverse Reactions from ASCEND-D Trial

Reaction	Daprodostat N = 1,482	EPO N = 1,474
Hypertension	24%	24%
Abdominal pain	11%	8%
Dizziness	7%	6%
Hypersensitivity	7%	7%

Jesduvroq (daprodustat) prescribing information. Durham NC: GlaxoSmithKline; February 2023.

Vascular Event Rate per 100 patient years
ASCEND-D Trial

Event	Daprodostat N = 1,482	EPO N = 1,474
Vascular access thrombosis	5	6.3
Myocardial infarction	3.4	4.1
Stroke	1.2	1.5
Deep vein thrombosis	0.7	0.6
Pulmonary embolism	0.3	0.4

Jesduvroq (daprodustat) prescribing information. Durham NC: GlaxoSmithKline; February 2023.

ASCEND-D Trial Primary Outcomes

Reaction	Daprodostat N = 1,487	EPO N = 1,477	Treatment Effect (95% CI) P-value
Change in Hgb from baseline to week 28-52 (g/dl)	0.28	0.1	Difference 0.18 (0.12, 0.24) < 0.001*
MACE* (%)	25.2	26.7	Hazard ratio 0.93 (0.81, 1.07) < 0.001
Death from any cause	16.4	15.8	--
Nonfatal MI	6.8	8.5	--
Nonfatal stoke	2.0	2.4	--

*Major Adverse Cardiovascular Events

Singh A, et al. N Engl J Med 2021;385:2325-35.

Daprodustat Dosing for Dialysis patients NOT receiving an ESA	
Pre-Treatment Hgb level (g/dl)	Starting dose (once daily)
< 9	4 mg
9-10	2 mg
>10	1 mg

Jesduvroq (daprodustat) prescribing information. Durham NC: GlaxoSmithKline; February 2023.

Daprodustat Dosing for Dialysis patients receiving an ESA

Epoetin IV (units/week)	Darbepoetin SubQ/IV (mcg/4 weeks)	Methoxy PEG-Epoetin SubQ/IV (mcg/month)	Starting dose (once daily)
≤ 2,000	20-30	30-40	4 mg
2001 to < 10,000	31-150	41-180	6 mg
10,000 to < 20,000	151-300	181-360	8 mg
≥ 20,000	> 300	> 360	12 mg

Jesduvroq (daprodustat) prescribing information. Durham NC: GlaxoSmithKline; February 2023.

Dose Levels of Daprodustat								
Daily Dose	1 mg	2 mg	4 mg	6 mg	8 mg	12 mg	16 mg	24 mg

- May dose adjust every 4 weeks by one level
- Decrease dose by one level if Hgb increases by more than 1 g/dl over 2 weeks or more than 2 g/dl over 4 weeks
- Stop treatment if Hgb is > 12 g/dl
- Stop after 24 weeks if no meaningful increase in Hgb

Jesduvroq (daprodustat) prescribing information. Durham NC: GlaxoSmithKline; February 2023.

Daprodustat (Jesduvroq®)

- Monitoring
  - Evaluate iron stores before and during treatment
  - LFT's at baseline and repeat if signs of liver disease
- Cost
  - Pending CMS documentation
  - 87% of dialysis patients are on Medicare
  - Expected launch 4th quarter 2023 or 1st quarter 2024

Jesduvroq (daprodustat) prescribing information. Durham NC: GlaxoSmithKline; February 2023.

Daprodustat (Jesduvroq®)

- Bottom line
  - Daily oral option for anemia in patients on dialysis
  - Check iron stores
  - Similar CV risks as other ESA agents
  - Cost???
- Additional review
  - Ishii T, et al. Ther Clin Risk Manag 2021;17:155-63.

A potential barrier for patients to take dextromethorphan/bupropion for depression is:

A. Weight gain
B. Cost
C. Slow onset of action
D. Sexual dysfunction

Dextromethorphan/Bupropion (Auvelity™)

- Indication
  - Major depressive disorder in adults
- Pharmacology
  - Dextromethorphan
    - NMDA receptor antagonist and sigma-1 receptor agonist
    - Both modulate glutamate neurotransmission
  - Bupropion
    - Weak reuptake inhibition of NE and DA
    - Inhibits metabolism of dextromethorphan (CYP2D6)

Auvelity (dextromethorphan/bupropion) prescribing information. New York, NY: Axsome Therapeutics Inc.; August 2022.

Dextromethorphan/Bupropion (Auvelity™)

- Pharmacokinetics
  - Tmax in 2-3 hours
  - Steady state in ~ 8 days
  - Dextromethorphan t ½ ~ 22h with bupropion (3x higher vs. monotherapy)
    - Metabolized by CYP2D6
  - Bupropion t ½ ~ 15 hours
    - Metabolized by CYP2B6
  - Avoid in severe renal or hepatic impairment

Auvelity (dextromethorphan/bupropion) prescribing information. New York, NY: Axsome Therapeutics Inc.; August 2022.

Dextromethorphan/Bupropion (Auvelity™)

- Contraindications
  - Seizure disorder
  - Bulimia or anorexia nervosa
  - Abrupt discontinuation of alcohol, benzodiazepines, barbiturates and antiepileptics
  - MAOI within 14 days
- Warnings and precautions
  - Increased blood pressure (monitor)
  - Mania and other neuropsychiatric reactions
  - Angle-closure glaucoma
  - Dizziness (~ 14% vs. 6% placebo)
  - Serotonin syndrome
  - Fetal harm
  - Suicidal thoughts in adolescents and young adults

Auvelity (dextromethorphan/bupropion) prescribing information. New York, NY: Axsome Therapeutics Inc.; August 2022.

Dextromethorphan/Bupropion (Auvelity™)

- Drug interactions
  - Strong CYP2D6 inhibitors (limit dose to once daily)
  - Strong CYP2B6 inducers (avoid use)
  - May decrease digoxin levels (monitor)
  - Dopaminergic agents
  - False-positive amphetamine urine drug test

Auvelity (dextromethorphan/bupropion) prescribing information. New York, NY: Axsome Therapeutics Inc.; August 2022.

Adverse Events of Gemini Study

Reaction	Dextromethorphan/bupropion N = 162	Placebo N = 164
Dizziness	16%	6.1%
Nausea	13%	8.5%
Headache	8%	3.7%
Diarrhea	6.8%	3%
Somnolence	6.8%	3%
Dry mouth	5.6%	2.4%
Hyperhidrosis	4.9%	0%
Anxiety	4.3%	1.2%

Iosifescu DV, et al. J Clin Psychiatry 2022;83:21m14345

Gemini Trial

Primary Outcome (week 6)	Dex/bupropion N = 156	Placebo N = 162	Difference (95% CI)
Change from baseline in MADRS total score	-15.9	-12	-3.9 (-1.4 to -6.4)

ASCEND Trial

Primary Outcome (week 6)	Dex/bupropion N = 43	Bupropion N = 37	Difference (95% CI)
Change from baseline in MADRS total score	-13.7	-8.8	-4.9 (-3.1, -6.8)

Iosifescu DV, et al. J Clin Psychiatry 2022;83:21m14345.

Tabuteau H, et al. Am J Psychiatry 2022;179:490-99.

Dextromethorphan/Bupropion (Auvelity™)

- Dosing and Administration
  - Dextromethorphan 45 mg/bupropion 105 mg once daily in the AM
  - Increase to twice daily after three days (give at least eight hours apart)
  - Do not crush or divide tablet
  - Max of once daily if eGFR 30-59 ml/min
- Availability
  - 45/105 mg controlled release tablet
- Cost
  - AWP = $1260 for 60 tabs

Auvelity (dextromethorphan/bupropion) prescribing information. New York, NY: Axsome Therapeutics Inc.; August 2022.

Dextromethorphan/Bupropion (Auvelity™)

- Bottom line
  - Oral agent with unique mechanism for depression
  - Data suggests better than bupropion
  - Works as early as week one
  - Overall, well tolerated; watch for dizziness
- Additional review
  - Henter ID, et al. CNS Drugs. 2021;35:527-43.

When administering teplizumab, monitor patients for:

A. Diarrhea
B. Liver failure
C. Cytokine release syndrome
D. Toxic epidermal necrolysis

Teplizumab (Tzield™)

- Indication
  - Delay onset of Stage 3 type 1 diabetes
  - For patients ages 8 and older with Stage 2 type 1 diabetes
- Pharmacology
  - Binds to CD3 (antigen on T lymphocytes)
  - May deactivate pancreatic beta cell autoreactive T lymphocytes
- Pharmacokinetics
  - Mean terminal t ½ = 4.5 days
  - Catabolic metabolism

Tzield (Teplizumab) prescribing information. Red Bank, NJ: Provention Bio, Inc; November 2022.

Teplizumab (Tzield™)

- Warnings and precautions
  - Cytokine Release Syndrome (CRS)
    - Pre-medicate, monitor LFT's
  - Serious infections
  - Lymphopenia
    - Common; nadir 5 days after treatment
    - Counts recover within 2 weeks of treatment
  - Hypersensitivity reactions
  - Vaccine
    - May interfere with response
    - Not studied with live vaccines

Tzield (Teplizumab) prescribing information. Red Bank, NJ: Provention Bio, Inc; November 2022.

Adverse Reactions from Phase 2 Trial

Reaction	Teplizumab N = 44	Placebo N = 32
Lymphopenia*	73%	6%
Rash*	36%	0%
Neutropenia	5%	3%
Infection	11%	9%
Increased ALT	5%	3%
Headache	11%	6%
Allergy or immunologic	5%	0

Herold KC, et al. N Engl J Med 2019;381:603-13.3; Tzield (Teplizumab) prescribing information. Red Bank, NJ: Provention Bio, Inc; November 2022.

Phase 2 Trial in Relatives at Risk for Type 1 Diabetes

Outcome	Teplizumab N = 44	Placebo N = 32	Hazard ratio; Confidence interval
Time from randomization to diabetes diagnosis*	48.4 months	24.4 months	0.41; 0.22 to 0.78
Diagnosed with diabetes	43%	72%	NR
Annualized rate of diagnosis	14.9%	35.9%	NR
Diagnosed in year 1	7%	44%	0.13; 0.05 to 0.34

Teplizumab (Tzield™)

- Dosing
  - Day 1: 65 mcg/m2
  - Day 2: 125 mcg/m2
  - Day 3: 250mcg/m2
  - Day 4: 500 mcg/m2
  - Day 5-14: 1030 mcg/m2
  - Premedicate NSAID/APAP, antihistamine and/or antiemetic for first 5 days
  - 30-minute infusion, medication added to 25 ml normal saline
- Monitoring & Cost
  - CBC & LFT's baseline
  - AWP: 2mg vial = $8,310

Tzield (Teplizumab) prescribing information. Red Bank, NJ: Provention Bio, Inc; November 2022.

Teplizumab (Tzield™)

- Bottom line
  - First approved agent to delay Type 1 diabetes
  - Monitor closely for side effects (rash, lymphocytes)
  - Benefit appears greatest in first year
  - Further investigation on-going (best candidates, stage to start, optimal dosing)
- Additional Review
  - Ishii T, et al. Am J Health-Syst Pharm. 2022;79:2099-2117.

Sulbactam has antimicrobial properties against which of the following bacteria?

A. *Pseudomonas aeruginosa*
B. MRSA
C. *Clostridioides difficile*
D. *Acinetobacter baumannii*

Sulbactam/durlobactam (Xacduro®)

- Indication
  - HAP/VAP cause by susceptible *Acinetobacter baumannii*
- Pharmacology
  - Sulbactam
    - Semi-synthetic penicillinate sulfone
    - Beta-lactam ring, intrinsic activity against limited microbes
  - Durlobactam
    - Next generation beta-lactamase inhibitor (BLI)
    - Potent Class A & C BLI activity as well as Class D (OXA)

Xacduro (sulbactam/durlobactam) prescribing information. Waltham, MA: Innoviva; May 2023.

Sulbactam/durlobactam (Xacduro®)

- Pharmacokinetics
  - Similar for both agents
  - T ½ 2-2.5h
  - Minimal metabolism
  - Renally excreted: 75-85%

Xacduro (sulbactam/durlobactam) prescribing information. Waltham, MA: Innoviva; May 2023.

Sulbactam/durlobactam (Xacduro®)

- Contraindications
  - Hypersensitive (including other beta-lactams)
- Warnings and Precautions
  - *Clostridioides difficile*
  - Development of drug resistant bacteria
- Drug interactions
  - Probenecid (OAT1 inhibitor)

Xacduro (sulbactam/durlobactam) prescribing information. Waltham, MA: Innoviva; May 2023.

Most Common Adverse Reactions

Reaction	Sulbactam/Durlobactam N = 91	Colistin N = 86
LFT increase	19%	21%
Diarrhea	17%	11%
Anemia	13%	14%
Hypokalemia	12%	11%
Acute kidney injury	6%	36%
Thrombocytopenia	6%	4%

Xacduro (sulbactam/durlobactam) prescribing information. Waltham, MA: Innoviva; May 2023.

ATTACK Phase 3 Trial Data

Outcome	Sulbactam/Durlobactam N = 63	Colistin N = 62	Treatment Difference
All-Cause Mortality* (Day 28)	19%	32.3%	-13.2 (-30, 3.5)
Clinical Cure 7 days after treatment	61.9%	40.3%	NR

*primary outcome

Xacduro (sulbactam/durlobactam) prescribing information. Waltham, MA: Innoviva; May 2023.

Sulbactam/durlobactam (Xacduro®)

- Dosing
  - Sulbactam 1g/durlobactam 1g every 6 hours for 7-14 days
  - Dose adjustments for renal impairment;
  - Increase to every 4 hour dosing for CrCl $\geq$ 130 ml/min
  - Infused over 3 hours
- Availability & Cost
  - Kit of 3 vials (1 clear vial of sulbactam 1g; 2 amber vials of durlobactam 0.5g)
  - Use within 24 hours of reconstitution
  - Expected release 2nd half 2023

Xacduro (sulbactam/durlobactam) prescribing information. Waltham, MA: Innoviva; May 2023.

Sulbactam/durlobactam (Xacduro®)

- Bottom line
  - Provides needed treatment for carbapenem-resistant *Acinetobacter baumannii* (CRAB) infections
  - Currently approved for pneumonia due to CRAB
  - Improved outcomes and tolerability vs. colistin
- Additional review
  - El-Ghali A, et al. Pharmacotherapy 2023;43:502-513.

Monitoring patients taking fezolinetant involves checking _____.

A. Cardiac ejection fraction (i.e. echocardiogram)
B. Brain MRI
C. Liver function tests and bilirubin
D. Thyroid function (i.e. TSH)

Fezolinetant (Veozah™)

- Indication
  - Moderate to severe vasomotor menopausal symptoms
- Pharmacology
  - Neurokinin 3 (NK3) receptor antagonist
  - Blocks NK B binding to the kisspeptin/neurokinin/dynorphin (KNDy) neuron to moderate activity in the hypothalamus
  - Key regulatory mediator for vasomotor symptoms
  - Estrogen inhibits the process

Veozah (fezolinetant) prescribing information. Northbrook, IL: Astellas; May 2023.

Fezolinetant (Veozah™)

- Pharmacokinetics
  - Peaks 1.5 hr (range 1-4 hr)
  - T ½ ~ 10 hr
  - CYP1A2 metabolism
  - Renal clearance 77%

Veozah (fezolinetant) prescribing information. Northbrook, IL: Astellas; May 2023.

Fezolinetant (Veozah™)

- Contraindications
  - Cirrhosis
  - End stage renal disease (CrCl < 30 ml/min)
  - CYP1A2 inhibitors
- Warnings and precautions
  - Liver function test elevation

Veozah (fezolinetant) prescribing information. Northbrook, IL: Astellas; May 2023.

Fezolinetant (Veozah™)

- Drug interactions
  - CYP1A2 inhibitors
    - Fluvoxamine (strong): 840% increase in AUC
    - Mexiletine (moderate): 360% increase in AUC
    - Cimetidine (weak): 100% increase in AUC

Veozah (fezolinetant) prescribing information. Northbrook, IL: Astellas; May 2023.

Adverse Effects from SKYLIGHT-4 Safety Trial

	Fezolinetant 45 mg N = 609	Placebo N = 611
Abdominal pain	4.3%	2.1%
Diarrhea	3.9%	2.6%
Insomnia	3.9%	1.8%
Back pain	3%	2.1%
LFT elevation	2.3%	0.8%

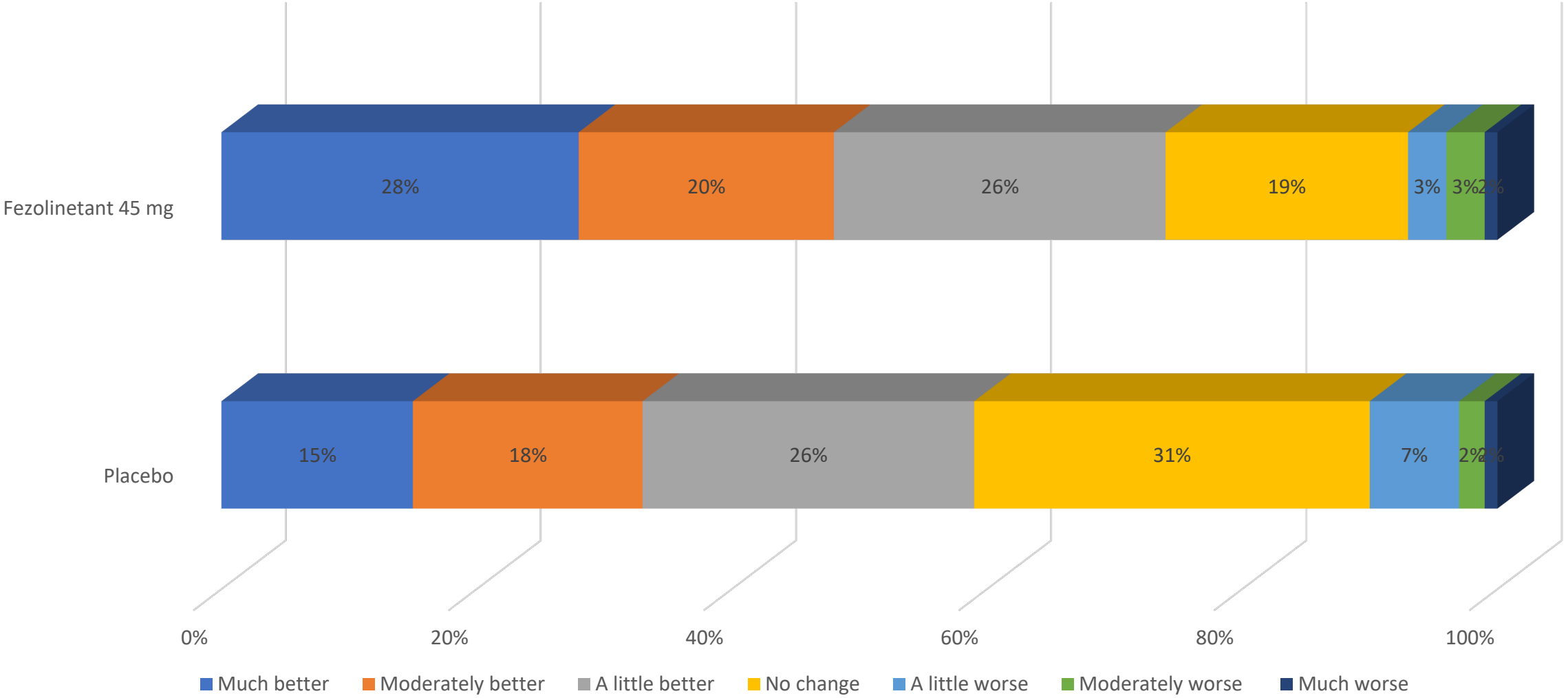
Veozah (fezolinetant) prescribing information. Northbrook, IL: Astellas; May 2023.

Efficacy Data from Phase 3 Skylight-1 Trial

Parameter	Fezolinetant 45 mg N = 174	Placebo N = 175	Difference (95% CI) P-value
Baseline # of daily moderate to severe vasomotor symptoms	10.4	10.5	N/A
Change from Baseline to Week 4	-5.4	-3.3	-2.1 (-2.9, -1.3) < 0.001
Change from Baseline to Week 12	-6.4	-3.9	-2.6 (-3.4, -1.7) < 0.001

Veozah (fezolinetant) prescribing information. Northbrook, IL: Astellas; May 2023.
Lederman S., et al. Lancet 2023; 401:1091-102.

Change from Baseline in Distribution of Patient Global Impression of Change in Sleep Disturbance at week 12



Lederman S., et al. Lancet 2023; 401:1091-102.

Fezolinetant (Veozah™)

- Dosing
  - 45 mg tablet once daily
- Monitoring
  - Baseline AST, ALT and bilirubin, then every 3 months
- Availability and Cost
  - WAC = $550 per month

Veozah (fezolinetant) prescribing information. Northbrook: Astellas; May 2023.

Fezolinetant (Veozah™)

- Bottom line
  - Novel mechanism for moderate to severe menopausal symptoms
  - Non-hormone therapy
  - Monitor LFT's
- Additional review
  - Menopause 2023;30:573-90.

What is the dosing frequency for rezafungin?

A. Daily
B. Twice daily
C. Weekly
D. Monthly

Rezafungin (Rezzayo™)

- Indication
  - Adults with candidemia and invasive candidiasis
  - Limited use approval
- Pharmacology
  - Echinocandin
  - Inhibits 1,3 ß-D-glucan synthase
  - Similar to caspofungin, micafungin and anidulafungin

Rezzayo (rezafungin) prescribing information. Lincolnshire, IL: Melinta Therapeutics; March 2023.

Rezafungin (Rezzayo™)

- Pharmacokinetics
  - T ½ ~ 150 hours
  - Minimal metabolism
  - Excreted unchanged via GI

Rezzayo (rezafungin) prescribing information. Lincolnshire, IL: Melinta Therapeutics; March 2023.

Rezafungin (Rezzayo™)

- Contraindications
  - Hypersensitivity to other echinocandins
- Warnings and precautions
  - Infusion reactions
  - Photosensitivity
  - Hepatic reactions
- Drug interactions
  - None noted

Rezzayo (rezafungin) prescribing information. Lincolnshire, IL: Melinta Therapeutics; March 2023.

Adverse Reactions Summary

Reaction	Rezafungin N = 151	Caspofungin N = 166
Diarrhea	11%	10%
Vomiting	9%	4%
Nausea	9%	5%
Hypokalemia	15%	10%
Hypomagnesemia	8%	3%
Pyrexia	12%	7%

Rezzayo (rezafungin) prescribing information. Lincolnshire, IL: Melinta Therapeutics; March 2023.

Clinical Efficacy ReSTORE Phase 3 Trial

Primary Outcomes	Rezafungin N = 93	Caspofungin N = 94	Difference (95% CI)
Mortality at 30 days	23.7%	21.3%	2.4 (-9.7, 14.4)
Global cure at 14 days	59.1%	60.6%	-1.5 (-15.4, 12.5)

Rezzayo (rezafungin) prescribing information. Lincolnshire, IL: Melinta Therapeutics; March 2023.

Rezafungin (Rezzayo™)

- Dosing
  - 400 mg x 1 then 200 mg once weekly
  - No data beyond 4 weeks
- Availability
  - 200 mg single-dose vials, reconstituted with 10 ml of sterile water
  - Dilute 10 ml reconstituted solution in 240 ml of NS, ½ NS or D5W and give over 1 hour
- Cost
  - AWP = $2,340 per 200 mg vial (~ $11,700 for 4-week course)

Rezzayo (rezafungin) prescribing information. Lincolnshire, IL: Melinta Therapeutics; March 2023.

Rezafungin (Rezzayo™)

- Bottom line
  - Once weekly echinocandin
  - Option for outpatients unable to de-escalate to oral azole
  - Warn for sun exposure
- Additional review
  - Hoenlgl M et al. Drugs 2021;81:1703-29.

Patients on lecanemab must be monitored with:

A. Echocardiogram
B. CT
C. MRI
D. Ultrasound

Lecanemab (Leqembi™)

- Indication
  - Alzheimer's with mild cognitive impairment or mild dementia
- Pharmacology
  - Human immunoglobulin gamma 1 monoclonal antibody
  - Reduces amyloid beta plaques

Leqembi (lecanemab) prescribing information. Nutley, NJ: Eisai; January 2023.

Lecanemab (Leqembi™)

- Pharmacokinetics
  - Steady-state after 6 weeks
  - T ½ 5-7 days
  - Degraded by proteolytic enzymes
  - No data with hepatic or renal impairment; not expected to impact clearance
- Contraindications
  - None

Leqembi (lecanemab) prescribing information. Nutley, NJ: Eisai; January 2023.

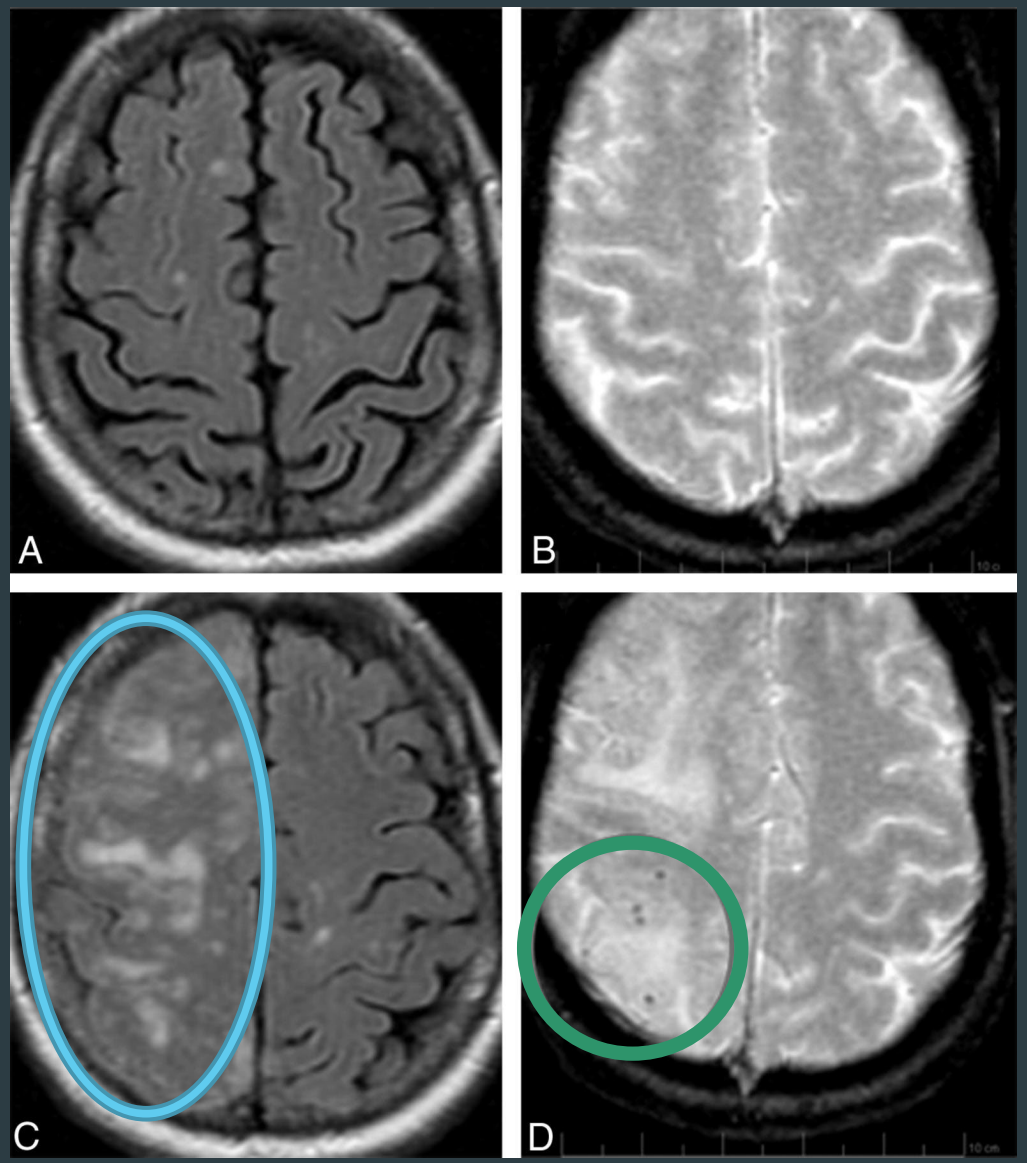
Lecanemab (Leqembi™)

- Warnings and precautions
  - Amyloid Related Imaging Abnormalities associated with edema (ARIA-E) or hemosiderin (ARIA-H)
    - More common within first 3 months
    - Symptoms resolved within 4 months
  - Infusion-related reactions
    - 44% of patients took preventative medication

Leqembi (lecanemab) prescribing information. Nutley, NJ: Eisai; January 2023.
Van Dyck, et al. N Engl J Med 2023;388:9-21

BASELINE

BASELINE



ARIA-E

ARIA-H

Barakos J, Sperling R, Salloway S, Jack C, Gass A, Fiebach JB, Tampieri D, Melançon D, Miaux Y, Rippon G, Black R, Lu Y, Brashear HR, Arrighi HM, Morris KA, Grundman M. MR imaging features of amyloid-related imaging abnormalities. AJNR Am J Neuroradiol. 2013 Oct;34(10):1958-65. doi: 10.3174/ajnr.A3500. Epub 2013 Apr 11. PMID: 23578674; PMCID: PMC7965435.

ARIA-E in Clarity AD Phase 3 Clinical Trial

	Lecanemab N = 898	Placebo N = 897
ARIA-E Overall incidence	12.6%	1.7%
Symptomatic	2.8%	0%
Apolipoprotein E ε4 carriers	15.8%	2.3%
Apolipoprotein E ε4 non-carriers	5.4%	0.3%

Van Dyck, et al. N Engl J Med 2023;388:9-21

ARIA-H in Clarity AD Phase 3 Clinical Trial

	Lecanemab N = 898	Placebo N = 897
ARIA-H Overall incidence	17.3%	9%
Microhemorrhage	14%	7.6%
Superficial siderosis	5.6%	2.3%
Symptomatic	0.7%	0.2%
Apolipoprotein E ε4 carriers	19.7%	11.3%
Apolipoprotein E ε4 non-carriers	11.9%	4.2%

Van Dyck, et al. N Engl J Med 2023;388:9-21

Adverse Reactions from Clarity AD Phase 3 Trial

Reaction	Lecanemab N = 898	Placebo N = 897
Any event related to treatment	44.7%	22%
Infusion-related	26.4%	7.4%
Headache	11.1%	8.1%
Fall	10.4%	9.6%
Dizziness	5.5%	5.1%

Leqembi (lecanemab) prescribing information. Nutley, NJ: Eisai; January 2023.

Lecanemab (Leqembi™)

- Drug interactions
  - Caution with antithrombotic or thrombolytic agents
  - Fatal cerebral hemorrhage case in one patient who was treated with alteplase following a stroke
  - Cerebral hemorrhage case in one patient on apixaban for atrial fibrillation

Leqembi (lecanemab) prescribing information. Nutley, NJ: Eisai; January 2023.
Reish N, et al. N Engl J Med 2023; 388; 478-79.

Efficacy from Clarity AD Phase 3 Trial

Endpoint	Lecanumab N = 859	Placebo N = 875	Difference (95% CI) p-value
Baseline CDR-SB Score	3.17	3.22	NR
Change from Baseline at 18 months	1.21	1.66	-0.45 (-0.67 to -0.23) < 0.001

Van Dyck, et al. N Engl J Med 2023;388:9-21

Clinical Application

- Clinical significance is questionable
- Placebo: 3.22 to 4.88 (+1.66)
- Lecanumab: 3.17 to 4.38 (+1.21)

CDR Sum of Boxes	Staging Category
0	Normal
0.5 - 4	Questionable cognitive impairment
0.5-2.5	Questionable impairment
3 - 4	Very mild dementia
4.5 - 9	Mild dementia
9.5 – 15.5	Moderate dementia
16 – 18	Severe dementia

Andrews JS, et al. Alzheimers Demet 2019;5: 354-63.

Lecanemab (Leqembi™)

- Dosing
  - 10 mg/kg every 2 weeks
- Administration
  - 1-hour infusion
- Monitoring
  - Baseline MRI (within 1 year of starting)
  - MRI prior to 5th, 7th and 14th infusion
- Cost for 70 kg patient
  - ~$1,000 per infusion
  - ~ $26,500 per year

Leqembi (lecanemab) prescribing information. Nutley, NJ: Eisai; January 2023.

Lecanemab (Leqembi™)

- Bottom line
  - 2nd drug approved for reducing plaque in mild Alzheimer's
  - Questionable meaningful benefit; monitor for edema and bleeding
  - Expensive!
  - Further research in this area
- Additional review
  - Van Dyck CH, et al N Engl J Med 2023; 388;9-21

Zavegepant is given via which route?

A. Oral
B. Subcutaneous
C. Intravenous
D. Intranasal

Zavegepant (Zavzpret™)

- Indication
  - Treatment of acute migraines in adults
  - Rimegepant (Nurtec® ODT) approved for prevention and acute treatment
  - Ubrogepant (Ubrelvy™) approved for acute treatment
  - Atogepant (Qulipta™) approved for prevention
- Pharmacology
  - Calcitonin gene-related peptide receptor antagonist

Zavzpret (zavegepant) prescribing information. New York, NY: Pfizer Inc; March 2023
Qulipta (atogepant) prescribing information. North Chicago, IL: AbbVie Inc; October 2021
Nurtec ODT (rimegepant) prescribing information. New Haven, CT: Biohaven Pharmaceuticals Inc; May 2021
Ubrelvy (ubrogepant) prescribing information. Madison, NJ: Allergan USA; March 2021

Acute Treatments CGRP Pharmacokinetic Comparison

	Zavegepant	Ubrogepant	Rimegepant
Tmax	0.5 hours	1-2 hours	1.5 hours
Metabolism/ elimination	CYP3A4 (major) CYP2D6 (minor)	CYP3A4 (major) CYP2D6 (minor) Biliary excretion	Primarily eliminated unchanged; Metabolized CYP3A4, CYP2C9
T ½	5-8 hours	~ 11 hours	~ 11 hours

Zavzpret (zavegepant) prescribing information. New York, NY: Pfizer Inc; March 2023
Ubrelvy (ubrogepant) prescribing information. Madison, NJ: Allergan USA; March 2021
Nurtec ODT (rimegepant) prescribing information. New Haven, CT: Biohaven Pharmaceuticals Inc; May 2021

Zavegepant (Zavzpret™)

- Contraindications
  - Hypersensitivity
- Warnings and precautions
  - No data in pregnancy, breast-feeding or pediatrics
  - No data in severe hepatic impairment (Child-Pugh C)
- Drug interactions
  - OATP1B3 or NTCP inhibitors and inducers
  - Avoid nasal decongestants

Zavzpret (zavegepant) prescribing information. New York, NY: Pfizer Inc; March 2023

Adverse Reactions Phase 3 trials

Outcome	Zavegepant N = 1023	Placebo N = 1056
Taste disorders	18%	4%
Nausea	4%	1%
Nasal discomfort	3%	1%
Vomiting	2%	<1%

Zavzpret (zavegepant) prescribing information. New York, NY: Pfizer Inc; March 2023

Clinical Efficacy

	Zavegepant 10 mg N = 623	Placebo N = 646
Pain free at 2 hours*		
% Responders	23.6	14.9
Difference from placebo %, p-value	8.8, <0.001	--
Most bothersome symptom free at 2 hours*		
% Responders	39.9	31.1
Difference from placebo %, p-value	8.7, 0.001	--

Lipton RB, et al. Lancet Neurol. 2023;22:209-17.

Zavegepant (Zavzpret™)

- Dosing
  - 10mg single spray in one nostril as needed
  - Max of 10mg per 24h
  - Recommend max of 8 doses per 30 days
- Availability
  - Single spray device
  - 6 doses per carton

Zavzpret (zavegepant) prescribing information. New York, NY: Pfizer Inc; March 2023

CGRP Price Comparison			
	Zavegepant 10 mg	Ubrogepant 50 mg or 100 mg	Rimegepant 75 mg ODT
Average wholesale price per dose	$220	$118	$143
Monthly AWP based on 8 doses per month	$1760	$945	$1,144

Zavegepant (Zavzpret™)

- Bottom line
  - Another CGRP receptor antagonist
  - Acute migraine treatment
  - Well-tolerated
  - No direct comparison with other treatment agents
  - Nasal formulation may benefit patients with severe nausea and vomiting
- Additional review
  - Dos Santos JBR, da Silva MRR. Eur J Pharmacol 2022;922:174902

Other approvals

- Fecal Microbiota (Rebyota™)
  - Approved for recurrent C. diff infection after treatment with antibiotics
  - Given 24-72 hours after antibiotics completed
  - Administered rectally
  - Symptoms resolved in 70% vs 58% placebo

Rebyota prescribing information. Roseville, MN: Rebiotix Inc; November 2022.

Other approvals

- Fecal Microbiota spores (Vowst™)
  - Approved for recurrent C. diff infection after treatment with antibiotics
  - 4 capsules orally daily x 3 days on empty stomach
  - Start 2-4 days after C. diff treatment
  - 10 oz Mag citrate on day prior to starting
  - CDI recurrent rates at 8 weeks: 12.4% vs. 39.8% placebo

Vowst prescribing information. Cambridge, MA: Seres Therapeutics; April 2023.

Other Approvals

- Sotagliflozin (Inpefa™)
  - Approved to reduce risk of CV death, hospitalization for heart failure and urgent heart failure visits
  - Heart failure, T2 Diabetes, chronic kidney disease or other CV risk factors
  - SGLT-2 inhibitor and SGLT-1 inhibitor
- Bexaglifozin (Brenzavvy™)
  - Type 2 diabetes mellitus
  - SGLT-2 inhibitor

Inpefa (sotagliflozin) prescribing information. The Woodlands, TX: Lexicon; May 2023.
Brenzavvy (bexagliflozin) prescribing information. Marlborough, MA: TheracosBio; Jan 2023.

Other Approvals That May Make You Go Hmmmm…..

- Omeprazole delayed-release “Mini Capsules”
  - 70% smaller than current version
- Vibrant®
  - Not a drug; Indicated for chronic idiopathic constipation if no response to laxatives after 1 month
  - Vibrating capsule mechanically stimulates the colon
  - 40.5% vs. 23% placebo achieved > 1 complete spontaneous bowel movement per week

Vibrant prescribing information. Yokneam, Israel: Vibrant LTD; 2022.

Questions?