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PHARMACY EDUCATION

GameChangers: New Drugs

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Pharmacist Learning Objectives

Upon successful completion of this course, learners should 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 the new medications.
- Identify the normal dose and dosage forms of the new medications.
- Describe limitations to implementing the new medications into clinical practice.

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Pharmacy Technician Learning Objectives

Upon successful completion of this course, learners should 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 information for new medications.
- Discuss the cost associated with each of the new medications.

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Disclosure Statement

- Joe Strain reports no actual or potential conflicts of interest associated with this presentation.
  - Off-label medication use will not be discussed during this presentation

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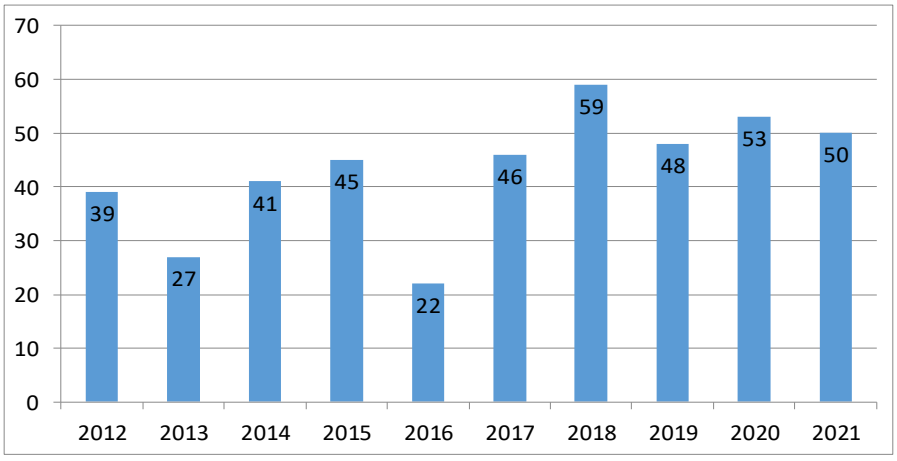
CDER's Novel Drug Approval Trends



https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2021. Accessed January 3rd, 2022.

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Agenda

- Vericiguat (Verquvo™)
- Viloxazine (Qelbree™)
- Olanzapine/samidorphan (Lybalvi™)
- Lemborexant (Dayvigo®)
- Ibrexafungerp (Brexafemme®)
- Aducanumab (Aduhelm™)
- Tirbanibulin (Klisyri®)
- Semaglutide (Wegovy™)
- Finerenone (Kerendia®)
- Brincidofovir (Tembexa®)
- Aspirin (Vazalore™)

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Vericiguat (Verquvo™)

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Vericiguat (Verquvo™)

- Indication
  - Adults with symptomatic chronic heart failure (EF < 45%)
  - Reduces risk of CV death and HF hospitalization after a HF hospitalization or need for outpatient IV diuretics
- Pharmacology
  - Soluble guanylate cyclase (sGC) stimulator
  - Enzyme involved in nitric oxide signaling pathway
  - Smooth muscle relaxation & vasodilation

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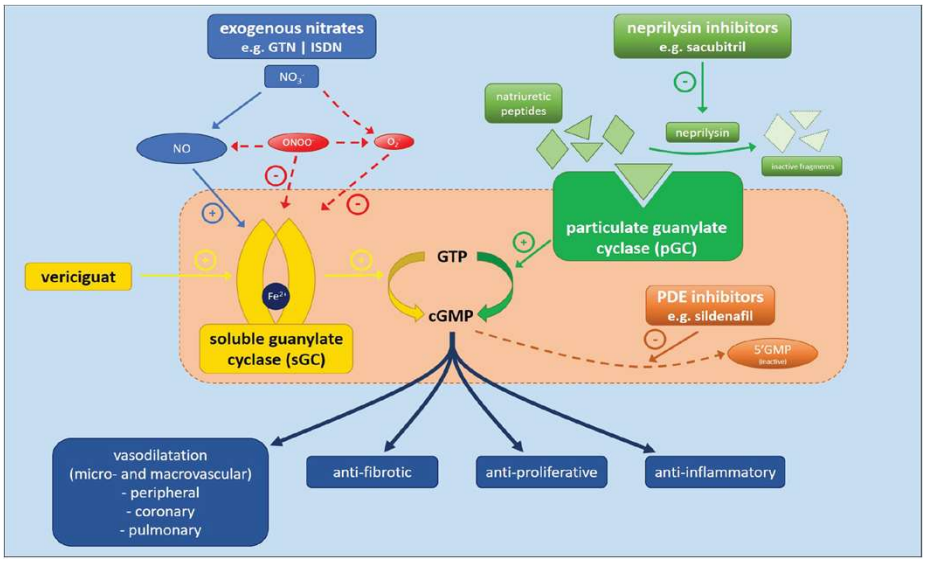
Therapies targeting the NO/sGC and neprilysin/pGC pathways to increase cGMP generation.



Cardiovasc Res, Volume 116, Issue 12, 1 October 2020, Pages e152–e155, https://doi.org/10.1093/cvr/cvaa247

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Vericiguat (Verquvo™)

- Pharmacokinetics
  - Well-absorbed with food (~93%)
  - T ½ ~ 30h
  - Metabolized by glucuronidation to inactive metabolite
    - No adjustment for hepatic impairment (not studied in Child-Pugh C)
  - ~45% renal elimination
    - No dose adjustment for renal impairment

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Vericiguat (Verquvo™)

- Contraindications
  - Use with riociguat (Adempas®)
  - Pregnancy
    - Must rule out prior to treatment
    - Avoid pregnancy for 1 month after stopping treatment
- Drug Interactions
  - Use of PDE-5 inhibitors (e.g., sildenafil) due to hypotension risk

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Adverse Reactions from Victoria Trial		
	Vericiguat N = 2519	**Placebo N = 2525**
Hypotension	15.4%	14.1%
Symptomatic Hypotension	9.1%	7.9%
Anemia	7.6%	5.7%
Syncope	4%	3.5%

Armstrong PW, et al. N Engl J Med 2020;382:1883-93.

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Efficacy Data from Victoria Trial				
Outcome	**Vericiguat (N=2526)**	**Placebo (N=2524)**	**Hazard Ratio (95% CI)**	**P Value**
Death from cardiovascular causes or first hospitalization for heart failure	35.5%	38.5%	0.90 (0.82-0.98)	0.02
Hospitalization for heart failure	27.4%	29.6%	0.90 (0.81-1.00)	
Death from cardiovascular causes	16.4%	17.5%	0.93 (0.81-1.06)	
Death from any cause or first hospitalization for heart failure	37.9%	40.9%	0.90 (0.83-0.98)	0.02

Armstrong PW, et al. N Engl J Med 2020;382:1883-93.

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Vericiguat (Verquvo™)

- Dosing
  - 2.5 mg orally once daily with food
    - May increase every 2 weeks to max dose of 10 mg daily
    - Adjusted primarily based on systolic blood pressure
    - Tablet may be crushed if necessary
- Availability
  - 2.5 mg, 5 mg, and 10 mg tablets
- Cost
  - AWP = $700 per 30 tablets

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Vericiguat (Verquvo™)

- Bottom Line
  - New mechanism approved for heart failure
  - Reduces risk of CV death and HF hospitalization
  - Approved for EF < 45%
  - Add-on for existing treatments, no comparator trials
  - Well-tolerated
- Additional Review
  - Murphy SP, et al. JAMA. 2020;324;488-504.

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Viloxazine (Qelbree™)

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Viloxazine (Qelbree™)

- Indication
  - ADHD in ages 6-17 years
- Pharmacology
  - Selective norepinephrine reuptake inhibitor with serotonergic activity
  - Proposed that both mechanisms have a role in ADHD
  - No effect on histamine or cholinergic receptors

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Viloxazine (Qelbree™)

- Pharmacokinetics
  - T ½ ~ 7 hours
  - Metabolized by CYP2D6, UGT1A9, and UGT2B15
  - Excretion
    - 90% renal
    - No adjustment for mild to moderate renal impairment

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Viloxazine (Qelbree™)

- Contraindications
  - Monoamine oxidase inhibitors
  - CYP1A2 substrates with narrow therapeutic range
- Warnings and Precautions
  - Suicidal thoughts & behaviors (0.9% vs. 0.4% placebo)
  - Blood pressure and heart rate increases
  - Mania activation
  - Somnolence and fatigue

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Viloxazine (Qelbree™)

- Drug Interactions
  - MAOI
  - CYP1A2 substrates
    - e.g., duloxetine, tizanidine, and clozapine
  - CYP2D6 substrates
    - e.g., dextromethorphan, venlafaxine, and risperidone
  - CYP3A4 Substrates
    - e.g., buspirone

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Viloxazine Adverse Reactions in Ages 6 to 17 Years Old				
Reaction	**100 mg N = 154**	**200 mg N = 367**	**400 mg N = 305**	**Placebo N = 463**
Somnolence	12%	16%	19%	4%
Headache	10%	11%	11%	7%
Decreased appetite	5%	8%	8%	0.4%
Fatigue	4%	5%	9%	2%

Qelbree (Viloxazine) package insert. Rockville, MD: Supernus Pharmaceuticals; April 2021.

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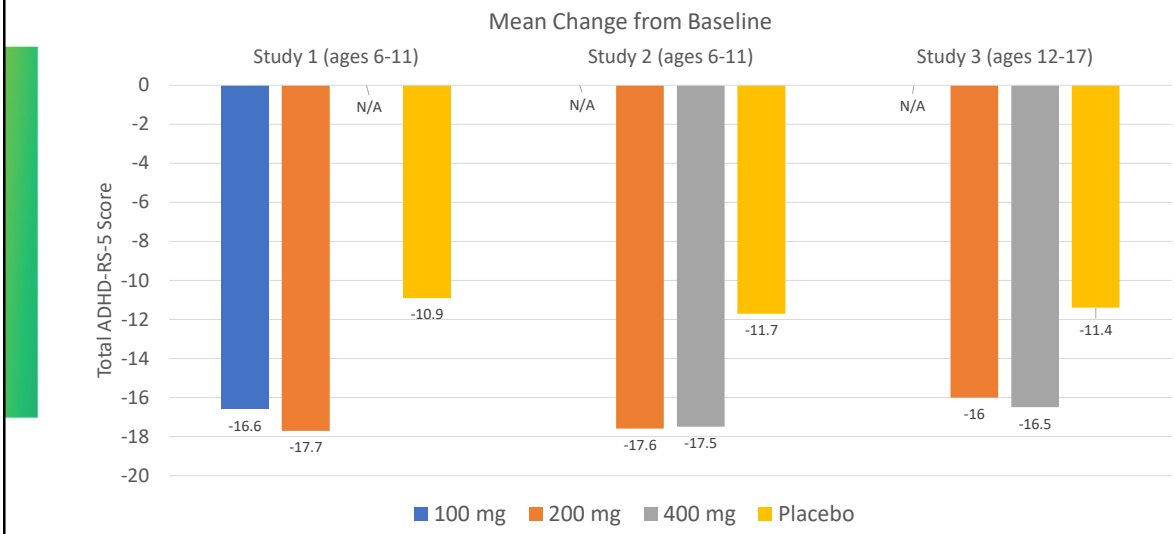
Viloxazine Efficacy Based on ADHD-RS-5 Scores



Qelbree (Viloxazine) package insert. Rockville, MD: Supernus Pharmaceuticals; April 2021.

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Viloxazine (Qelbree™)

- Dosing
  - Ages 6-11
    - 100 mg orally once daily
    - Titrated by 100 mg every week to max dose of 400 mg based on response & tolerability
  - Ages 12-17
    - 200 mg orally once daily
    - Titrate up to max of 400 mg after one week
- Availability & Cost
  - 100 mg, 150 mg, and 200 mg ER capsules
  - AWP = $360 for 30 capsules

Qelbree (Viloxazine) package insert. Rockville, MD: Supernus Pharmaceuticals; April 2021.

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Viloxazine (Qelbree™)

- Bottom Line
  - Another non-stimulant option for ADHD
  - No direct comparator trials to other agents
  - Well-tolerated
  - Long-term trials on-going
- Additional Review
  - Findling RL, et al. CNS Drugs 2021;35:643-53.

Qelbree (Viloxazine) package insert. Rockville, MD: Supernus Pharmaceuticals; April 2021.

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Olanzapine/Samidorphan (Lybalvi™)

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Olanzapine/Samidorphan (Lybalvi™)

- Indications
  - Schizophrenia
  - Bipolar I Disorder
- Pharmacology
  - Olanzapine: atypical antipsychotic
  - Samidorphan: mu opioid antagonist, kappa opioid, and delta opioid partial agonist
    - Structurally similar to naltrexone with high affinity for mu-opioid receptors
    - Role for attenuating weight gain from olanzapine

Lybalvi (Olanzapine and samidorphan) package insert. Waltham, MA: Alkermes; May 2021.
Potkin SD, et al. J Clin Psychiatry 2020;81:19m12769

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Olanzapine/Samidorphan (Lybalvi™)

- Pharmacokinetics
  - T ½ 7-11 hours
  - Metabolism
    - CYP3A4 (Major)
    - CYP3A5, CYP2C19, and CYP2C8 (Minor)
  - Excretion
    - Urine 67%

Lybalvi (Olanzapine and samidorphan) package insert. Waltham, MA: Alkermes; May 2021.

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Olanzapine/Samidorphan (Lybalvi™)

- Contraindications
  - Patients using opioids
  - Patients in opioid withdrawal
- Warnings and Precautions
  - Vulnerability to life-threatening opioid overdose
    - Use of high dose opioids to overcome antagonistic action of samidorphan

Lybalvi (Olanzapine and samidorphan) package insert. Waltham, MA: Alkermes; May 2021.

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Olanzapine/Samidorphan (Lybalvi™)

- Drug Interactions with samidorphan
  - CYP3A4 inducers (e.g., rifampin)
  - Opioids

Lybalvi (Olanzapine and samidorphan) package insert. Waltham, MA: Alkermes; May 2021.

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Efficacy Results for Change in Weight Over 24 weeks

Treatment group	% Change from Baseline in Body Weight			≥ 10% Body Weight Gain	
	Mean Baseline Weight (kg)	Mean Change from Baseline	Olanzapine-subtracted difference (95% CI)	Patients (%)	Olanzapine-subtracted Risk Difference (95% CI)
Olanzapine/ Samidorphan N = 266	77	4.2	-2.4 (0.39, -0.9)	17.8	-13.7 (-22.8,-4.6)
Olanzapine N = 272	77.5	6.6	NA	29.8	NA

Lybalvi (Olanzapine and samidorphan) package insert. Waltham, MA: Alkermes; May 2021.

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Olanzapine/Samidorphan (Lybalvi™)

- Dosing and Availability
  - 10 mg tablets of samidorphan combined with 5 mg, 10 mg, 15 mg, or 20 mg of olanzapine
  - Once daily dosing
- Cost
  - AWP $1,668 per month

Lybalvi (Olanzapine and samidorphan) package insert. Waltham, MA: Alkermes; May 2021.

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Olanzapine/Samidorphan (Lybalvi™)

- Bottom Line
  - Added to olanzapine to minimize weight gain
  - Efficacy attributed to olanzapine
  - Watch out for concomitant opioid use
- Additional Review
  - Kahn RS, et al. Schizophr Res. 2021;232:45-53.
  - Chaudhary AMD, et al. Cureus. 2019;11:e5139.

Lybalvi (Olanzapine and samidorphan) package insert. Waltham, MA: Alkermes; May 2021.

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Lemborexant (Dayvigo®)

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Lemborexant (Dayvigo®)

- Indication
  - Insomnia, sleep onset, and/or sleep maintenance
- Pharmacology
  - Dual orexin receptor antagonist (Ox1R and Ox2R)
  - Orexin is a neuropeptide involved with arousal and wakefulness
  - Similar to suvorexant (Belsomra®)
    - T ½ 17-19 hours vs. 12 hours for suvorexant

Dayvigo (Lemborexant) package insert. Woodcliff Lake, NJ: Eisai; March 2021.

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Lemborexant (Dayvigo®)

- Contraindications
  - Narcolepsy
- Warnings and Precautions
  - Daytime somnolence
  - Impaired driving ability
  - Alcohol and other CNS depressants
  - Cognitive changes
  - Depression/suicidal ideation
  - No data in severe COPD
  - Sleep paralysis, vivid-disturbing perceptions, and/or cataplexy-like symptoms

Dayvigo (Lemborexant) package insert. Woodcliff Lake, NJ: Eisai; March 2021.

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Adverse Effects from Phase 3 Clinical Trial				
Event	**Zolpidem ER 6.25 mg N = 263**	**Lemborexant 5 mg N = 266**	**Lemborexant 10 mg N = 268**	**Placebo N = 209**
Headache	5.3%	6.4%	4.9%	6.2%
Somnolence	1.5%	4.1%	7.1%	1.9%
Dizziness	3%	1.1%	0.7%	1.9%

Rosenberg R, et al. JAMA Netw Open 2019;2:e1918254.

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Polysomnographic Time to Sleep Onset (Sunrise 1 Trial)				
Time to Sleep Onset	**Lem 5 mg N = 266**	**Lem 10 mg N = 269**	**Zolp 6.25 mg N = 263**	**Placebo N= 208**
Nights 1 & 2 mean (min)	28.3	25.1	31.9	37.4
Mean change from baseline (min)	-16.6	-19.5	-12.6	-6.5
Time to Sleep Onset	**N = 260**	**N = 260**	**N = 250**	**N = 200**
Nights 29 & 30 mean (min)	25.8	22.8	37.1	36
Mean change from baseline (min)	-19.5	-21.5	-7.5	-7.9

Rosenberg R, et al. JAMA Netw Open 2019;2:e1918254.

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Lemborexant (Dayvigo®)

- Dosing
  - 5 mg once nightly immediately before bedtime
  - Must take with at least 7 hours of sleep remaining
  - Increase to max of 10 mg based on response
  - Food may delay time to onset
  - Max of 5 mg if moderate hepatic impairment or on weak CYP3A inhibitors
  - Avoid if on moderate to strong CYP3A inhibitors

Dayvigo (Lemborexant) package insert. Woodcliff Lake, NJ: Eisai; March 2021.

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Lemborexant (Dayvigo®)

- Availability
  - 5 mg and 10 mg tablets
- Cost
  - AWP ~ $350 for 30 tablets
- Controlled substance
  - C-IV

Dayvigo (Lemborexant) package insert. Woodcliff Lake, NJ: Eisai; March 2021.

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Lemborexant (Dayvigo®)

- Bottom Line
  - Another orexin inhibitor
  - No direct comparison to suvorexant
  - Clinical study up to 6 months
  - Lower dose associated with less CNS adverse effects
- Additional review
  - Kishi T, et al. J Psychiatr Res. 2020;128:68-74.

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Ibrexafungerp (Brexafemme®)

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Ibrexafungerp (Brexafemme®)

- Indication
  - Adults with vulvovaginal candidiasis
- Pharmacology
  - Triterpenoid antifungal
  - Inhibits glucan synthase, enzyme involved in cell wall
  - Concentration dependent fungicidal activity

Brexafemme (Ibrexafungerp) package insert. Jersey City, NJ: Scynexis; June 2021.

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Ibrexafungerp (Brexafemme®)

- Clinical and in vitro
  - C. albicans
- In vitro
  - C. auris
  - C. dubliniensis
  - C. glabrata
  - C. guilleirmondii
  - C. keyfr
  - C. krusei
  - C. lusitaniae
  - C. parapsilosis
  - C. tropicalis

Brexafemme (Ibrexafungerp) package insert. Jersey City, NJ: Scynexis; June 2021.

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Ibrexafungerp (Brexafemme®)

- Pharmacokinetics
  - Tmax 4-6 hours
  - T ½ ~ 20 hours
  - Metabolism
    - CYP3A4
  - Excretion
    - 90% feces

Brexafemme (Ibrexafungerp) package insert. Jersey City, NJ: Scynexis; June 2021.

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Ibrexafungerp (Brexafemme®)

- Contraindications
  - Pregnancy (toxicities based on animal data)
- Warnings and Precautions
  - Verify pregnancy status
  - Contraception for 4 days after last dose

Brexafemme (Ibrexafungerp) package insert. Jersey City, NJ: Scynexis; June 2021.

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Ibrexafungerp (Brexafemme®)

- Drug Interactions
  - Strong CYP3A4 inhibitors (e.g., itraconazole and ketoconazole)
    - Dose adjustment required
  - Moderate-strong CYP3A4 inducers (e.g., rifampin, phenytoin, St. John's Wort, and carbamazepine)
    - Avoid use due to significantly decreased ibrexafungerp levels
  - Ibrexafungerp inhibits CYP3A4, P-gp & OATP1B3 transporter
    - Due to short treatment duration effects not clinically significant

Brexafemme (Ibrexafungerp) package insert. Jersey City, NJ: Scynexis; June 2021.

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Adverse Reactions from Clinical Trials		
Reaction	**Ibrexafungerp N = 545**	**Placebo N = 275**
Diarrhea	16.7%	3.3%
Nausea	11.9%	4%
Abdominal pain	11.4%	5.1%
Dizziness	3.3%	2.5%
Vomiting	2%	0.7%

Brexafemme (Ibrexafungerp) package insert. Jersey City, NJ: Scynexis; June 2021.

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Phase 3 Clinical Trial Data				
	Study 1		Study 2	
Outcome*	**Ibrexafungerp N = 190**	**Placebo N = 100**	**Ibrexafungerp N = 189**	**Placebo N = 89**
Clinical Response at TOC	50%	28%	63.5%	44.9%
Negative Culture at TOC	49.5%	19%	58.7%	29.2%
Clinical Response at follow-up†	59.5%	44%	72.5%	49.4%

TOC = test of cure (8-14 days)
†Day 21-29

*All outcomes met statistical significance

Brexafemme (Ibrexafungerp) package insert. Jersey City, NJ: Scynexis; June 2021.

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Ibrexafungerp (Brexafemme®)

- Dosing and Availability
  - 300 mg every 12 hours x 2 doses
  - 150 mg tablets
  - With or without food
- Cost
  - Now available
  - AWP $142.50 per tablet ($570 total)

Brexafemme (Ibrexafungerp) package insert. Jersey City, NJ: Scynexis; June 2021.

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Ibrexafungerp (Brexafemme®)

- Bottom Line
  - Novel antifungal agent
  - No comparison data currently to fluconazole
  - Likely limited use for vulvovaginal candidiasis
  - Off-label potential for highly resistant fungal infections
- Additional Review
  - Ghannoum M, et al. Antibiotics (Basel). 2020;9:539.

Brexafemme (Ibrexafungerp) package insert. Jersey City, NJ: Scynexis; June 2021.

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Aducanumab (Aduhelm™)

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Aducanumab (Aduhelm™)

- Indication
  - Alzheimer's disease; mild cognitive impairment/dementia
  - Accelerated approval based on a reduction in amyloid plaques
- Pharmacology
  - Human immunoglobulin gamma 1 monoclonal antibody
  - Reduces amyloid beta plaques

Aduhelm (aducanumab) package insert. Cambridge, MA: Biogen; June 2021.

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Aducanumab (Aduhelm™)

- Pharmacokinetics
  - T ½ ~ 25 hours
  - Elimination via catabolic pathways
  - No data with hepatic or renal impairment; not expected to impact clearance
- Contraindications
  - None

Aduhelm (aducanumab) package insert. Cambridge, MA: Biogen; June 2021.

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Aducanumab (Aduhelm™)

Warning and Precautions

- Amyloid Related Imaging Abnormalities-edema (ARIA-E)
  - 35% vs. 3% placebo
  - Incidence higher in apolipoprotein E ε4 carriers vs. noncarriers (42% vs. 20%)
  - More common within first 8 doses
- Amyloid Related Imaging Abnormalities-hemosiderin (ARIA-H)
  - 21% vs. 1% placebo
  - Microhemorrhage
  - Superficial siderosis

Symptoms resolved in 88% of cases during observation.

Aduhelm (aducanumab) package insert. Cambridge, MA: Biogen; June 2021.

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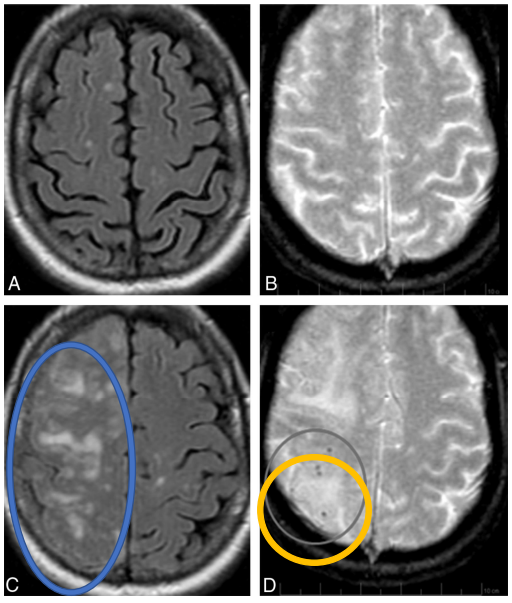
BASELINE



BASELINE

- **ARIA-E**
- **ARIA-H**

Barakos J, et al. AJNR Am J Neuroradiol. 2013 Oct;34(10):1958-65.

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Adverse Reactions from Phase 3 Trials		
	Aducanumab 10 mg/kg N = 1105	**Placebo N = 1087**
ARIA-E	35%	3%
Headache	21%	16%
ARIA-H microhemorrhage	19%	7%
ARIA-H superficial siderosis	15%	2%
Fall	15%	12%
Diarrhea	9%	7%
Altered mental status*	8%	4%

*confusion, delirium, disorientation

Aduhelm (aducanumab) package insert. Cambridge, MA: Biogen; June 2021.

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Aducanumab (Aduhelm™)

- Conflicting data from two identical major trials (EMERGE & ENGAGE)
- Both trials stopped early in March 2019; lack of benefit
  - Clinical Dementia Rating Scale-sum of the boxes (CDR-SB) declined in treatment & placebo groups
- Subsequent sub-analysis of EMERGE trial
  - 22% reduction in rate of cognitive decline based on CDR-SB in the high dose aducanumab group after 78 weeks (p = 0.012)
- No clinical benefit in ENGAGE trial
- Both trials showed reduction in brain β-amyloid levels
  - Debatable clinical significance

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Primary Efficacy Endpoint-Engage Study

CDR-SB at Week 78	High dose Aducanumab (N = 547)	Placebo (N = 548)
Mean baseline	2.51	2.47
Change from baseline	1.35	1.74
Difference from placebo	-0.39 (-22%) P= 0.0120	--

Aduhelm (aducanumab) package insert. Cambridge, MA: Biogen; June 2021.

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Primary Efficacy Endpoint- Clinical Application

- Clinical significance is not compelling for primary endpoint
- Placebo: 2.47 to 4.21 (+1.74)
- Aducanumab: 2.51 to 3.86 (+1.35)

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

Aduhelm (aducanumab) package insert. Cambridge, MA: Biogen; June 2021.

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Aducanumab (Aduhelm™)

Aducanumab Dosing Schedule	
IV Infusion given every 4 weeks	Dose based on actual body weight
Infusion 1 & 2	1 mg/kg
Infusion 3 & 4	3 mg/kg
Infusion 5 & 6	6 mg/kg
Infusion 7 +	10 mg/kg

- MRI monitoring schedule
  - Baseline and prior to 7th and 12th infusion
  - If > 10 new microhemorrhages or > 2 focal areas of superficial siderosis, must see stabilization before treatment is continued

Aduhelm (aducanumab) package insert. Cambridge, MA: Biogen; June 2021.

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Aducanumab (Aduhelm™)

- Dosage Forms
  - 170 mg/1.7ml single dose vial
  - 300 mg/3 ml single dose vial
- Administration
  - Added to 100 ml of normal saline and preferably used immediately
    - May be refrigerated for up to 3 days or stored at room temperature for up to 12 hours
    - Warm to room temperature before administration
  - Use 0.2 or 0.22 micron in-line filter
  - Infuse over 1 hour

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Aducanumab (Aduhelm™)

- Preliminary reports by the Institute for Clinical and Economic Review determined aducanumab is cost-effective at $3,000 to $8,400 per year1
  - Annual WAC ~~$56,000~~ $28,200 based on 77 kg patient
- Medicare Coverage2
  - Using a conservative analysis by Altarum including only drug cost
    - 1.2% of all costs; adds $73 billion in expenditures by 2028 (based on old pricing)

1. The Institute for Clinical and Economic Review https://icer.org/news-insights/press-releases/in-revised-evidence-report-icer-confirms- judgment-that-evidence-is-insufficient-to-demonstrate-net-health-benefit-of-aducanumab-for-patients-with-alzheimers-disease/

2. Miller, G., Turner, A., & Rhyan, C. (C. (2021, June 16). *New Alzheimer's Drug Projected to Increase National Health Expenditures by More Than One Percent*. Altarum. https://altarum.org/news/new-alzheimer-s-drug-projected-increase-national-health-expenditures-more-one-percent#:~:text=New%20Alzheimer%27s%20Drug%20is%20Projected,Altarum.

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Aducanumab (Aduhelm™)

- Bottom Line
  - Highly controversial approval
  - Based on a biomarker vs. mixed clinical improvement
  - On-going data collection will determine future use
    - Company projects it may take until 2030 to complete
- Additional Review
  - Tolar M, et al. Alzheimer's Res Ther. 2020;12:95.

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Tirbanibulin (Klisyri®)

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CEimpact

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Tirbanibulin (Klisyri®)

- Indication
  - Topical treatment of actinic keratosis on face or scalp
- Pharmacology
  - Microtubule inhibitor
  - Exact mechanism unknown for actinic keratosis

Klisyri (tirbanibulin) package insert. Exton, PA: Almirall; Dec 2020.

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Tirbanibulin (Klisyri®)

- Pharmacokinetics
  - Systemic absorption is minimal
- Contraindications
  - None
- Warnings and Precautions
  - Avoid eye contact (irritating)
  - Local skin reactions
- Drug Interactions
  - No studies; none expected

Klisyri (tirbanibulin) package insert. Exton, PA: Almirall; Dec 2020.

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Local Skin Reactions from Phase 3 Trials						
Reaction	**Tirbanibulin N = 353**			**Placebo N = 349**		
	Mild	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Erythema	22%	63%	6%	28%	6%	0
Flaking/Scaling	26%	47%	9%	25%	9%	< 1%
Crusting	30%	14%	2%	9%	2%	0
Swelling	29%	9%	< 1%	4%	< 1%	0
Vesicles/Pustules	7%	< 1%	< 1%	< 1%	0	0
Erosion/Ulcers	9%	3%	0	3%	0	0

Blauvelt A, et al. N Engl J Med 2021;384:512-20.

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Phase 3 Clinical Trial Data						
	Study 1			Study 2		
Variable	Tirbanibulin N = 175	Placebo N = 176	Difference (95% CI)	Tirbanibulin N = 178	Placebo N = 173	Difference (95% CI)
100% clearance*	44%	5%	40 (32-47)	54%	13%	42 (33-51)
≥ 75% clearance	68%	16%	52 (43-60)	76%	20%	57 (48-65)

*Primary outcome

Blauvelt A, et al. N Engl J Med 2021;384:512-20.

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Tirbanibulin (Klisyri®)

- Dosing
  - Apply once daily for 5 days
  - Avoid areas near mouth and lips
  - Avoid washing/touching area for 8 hours after treatment
  - Wash hands after applying
- Availability and Cost
  - Single dose packets with 250 mg of 1% ointment
  - AWP = $1,188 for 5-day course

Klisyri (tirbanibulin) package insert. Exton, PA: Almirall; Dec 2020.

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Tirbanibulin (Klisyri®)

- Bottom Line
  - Well-tolerated, effective agent for actinic keratosis
  - No direct comparator trials to other agents
  - Convenient once daily dosing x 5 days
  - Expensive; patient assistance card available
- Additional Review
  - Blauvelt A, et al. N Engl J Med 2021;384:512-20.

Klisyri (tirbanibulin) package insert. Exton, PA: Almirall; Dec 2020.

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Semaglutide (Wegovy™)

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Semaglutide (Wegovy™)

- Indication
  - Adjunct to diet and exercise for weight management
    - BMI > 30 kg/m2
    - BMI > 27 kg/m2 with at least one weight-related condition (e.g., hypertension, T2DM, and dyslipidemia)
- Pharmacology
  - Glucagon-like peptide-1 agonist
  - GLP-1 receptor involved in regulation of food intake

Wegovy (Semaglutide) package insert. Plainsboro, NJ: Novo Nordisk; June 2021.

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Semaglutide (Wegovy™)

- Pharmacokinetics
  - Max levels in 1-3 days post-dose
  - Similar absorption from abdomen, thigh, or upper arm
  - T ½ ~ 7 days
  - Metabolism through protein breakdown

Wegovy PI 2021.

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Adverse Reactions		
Reaction	**Semaglutide N = 1261**	**Placebo N = 1261**
Nausea	44%	16%
Diarrhea	30%	16%
Vomiting	24%	6%
Constipation	24%	11%
Abdominal Pain	20%	10%
Headache	14%	10%
Hypoglycemia in T2DM	6%	2%

Wegovy (Semaglutide) package insert. Plainsboro, NJ: Novo Nordisk; June 2021.

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Summary of Phase 3 Clinical Trials Change in Weight at week 68						
	Study 1		**Study 2**		**Study 3**	
	Semaglutide N = 1306	**Placebo N = 655**	**Semaglutide N = 404**	**Placebo N = 403**	**Semaglutide N = 407**	**Placebo N = 204**
Baseline	105.4 kg	105.2 kg	99.9 kg	100.5 kg	106.9 kg	103.7 kg
% Change from baseline	-14.85	-2.41	-9.6	-3.4	-16	-5.7
% difference from placebo (95% CI)	-12.44 (-13.37, -11.51)		-6.2 (-7.3, -5.2)		-10.3 (-12, -8.6)	

Wilding JPH, et al. N Engl J Med 2021; 384:989-1002.
Wegovy (Semaglutide) package insert. Plainsboro, NJ: Novo Nordisk; June 2021.
Wadden TA, et al. JAMA 2021;325;1403-13.

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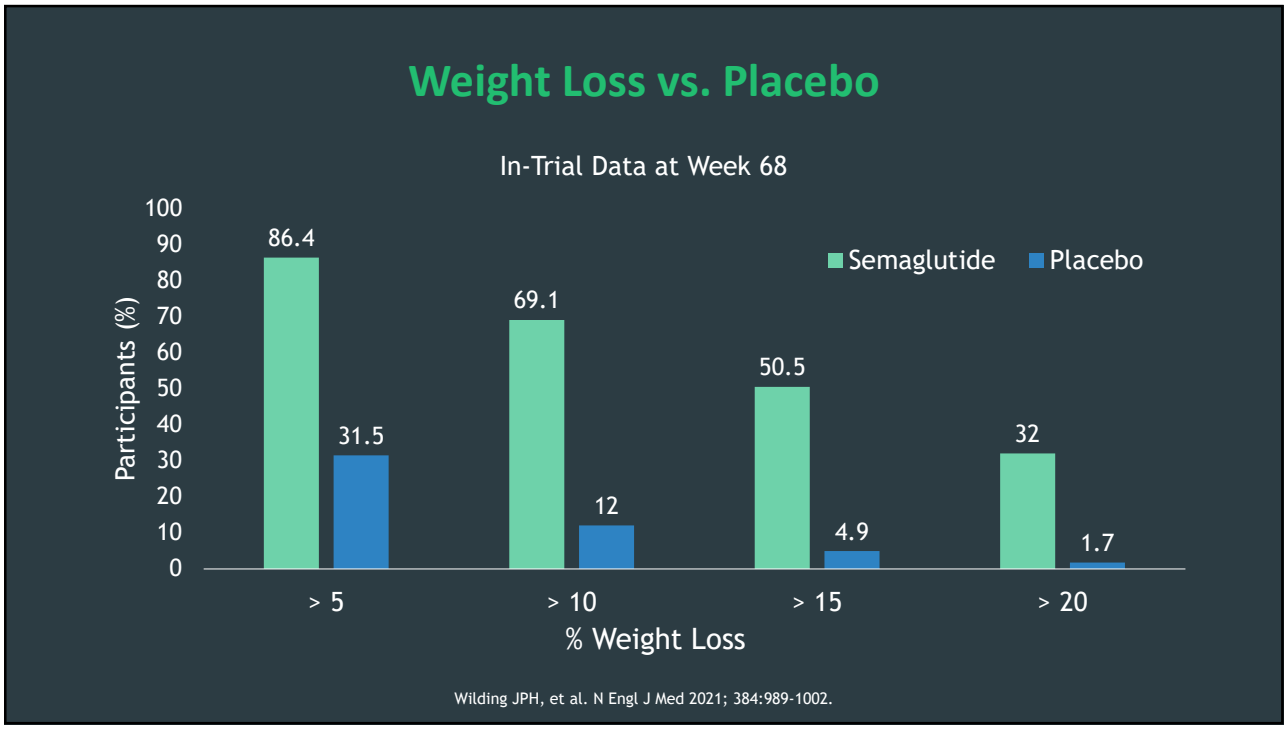

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Semaglutide (Wegovy™)

- If a dose is not tolerated, may delay escalation for 4 weeks
- May use the 1.7 mg dose for an additional 4 weeks
- If 2.4 mg dose is not tolerated, then discontinue

Dose Escalation Schedule	
Weeks	Weekly Dose
1-4	0.25 mg
5-8	0.5 mg
9-12	1 mg
13-16	1.7 mg
17 +	2.4 mg

Wegovy PI 2021.

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Semaglutide (Wegovy™)

- AWP ~ $400 per week
- Storage
  - Refrigerator (do NOT freeze)
  - Room temperature up to 28 days
- Dosage Forms
  - 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, and 2.4 mg auto-injector
  - Discard after use

Wegovy (Semaglutide) package insert. Plainsboro, NJ: Novo Nordisk; June 2021.

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Supply Challenges for Semaglutide (Wegovy™)

- "Since Wegovy® was made available in the US, the requests for this medicine have been unlike anything we could have anticipated. We made progress to meet this unprecedented demand and had projected Wegovy® supply would be back on track in early 2022. Unfortunately, there will be a further delay."
- "We have been informed that the manufacturer Novo Nordisk contracts with to fill Wegovy® pens for the US market has temporarily stopped manufacturing and deliveries due to issues related to Good Manufacturing Practices……we currently expect all Wegovy® doses to be available again in the second half of 2022."

Novo Nordisk Press Release, December, 17th 2021

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Semaglutide (Wegovy™)

- Bottom Line
  - Effective as an adjunct to diet and exercise for weight loss
  - Patients lost 6-12% more weight vs. placebo at 1 year (~ 15-30 pounds)
  - Slow titration due to GI side effects (e.g., nausea)
  - May be used in patients without diabetes
- Additional Review
  - Christou GA, et al. Obes Rev 2019;20:805-815.

Wegovy (Semaglutide) package insert. Plainsboro, NJ: Novo Nordisk; June 2021.

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Finerenone (Kerendia®)

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Finerenone (Kerendia®)

- Indication
  - Adult patients with chronic kidney disease associated with Type 2 diabetes mellitus
  - Reduces risk of renal disease and cardiovascular death, non-fatal myocardial infarction and heart failure hospitalization
- Pharmacology
  - Non-steroidal mineralocorticoid receptor antagonist
  - Blocks sodium reabsorption and overaction of mineralocorticoid receptors in kidney, heart, and blood vessels
    - Reduces fibrosis and inflammation

Kerendia (Finerenone) package insert. Whippany, NJ: Bayer; July 2021.

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Finerenone (Kerendia®)

- Pharmacokinetics
  - T ½ 2-3 hours
  - Metabolized by CYP3A4 (~ 90%) and CYP2C8 (~ 10%)
    - Inactive metabolites
    - Moderate hepatic impairment (Child Pugh B) = 38% increase in AUC
    - Not studied in severe hepatic impairment (Child Pugh C)
  - Metabolites excreted via kidneys

Kerendia (Finerenone) package insert. Whippany, NJ: Bayer; July 2021.

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Finerenone (Kerendia®)

- Contraindications
  - Strong CYP3A4 inhibitors
  - Adrenal insufficiency
- Warnings and Precautions
  - Hyperkalemia
    - Do not use if serum potassium is > 5 mEq/L

Kerendia (Finerenone) package insert. Whippany, NJ: Bayer; July 2021.

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Finerenone (Kerendia®)

- Drug Interactions
  - Avoid strong CYP3A4 inhibitors (> 400% AUC increase)
    - Itraconazole, Grapefruit juice
  - Moderate-to-weak CYP3A4 inhibitors
    - May increase risk of adverse reactions
  - Avoid strong CYP3A4 inducers (90% AUC decrease)
  - Potassium supplements
    - Monitor levels more frequently

Kerendia (Finerenone) package insert. Whippany, NJ: Bayer; July 2021.

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Finerenone Adverse Reactions

	Finerenone N = 2827	Placebo N = 2831
Hyperkalemia	18.3%	9%
Hospitalization due to Hyperkalemia	1.4%	0.3%
Hypotension	4.8%	3.4%
Hyponatremia	1.4%	0.7%

Kerendia (Finerenone) package insert. Whippany, NJ: Bayer; July 2021.
Bakris GL, et al. N Engl J Med 383; 2219-29.

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FIDELIO-DKD Clinical Trial Results

	Finerenone N = 2833	Placebo N = 2841	HR (95% CI)
Primary composite outcome	17.8%	21.1%	0.82 (0.73-0.93)
Kidney failure*	7.3%	8.3%	0.087 (0.72-1.05)
Sustained eGFR declined of ≥ 40%*	16.9%	20.3%	0.81 (0.72-0.92)
Renal death*	<0.1%	<0.1%	NR
Secondary CV composite outcome	13%	14.8%	0.86 (0.75-0.99)

*Component of composite outcome

Kerendia (Finerenone) package insert. Whippany, NJ: Bayer; July 2021.
Bakris GL, et al. N Engl J Med 2020; 383: 2219-29.

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FIGARO-DKD Clinical Trial Results			
	Finerenone N = 3686	**Placebo N = 3666**	**HR (95% CI)**
Primary composite outcome	12.4%	14.2%	0.87 (0.76-0.98)
Death from CV causes*	5.3%	5.8%	0.09 (0.74-1.09)
Nonfatal MI*	2.8%	2.8%	0.99 (0.76-1.31)
Nonfatal stroke*	2.9%	3%	0.97 (0.74-1.26)
Heart failure hospitalization*	3.2%	4.4%	0.71 (0.56-0.90)

*Component of composite outcome

Pitt B, et al. N Engl J Med 2021 385; 2252-2263.

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Finerenone (Kerendia®)

Starting Dose based on Renal Function	
eGFR (ml/min/1.73m²)	**Starting Dose**
≥ 60	20 mg once daily
25-60	10 mg once daily
< 25	Not recommended

Dose Titration Schedule based on Potassium Level			
Potassium level checked every 4 weeks		**Current Dose**	
		10 mg daily	20 mg daily
Potassium Level (mEq/L)	≤ 4.8	20 mg daily	20 mg daily
	4.9-5.5	10 mg daily	20 mg daily
	> 5.5	Hold & may restart at 10 mg when K ≤ 5	Hold & restart at 10 mg when K ≤ 5

Kerendia PI 2021.

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Finerenone (Kerendia®)

- Bottom Line
  - Non-steroidal mineralocorticoid receptor antagonist
  - Slows renal decline in T2DM patients
  - Favorable cardiovascular outcomes
  - Monitor potassium
- Additional Review
  - Rico-Mesa, et al. Curr Cardiol Rep. 2020;22:140.

Kerendia (Finerenone) package insert. Whippany, NJ: Bayer; July 2021.

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Brincidofovir (Tembexa®)

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Brincidofovir (Tembexa®)

- Indication
  - Smallpox
  - Concerns of potential bioterrorism
- Pharmacology
  - Prodrug converted to cidofovir intracellularly
  - Inhibits orthopoxvirus DNA polymerase thus blocking viral DNA synthesis

Tembexa (brincidofovir) package insert. Tredegar, UK: Penn Pharmaceutical Services; June 2021.

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Brincidofovir (Tembexa®)

- Clinical efficacy
  - Based on mouse and rabbit data
  - 80-90% survival if started on day 4 after inoculation
  - 34-69% survival if started on day 6 after inoculation
- Bottom Line
  - We have a treatment for smallpox
  - Hope we NEVER need it!

Tembexa (brincidofovir) package insert. Tredegar, UK: Penn Pharmaceutical Services; June 2021.

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Aspirin (Vazalore™)

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Aspirin (Vazalore™)

- New liquid-filled aspirin 81 mg and 325 mg capsule
- Lipid-based formulation
- Designed for fast-onset and improved gastrointestinal tolerability

Vazalore (Aspirin) Label. PLx Pharma: Houston, TX.

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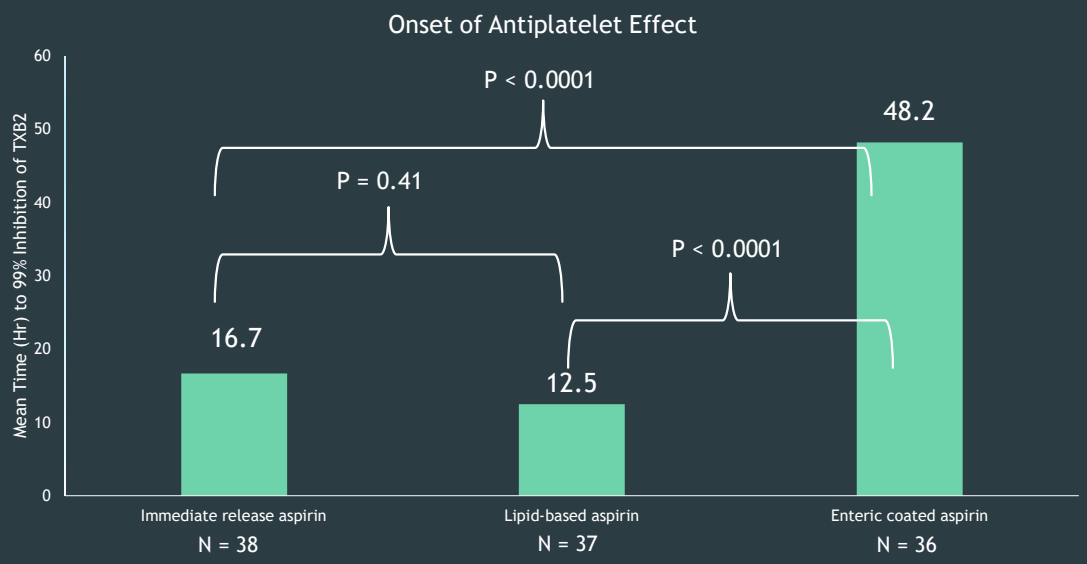
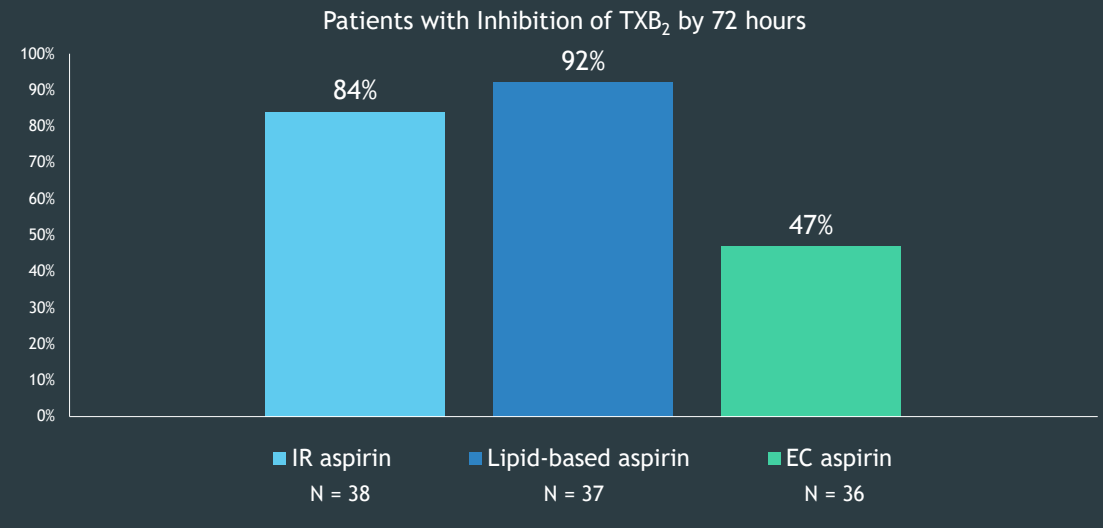
Onset of Antiplatelet Effect in Type 2 DM



Bhatt DL, et al. J Am Coll Cardiol 2017;69:603-12.

97

Platelet Inhibition at 72 Hours



Bhatt DL, et al. J Am Coll Cardiol 2017;69:603-12.

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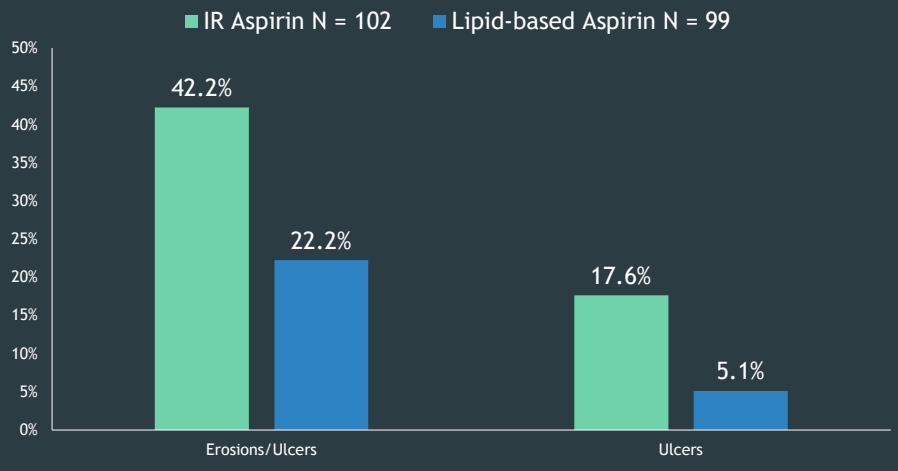
Gastroduodenal Injury



Cryer B, et al. Am J Gastroenterol 2011;106:272-7.

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Aspirin (Vazalore™)

- Bottom Line
  - Quick onset of platelet inhibition
  - GI side effects favorable based on small trial
  - No clinical data based on cardiovascular outcomes
  - Cost ~$25 for 30 capsules
- Additional Review
  - Bhatt DL, et al. J Am Coll Cardiol 2017;69:603-12.
  - Cryer B, et al. Am J Gastroenterol 2011;106:272-7.

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Sodium sulfate, magnesium sulfate & potassium chloride (Sutab®)

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CEimpact

Sodium sulfate, magnesium sulfate & potassium chloride (Sutab®)

- Indication
  - Colonoscopy preparation
- Pharmacology
  - Osmotic laxative
  - Similar to Suprep® (contains potassium sulfate)

Sutab (sodium sulfate, magnesium sulfate, & potassium chloride) package insert. Holbrook, MA: Braintree; Nov 2020.

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Outcome	Sutab® N = 281	PEG 3350 ELS N = 271
Clinical Success	92%*	89%
≥ 1 GI adverse effect	71%	34%
Nausea	52%	18%
Abdominal distention	34%	15%
Vomiting	16%	2%
Upper abdominal pain	23%	13%

*Non-inferior

Sutab (sodium sulfate, magnesium sulfate, & potassium chloride) package insert. Holbrook, MA: Braintree; Nov 2020.

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Sodium sulfate, magnesium sulfate & potassium chloride (Sutab®)

- Dose #1 (evening prior to colonoscopy)
  - 12 tablets with 16 oz of water over 15-20 min
  - 1 hour later drink 16 oz of water over 30 minutes
  - 30 minutes later drink 16 oz of water over 30 minutes
- Dose #2 (morning of colonoscopy)
  - Repeat above regimen
- Complete dose #2 at least 2 hours before colonoscopy
- Total volume = ~ 2840 ml
- Cost ~ $150 for 24 tablets

Sutab (sodium sulfate, magnesium sulfate, & potassium chloride) package insert. Holbrook, MA: Braintree; Nov 2020.

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Dabigatran (Pradaxa®)

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Dabigatran (Pradaxa®)

- New pediatric indication
  - Treatment of VTE in ages 3 months to 18 years old who were treated with a parenteral agent for at least 5 days
    - Capsule formulation approved in ages 8 and older
    - New oral pellet formulation for ages 3 months to 12 years
- Similar efficacy compared to warfarin, enoxaparin, or fondaparinux

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Dabigatran Pediatric Capsule Dosing Ages 8-17 Years	
Weight	**Dose**
11 to ≤ 26 kg	75 mg BID
16 to ≤ 26 kg	110 mg BID
26 to ≤ 41 kg	150 mg BID
41 to ≤ 61 kg	185 mg BID
61 kg to ≤ 81 kg	220 mg BID
≥ 81 kg	260 mg BID

Pradaxa (Dabigatran) package insert. Ridgefield, CT: Boehringer Ingelheim; June 2021.

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Dabigatran (Pradaxa®)

- Pellet Formulation for ages 3 months to 12 years old
  - 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, and 150 mg packets
- Dose based on age and weight
  - See labeling
  - Max dose of 260 mg BID for ages 2-12 years ≥ 41 kg
- Administration
  - Mix with soft foods (e.g., applesauce)
  - May add to 1-2 ounces of apple juice

Pradaxa (Dabigatran) package insert. Ridgefield, CT: Boehringer Ingelheim; June 2021.

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Rivaroxaban (Xarelto®)

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Rivaroxaban (Xarelto®)

- New pediatric indication
  - Treatment of VTE from birth to 18 years old who were treated with a parenteral agent for at least 5 days
- Similar efficacy compared to warfarin, enoxaparin, or fondaparinux

Xarelto (Rivaroxaban) package insert. Titusville, NJ: Janssen; Dec 2021.

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Rivaroxaban Dosing for Pediatric VTE Treatment					
Dosage Form	**Body Weight**	**Dosage**			**Total Daily Dose**
		Once daily	**Twice daily**	**Three times daily**	
Oral Suspension	2.6 kg to 2.9 kg			0.8 mg	2.4 mg
	3 kg to 3.9 kg			0.9 mg	2.7 mg
	4 kg to 4.9 kg			1.4 mg	4.2 mg
	5 kg to 6.9 kg			1.6 mg	4.8 mg
	7 kg to 7.9 kg			1.8 mg	5.4 mg
	8 kg to 8.9 kg			2.4 mg	7.2 mg
	9 kg to 9.9 kg			2.8 mg	8.4 mg
	10 kg to 11.9 kg			3 mg	9 mg
	12 kg to 29.9 kg		5 mg		10 mg
Oral Suspension or Tablets	30 kg to 49.9 kg	15 mg			15 mg
	≥ 50 kg	20 mg			20 mg

Xarelto (Rivaroxaban) package insert. Titusville, NJ: Janssen; Dec 2021.

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Rivaroxaban (Xarelto®)

- Pediatric dosing
  - Tablets (15 mg or 20 mg)
    - 2.5 mg tablets not recommended
  - Suspension 155 mg bottle (1mg/ml)
  - Take all doses with food!

Xarelto (Rivaroxaban) package insert. Titusville, NJ: Janssen; Dec 2021.

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Questions?

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