

## Idaho Society of Health-System Pharmacists

# New Drug Update: Not All That Glitters is Gold

Idaho Society of Health-System Pharmacists 2018 Fall Meeting  
Sun Valley, Idaho | September 30, 2018

### PRESENTERS:

#### Boise VA Medical Center

#### *PGY2 Ambulatory Care Residents:*

Audra Wilson, PharmD; Kat Liu, PharmD;  
Nitz Bankova, PharmD

#### Idaho State University

#### *PGY2 Pharmacotherapy Resident:*

Kailee Morton, PharmD

#### *Infectious Disease Pharmacy Fellow:*

Benjamin Pontefract, PharmD

#### St. Luke's Health System

#### *PGY2 Oncology Pharmacy Residents:*

Andrew Li, PharmD; Amanda Wright,  
PharmD; Bryce Benson, PharmD

#### *PGY2 Mental Health Pharmacy Resident:*

Samantha Patton, PharmD



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## Disclosures

*No conflicts of interest to disclose*

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## Learning Objectives

- Describe clinical scenarios where newly approved medications are beneficial.
- Compare newly approved medications with current standards of care.
- Identify investigational new drugs and their potential clinical applications.



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## Overview of Topics

- Infectious Disease
- Ambulatory Care
  - Diabetes Mellitus
  - Women's Health
- Anticoagulation
- Pain Management
- Oncology
  - Acute Myeloid Leukemia (AML)



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## Infectious Disease:



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## Plazomicin (Zemdri®): Overview

- Systemic antibiotic in the aminoglycoside family
- **MoA:** disrupts the 30s ribosome to prevent protein synthesis
  - Concentration dependent bactericidal activity
- Approved to treat **UTIs** caused by *E. coli*, *K. pneumoniae*, *Proteus spp*, and *Enterobacter cloacae*

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## Aminoglycoside Shortcomings

### Toxicities

- Nephrotoxicity
- Ototoxicity
- Therapeutic drug monitoring

### Resistance

- Decreased cell permeability
- Altered ribosome binding sites
- AMG-modifying enzymes (AME)

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## Plazomicin: Efficacy

- Study 009:
  - RCT comparing plazomicin IV to meropenem IV for cUTI caused by enterobactereceae
  - **Plazomicin group was non-inferior to meropenem group**
- Study 007:
  - RCT comparing plazomicin IV to polymyxin E IV for BSI cause by carbapenem-resistant Enterobacteriaceae (CRE)
  - **Plazomicin was associated with less mortality compared to polymyxin E**

Connolly L, Achaogen, Inc. Clinicaltrials.gov: 2016; NCT02486627.  
Connolly L, Achaogen, Inc. Clinicaltrials.gov: 2016; NCT01970371.

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## Plazomicin: Toxicity

- **Nephrotoxicity:**
  - Slightly higher incidence compared to meropenem (rare)
    - Risk increased with CrCl <60 mL/min and elevated Cmin early in therapy
  - Less nephrotoxicity than polymyxin E (39 patients)
- **Ototoxicity**
  - Reported in ~2% of patients in phase 1 and 2 studies
    - Risk in other aminoglycosides is not well documented

Achaogen, Inc. Plazomicin antimicrobial drugs advisory committee presentation.  
<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM607643.pdf> Accessed 8/13/17

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## Plazomicin: Dosing

Estimated CrCl	Recommended Dosage	Dosing Interval
>60 mL/min	15 mg/kg	q24hr
30 – 60 mL/min	10 mg/kg	q24hr
15 – 30 mL/min	10 mg/kg	q48hr
<15 mL/min or HD	Not studied	Not studied

- **Duration:**
  - cUTI: 4-7 days
  - BSI: 7-14 days
- **Monitoring:**
  - cUTI: trough-based approach using 1 sample; desired trough <3 mcg/mL
  - BSI: AUC-based approach using 2 samples

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## Plazomicin: Cost

<b>Gentamicin</b>	<b>Meropenem</b>
\$140/treatment course	\$840/treatment course
 <b>Plazomicin</b> \$640/treatment course	

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## Plazomicin: Niche

- Consider using plazomicin in patients with **MDRO organisms with resistance** to other aminoglycosides
  - Structural modifications allow activity in the presence of most aminoglycoside modifying enzymes (AMEs)

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## Plazomicin: Summary

- Plazomicin is an effective option in the treatment cUTI caused by MDRO Enterobacteriaceae
- Plazomicin likely has less nephrotoxicity than other aminoglycosides but no head to head trials exist
  - Phase 2 trials showed nephrotoxicity of 6% if CrCl >60 and 14% if CrCl ≤60 with plazomicin
  - Studies report 10-58% nephrotoxicity with gentamicin depending on patient population
- Plazomicin's risk of ototoxicity is unclear but likely similar to other aminoglycosides
- Resistance to plazomicin has already been described
  - Subpopulations of enterobacteriaceae in Europe possess a inherently resistant 16S rRNA methyltransferase (rare in US)

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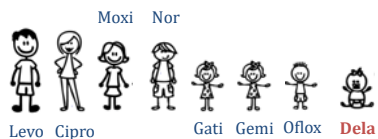
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## An Addition to the Family



Kailee Morton, PharmD

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## Delafloxacin (Baxdela®): Overview

Approved June 2017

- Systemic **anionic** fluoroquinolone
  - IV and PO dosage forms
- MoA: Directly inhibits DNA synthesis by inhibiting the actions of DNA gyrase and topoisomerase IV
  - Bactericidal; concentration dependent (AUC<sub>24</sub>/MIC)
- Indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI)
  - Gram positive – including MRSA
  - Gram negative bacteria

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## Fluoroquinolone Shortcomings

### Class Adverse Effects

- Tendinitis, tendon rupture
- CNS effects
- QTc interval prolongation
- Toxin mediated C. difficile colitis

### Resistance Mechanisms

- DNA gyrase or topoisomerase targets
- Efflux pumps or diffusion channels
- Plasmid-mediated resistance can occur

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## Delafloxacin: Unlike the Others?

### Spectrum of Activity

Organisms	Coverage?
Gram Positive • <i>Staph, Strep</i>	Active + MRSA coverage
Gram Negative	Active Less activity vs. <i>P. aeruginosa</i> *
Anaerobic Gram +/-	Active ( <i>Peptostreptococcus sp., Bacteroides fragilis</i> )
Atypical	<i>Legionella pneumophila, Mycobacterium tuberculosis</i>

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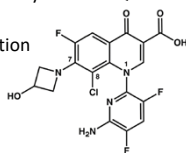
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## Delafloxacin: Unlike the Others?

- Weakly acidic = enhanced activity in inflammatory cells, biofilm-associated infections, abscesses, and skin and urinary infections
- Targets **both** DNA gyrase and topoisomerase IV
- Currently no photosensitivity or clinically relevant QT prolongation shown in trials
- Fewer DDIs with mild CYP3A4 induction
  - No relevant drug-drug interactions
- Oral absorption: 59%




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## Efficacy – 2 Phase III Trials

	Trial 1: (n=660)	Trial 2: (n=850)
Type of Trial	Multicenter, randomized, double-blind, non-inferiority studies	
Comparators	Delafloxacin 300mg IV BID vs. Vancomycin 15mg/kg IV BID + aztreonam 2g IV BID For 5-14 days	
Primary Endpoint	≥ 20% reduction in lesion size at 48 - 72hr	
Methods	Delafloxacin IV → PO after 6 doses, aztreonam was discontinued if warranted	

Charles JK. US Food and Drug Administration; 2017. Pullman, et al. J Antimicrob Chemother 2017; 72(12):3471-3480.

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## Efficacy cont.

Table 7 Clinical Response at 48–72 hours\* in the ITT Population with ABSSSI in Trial 1 and Trial 2

Trial	BANDELA (300 mg IV)	Vancomycin 15 mg/kg + Aztreonam	Treatment Difference† (2-sided 95% CI)
<b>Trial 1</b>			
Total n	331	329	
Responder, n (%)	259 (78.2%)	266 (80.9%)	-2.6 (-8.8, 3.6)
	BANDELA (300 mg IV and 450 mg oral)	Vancomycin 15 mg/kg + Aztreonam	
<b>Trial 2</b>			
Total N	423	427	
Responder, n/N (%)	354 (83.7%)	344 (80.6%)	3.1 (-2.0, 8.3)

CI = Confidence Interval, ITT = Intent to Treat and includes all randomized patients

**Conclusions** Delafloxacin was non-inferior to vancomycin + aztreonam for the primary end-point

BANDELA™ (delafloxacin) [package insert], Lincolnshire, Illinois, USA, Melinta Therapeutics, Inc. 2017.

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## Safety

### Most Common

- Nausea 8%
- Diarrhea 8%
- Vomiting
- Headache 3%
- Transaminase elevations
- Chelation with multivalent cations

### Severe

- Tendinitis
- CNS effects: considered rare
- *C. difficile*-associated diarrhea
- Peripheral neuropathy

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## Dosing Information

- Adults
  - 300mg IV Q12H [infuse over 1 hour]
  - 450mg PO Q12H
  - Duration 5-14 days ; recommend changing from IV → PO during treatment course

Renal Adjustment	Oral	IV
eGFR 30 – 89	No dosage adjustment	300 mg IV Q12H
eGFR 15 – 29	No dosage adjustment	200 mg IV Q12H OR 200 mg IV Q12H → 450 mg po Q12H
eGFR < 15, ESRD, hemodialysis	Not recommended	Not recommended

BAXDELA™ (delafloxacin) [package insert]. Lincolnshire, Illinois, USA. Melinta Therapeutics, Inc. 2017.

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## Cost

	Oral	IV
	Per unit 450mg	Per unit 300mg
	\$81	\$159
Delafloxacin	10 day course \$1,620	3 - 10 day course \$954 - \$3,180
	Per unit 500 mg	Per unit 400 mg/200mL
	\$5	\$0.15
Ciprofloxacin	10 day course \$100	3 - 10 day course \$0.90 - \$3
	Per unit 750mg	Per unit 750mg/150mL
	\$36.12	\$0.10
Levofloxacin	10 day course \$361.20	3-10 day course \$0.30 - \$1

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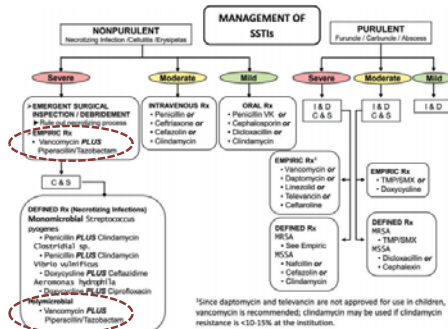
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## Delafloxacin's Niche




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## Summary

- Approved for ABSSSI
- Enhanced potency and intracellular penetration under acidic conditions
- Available in IV and PO forms
  - Ability to convert patients to oral dosing when appropriate
  - Bioavailability is 59% orally
- Enhanced MRSA coverage
  - ONLY FQ recommended for MRSA skin and soft tissue infections
- Broad spectrum of activity includes gram-negative bacteria including *E. coli* and *K. pneumoniae*
- **Beware of inappropriate use of this broad spectrum agent (MRSA & *Pseudomonas* coverage are usually not needed for SSTIs)**

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## ID Pipeline Drugs

- Cefiderocol – novel cephalosporin with efflux pump resistance, porin mutation resistance, and serine and metallo- $\beta$ -lactamase resistance
- lclaprim – selective inhibitor of bacterial enzyme dihydrofolate reductase (DHFR). It retains activity against trimethoprim-resistant DHFR and is thought to be 20-fold more potent than trimethoprim
- Murepavidin – novel antibiotic that is selective for the outer membrane proteins of *P. aeruginosa*. Appears effective against carbapenem-producing and polymyxin E-resistant *P. aeruginosa*

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## Quiz Question!

A 88 yo M has been in the ICU for the previous 6 days due to a snowboarding accident requiring intubation and vasopressor therapy. Two nights ago, he spiked a fever of 101.1°F and has been visibly more agitated. Urine cultures are growing MDRO *E. coli*, notably resistant to ciprofloxacin, tigecycline, meropenem, and amikacin. Blood culture are currently no growth. The team decides to start the patient on plazomicin and asks you for advice since none of them have used it before. How should you guide them?

- A. Plazomicin does not need renal dose adjustments
- B. We should treat the patient for a minimum of 14 days since this is a MDRO
- C. We do not need to confirm susceptibility with microbiology
- D. We will need to obtain trough levels

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# QUESTIONS?



Image credit: [https://blogs.bible.org/beatprints/sui\\_cilberti/asking\\_questions\\_that\\_change\\_lives](https://blogs.bible.org/beatprints/sui_cilberti/asking_questions_that_change_lives)

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## Ambulatory Care: What's New?

# Lots of Diabetes!



Kat Liu, PharmD

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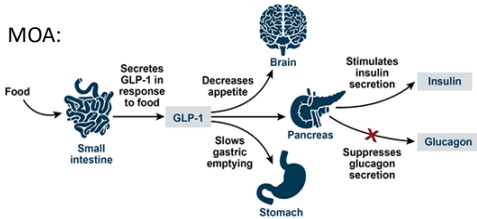
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## GLP-1 Agonist Overview:

- Newly approved:
  - Semaglutide (Ozempic®): 2017
  - Lixisenatide (Adlyxin®): 2016
- MOA:

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graph LR; Food --> SI[Small intestine]; SI -- "Secretes GLP-1 in response to food" --> GLP-1; GLP-1 -- "Decreases appetite" --> Brain; GLP-1 -- "Slows gastric emptying" --> Stomach; GLP-1 -- "Stimulates insulin secretion" --> Pancreas; GLP-1 -- "Suppresses glucagon secretion" --> Pancreas; Pancreas --> Insulin; Pancreas --> Glucagon;
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Meier JJ. Nat Rev Endocrinol. 2012;8:728-742.

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## GLP-1 Agonist Overview:

- Newly approved:
  - Semaglutide (Ozempic®): 2017
  - Lixisenatide (Adlyxin®): 2016
  - For treatment of type 2 DM
- Same considerations:
  - Avoid: h/o pancreatitis or thyroid C-cell tumors

Package insert: Semaglutide. Novo Nordisk. 2017.  
 Package insert: ADLYXIN. Sanofi-aventis. 2016.

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## Efficacy & Safety: Phase III Trials

	Semaglutide	Lixisenatide
<b>Average HbA1c ↓</b>	1.5 – 1.9%	0.8 – 0.9%
<b>With insulin</b>	1.2 – 1.6%	0.6%
<b>Average weight ↓</b>	8.2 lbs – 10 lbs	4 lbs
<b>ADEs</b>	N, diarrhea ↑ amylase, lipase ↑ retinopathy (?)	N/V, diarrhea Antibody development
<b>Hypoglycemia</b>	6 – 8%	2 – 5%

Lancet Diabetes Endocrinol. 2017 May;5(5):355-366  
 Lancet Diabetes Endocrinol. 2017 Apr;5(4):251-260.  
 Diabetes Care. 2013 Sep; 36(9): 2543-2550.

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## Efficacy & Safety: MACE

**SUSTAIN-6**

- RCT with duration of 104 weeks
- Semaglutide 0.5 mg or 1 mg vs. placebo
- Patients with baseline CVD, CKD or both

**Primary outcome:** Composite outcome of CV death, MI or stroke

- Semaglutide (6.6%) vs. placebo (8.9%) Noninferiority

**Secondary outcomes:**

- Less stroke with semaglutide: semaglutide (1.6%) vs. placebo (2.7%)
- No difference in CV death or MI
- More retinopathy complications: semaglutide (3%) vs. placebo (1.8%)  
 ↑ retinopathy risk?

N Eng J Med. 2016; 375:1834-1844.

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## Efficacy & Safety: MACE

<b>ELIXA</b>	<ul style="list-style-type: none"> <li>RCT with duration of ~25 months</li> <li><b>Lixisenatide 10 mcg daily (up to 20 mcg)</b></li> <li>Patients with recent ACS</li> </ul>
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**Primary outcome:** Composite outcome of CV death, MI, stroke or hospitalization for unstable angina

- Lixisenatide (13.4%) vs. placebo (13.2%) Noninferiority  
No superiority

**Secondary outcomes and safety:**

- No difference in individual components of the primary outcome or adverse events

N Engl J Med. 2015; 373:2247-2257.

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## Dosing & Administration

	Semaglutide	Lixisenatide
<b>Formulation</b>	Pen-injector (Subcutaneous injection)	Pen-injector (Subcutaneous injection)
<b>Dosing</b>	0.25 mg Q week x 4 weeks*, then ↑ to 0.5 mg daily x 4 weeks (max dose 1 mg) *Not effective for glycemic control	10 mcg daily x 14 days, then ↑ to 20 mcg daily
<b>Adjustments</b>	None	Renal: eGFR 15 – 29 ml/min: monitor for ↑ GI ADEs eGFR < 15 ml/min: avoid
<b>Administration</b>	Any time of the day (same day each week)	Give within 1 hour before 1 <sup>st</sup> meal
<b>Technique</b>	Rotation injection sites (abdomen, thigh, upper arm)	

Package insert: Semaglutide, Novo Nordisk, 2017.  
Package insert: ADLYXIN, Sanofi-aventis, 2016.

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## Summary of GLP-1 agonists

GLP-1 Agonist	Route	Dosing	Renal adjustment	CVD safety
Lixisenatide	Subcutaneous injection	Daily	✓	✓
Liraglutide		Daily	-	✓*
Exenatide		BID Q week	✓	✓ (Q week)
Dulaglutide		Q week	-	-
Semaglutide		Subcutaneous injection Pill (?)	Q week	-

\*Only GLP-1 agonist designated with MACE risk reduction

Package insert: Semaglutide, Novo Nordisk, 2017. Package insert: ADLYXIN, Sanofi-aventis, 2016.  
Update: Liraglutide, exenatide, dulaglutide. Accessed Aug 12, 2018.

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## Summary of GLP-1 agonists

GLP-1 Agonist	Route	Dosing	Renal adjustment	CVD safety
Lixisenatide		Daily	✓	✓
Liraglutide	Subcutaneous injection	Daily	-	✓*
Exenatide		BID Q week	✓	✓ (Q week)
Dulaglutide		Q week	-	-
Semaglutide	Subcutaneous injection Pill (?)	Q week	-	✓

\*Only GLP-1 agonist designated with MACE risk reduction

Package insert: Semaglutide. Novo Nordisk. 2017. Package insert: ADLYXIN. Sanofi-aventis. 2016. Update: Liraglutide, exenatide, dulaglutide. Accessed Aug 12, 2018.

## Semaglutide: Niche

- Alternative Q weekly GLP-1 agonist
  - May offer slightly more HbA1c lowering
- May cause retinopathy (?) → monitor
- Potential oral option in the future



Starting patients on once-weekly Ozempic. Novo Nordisk. 2018.

## Lixisenatide: Niche



### Lixisenatide

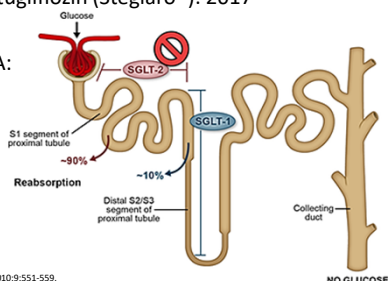
- Likely less clinical impact
  - Less HbA1c lowering vs. other once daily GLP-1 agonist
  - Renal adjustment and monitoring needed
  - Antibody development may ↓ efficacy

Starting Adlyxin. Sanofi-aventis. 2017.

### SGLT2 Inhibitor Overview:

- Newly approved:
  - Ertugliflozin (Steglaro®): 2017

MOA:



Nat. Rev Drug Discov. 2010;9:551-559.

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### SGLT2 Inhibitor Overview:

- Newly approved:
  - Ertugliflozin (Steglaro®): 2017
  - For treatment of type 2 DM
- Same considerations:
  - Warnings: UTIs, genital mycotic infections, lower limb amputation, DKA

ERTUGLIFLOZIN, Merck & Co., Inc. 2017.

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### Efficacy & Safety: Phase III & IV Trials

	Ertugliflozin
Average HbA1c ↓	~0.9 - 1.2% With sitagliptin: 0.4 - 1.6%
Average weight ↓	7 - 8 lbs (comparable with metformin/placebo)
ADEs	Genital mycotic infections UTIs
Hypoglycemia	1 - 5%
↓ SBP	5 mg dose: 4 mmHg 15 mg dose: 2 mmHg

Diabetes Obes Metab. 2017 May;19(5):721-728.  
Diabetes Obes Metab. 2018 Jun;20(6):1453-1460.  
Diabetes Obes Metab. 2018 Jun;20(6):1453-1460.

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## Dosing & Administration

	Ertugliflozin
<b>Formulation</b>	Oral tablet
<b>Dosing</b>	5 mg daily (may increase up to 15 mg daily)
<b>Renal adjustment</b>	eGFR 30 – 60 ml/min: avoid eGFR < 30 ml/min, ESRD, dialysis: CI
<b>Hepatic adjustment</b>	Severe impairment (Child-Pugh class C): avoid
<b>Administration</b>	qAM with or without food

ERTUGLIFLOZIN, Merck & Co., Inc. 2017.

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## Summary of SGLT2 inhibitors

SGLT2 inhibitor	Renal adjustment	Hepatic adjustment	CVD safety
Ertugliflozin	✓ (Avoid eGFR < 60 ml/min)	✓	TBD (Nov 2019)
Canagliflozin	✓ (Avoid eGFR < 45 ml/min)*	✓	✓*
Dapagliflozin	✓ (Avoid eGFR < 60 ml/min)	-	TBD (July 2018)
Empagliflozin	✓ (Avoid eGFR < 45 ml/min)	-	✓*

\*Exception: concurrent UGT enzyme inducers (avoid if eGFR < 60)  
\*Designated with MACE risk reduction

ERTUGLIFLOZIN, Merck & Co., Inc. 2017.  
Update: Canagliflozin, dapagliflozin, empagliflozin. Accessed Aug 12, 2018.

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## Summary of SGLT2 inhibitors

SGLT2 inhibitor	Renal adjustment	Hepatic adjustment	CVD safety
Ertugliflozin	✓ (Avoid eGFR < 60 ml/min)	✓	TBD (Nov 2019)
Canagliflozin	✓ (Avoid eGFR < 45 ml/min)*	✓	✓*
Dapagliflozin	✓ (Avoid eGFR < 60 ml/min)	-	TBD (July 2018)
Empagliflozin	✓ (Avoid eGFR < 45 ml/min)	-	✓*

\*Exception: concurrent UGT enzyme inducers (avoid if eGFR < 60)  
\*Designated with MACE risk reduction

ERTUGLIFLOZIN, Merck & Co., Inc. 2017.  
Update: Canagliflozin, dapagliflozin, empagliflozin. Accessed Aug 12, 2018.

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## Ertugliflozin: Niche

- Alternative SGLT2 inhibitor
- Likely not high clinical impact
  - Higher renal cutoff vs. other SGLT2 inhibitors with CV benefits

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## Insulin Update

Newly approved:

- Insulin aspart (Fiasp®): 2017
  - Vial, FlexTouch pen, and IV infusion



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## Insulin Update

Newly approved:

- Insulin aspart (Fiasp®): 2017
  - Vial, FlexTouch pen, and IV infusion
  - *Ultra-fast* acting insulin for type 1 and 2 DM

Additional MOA:

- Vitamin B3 and L-arginine added to ↑ absorption speed and stability

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### Comparison of insulin aspart formulations

	Fiasp <sup>®</sup>	Novolog <sup>®</sup>
<b>Peak effect</b>	~1.5 to 2.2 hours	1 to 3 hours
<b>Administration time</b>	First bite or within 20 min of starting meal	5 to 10 min prior to meal
<b>Duration</b>	5 to 7 hours	3 to 5 hours
<b>Hypoglycemia</b>	↑ within 2 hours post-prandial*	

\*In type 2 DM patients with bolus insulin

Fiasp: Novo Nordisk Inc. 2018.  
 Diabetes Care. 2017 Jul;40(7):951-957.  
 Update: Insulin aspart. Accessed Aug 12, 2018.

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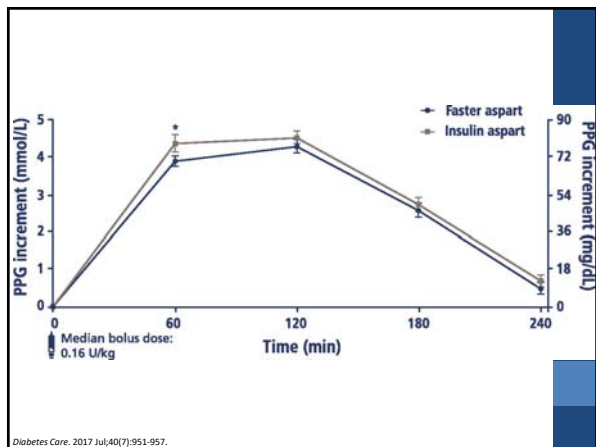
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Diabetes Care. 2017 Jul;40(7):951-957.

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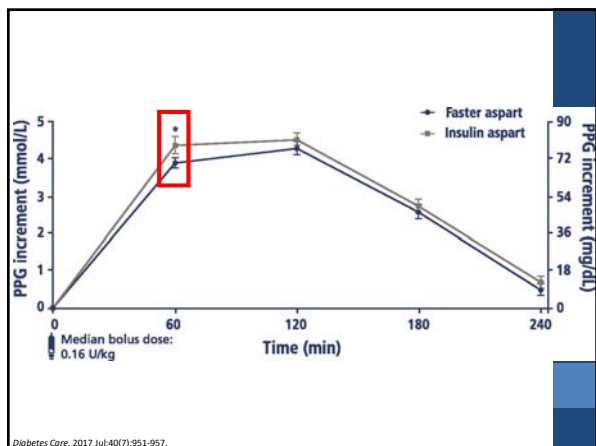
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Diabetes Care. 2017 Jul;40(7):951-957.

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## Insulin aspart (Fiasp®): Niche

- Alternative meal-time insulin
  - No significant clinically benefit over normal fast-acting insulin aspart
- Consider for patients who forget to take insulin prior to meals
- Monitor for post-prandial hypoglycemia

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## Women's Health



Audra Wilson, PharmD

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## Elagolix (Orilissa®): Overview

- First *ORAL* gonadotropin-releasing hormone (GnRH) antagonist
- MoA: competitive GnRH receptor antagonist that suppresses pituitary and ovarian hormone function (LH & FSH → estradiol & progesterone)
- FDA approved July 2018 for the treatment of moderate to severe pain associated with endometriosis

Package insert: ORILISSA, AbbVie Inc. 2018.

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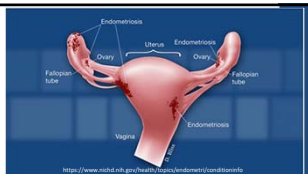
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## Endometriosis



- Pharmacologic treatments
  - First-line options:
    - NSAIDs AND/OR
    - Estrogen-progestin (COC) or progestin only pill
  - Alternatives:
    - GnRH agonists (goserelin, leuprolide)
      - Add-back therapy w/ norethindrone or COC pill
    - GnRH antagonists
    - Danazol → androgenic side effects (e.g. acne, hirsutism)
    - Aromatase inhibitors (anastrozole, letrozole)
    - Neuropathic pain treatments

UpToDate: Endometriosis. Accessed Aug 12, 2018.

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## Elagolix: Efficacy and Safety

- Two double-blind, randomized controlled trials (n=1700)
  - Elagolix 150mg vs. 200mg BID vs. placebo
  - Patients assessed at 3, 6, and 12 months
  - Elagolix improved dysmenorrhea, non-menstrual pain, and dyspareunia in a dose dependent manner
  - Hot flushes were the most common adverse effect
  - Also caused ↑LDL, HA, insomnia, and ↓BMD
- Monitoring
  - BMD, LFTs, and mental status changes

Taylor, et al. N Engl J Med. 2017;377(1):28-40.  
 UpToDate: Endometriosis. Accessed Aug 12, 2018.  
 Package insert: ORILISSA. Abbvie Inc. 2018.

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## Elagolix: Dosing and Administration

Indication	Dosage	Duration (MAX)	Comments
Endometriosis	150 mg once daily	24 months	Use the lowest effective dose and duration to avoid bone loss
Endometriosis with dyspareunia	200 mg BID	6 months	Contraindicated in severe hepatic impairment

- Try to administer at the same time each day without regard to food
- **Start therapy within 7 days of menstruation or exclude pregnancy prior to initiation**

Package insert: ORILISSA. Abbvie Inc. 2018.

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## Elagolix: Niche and Summary

- Niche:
  - Offers an easy-to-use (oral) alternative for women who fail NSAID and/or hormonal options (or have contraindications)
  - Preferred over GnRH agonists (LH/FSH surge must be suppressed)
- Clinical considerations
  - Consider supplemental calcium and vitamin D while receiving therapy
  - Contraindicated during pregnancy, known osteoporosis, severe hepatic impairment, and strong OATP1B1 inhibitors

Package insert: ORLISSA, AbbVie Inc. 2018  
UpToDate: Endometriosis. Accessed Aug 12, 2018.

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## WH Pipeline Drugs

- **Brexanolone (Zulresso®)**: injection for the treatment of severe postpartum depression; the FDA is anticipated to make a decision in December 2018
  - Allosteric GABA-A receptor modulator
  - Currently recruiting for phase 3 clinical trial: **NCT02978326**
- **Segesterone/ethinyl estradiol (Nesterone®)**: vaginal ring for the prevention of pregnancy designed to last for 12 months; expected decision date is November 2018
  - Segesterone is a nonandrogenic, 19-norprogesterone derivative that is only active when given non-orally
  - Ongoing phase 3 study: **NCT00263341**

Clinicaltrials.gov Web Site. Accessed August 12, 2018.

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## Quiz Question!

JT is a 45 YOM who presents to his primary care clinic.  
PMH s/f T2DM, HTN, OSA, obesity, NSTEMI (2015)  
9/10/18 labs: HbA1c 8.5%, electrolytes WNL, CrCl 25 ml/min

Which of the following is true about using a GLP-1 agonist in this patient?

- A. Monitor for increased GI ADEs with semaglutide and empagliflozin due to poor renal function
- B. Semaglutide would provide more A1c lowering than lixisenatide
- C. Lixisenatide is FDA approved to decrease his future ASCVD risk
- D. Avoid lixisenatide due to poor renal function

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## Another Quiz Question!

Select the correct statement regarding pipeline medications.

- A. Cefiderocol a cephalosporin with efflux pump resistance, porin mutation resistance, and serine and metallo- $\beta$ -lactamase resistance.
- B. Iclaprim is a novel antibiotic that is selective for the outer membrane proteins of *P. aeruginosa*.
- C. Brexanolone makers are seeking approval for the treatment of mild to moderate postpartum depression.
- D. Segesterone/ethinyl estradiol is a new contraceptive agent, that when given orally, prevents pregnancy for up to 12 months.

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## QUESTIONS?



Image credit: [https://blogs.bible.org/heartprints/suzi\\_cilberti/asking\\_questions\\_that\\_change\\_lives](https://blogs.bible.org/heartprints/suzi_cilberti/asking_questions_that_change_lives)

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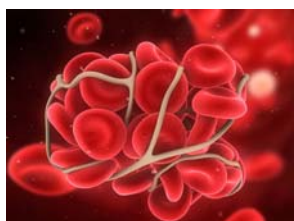


Image credit: [www.medscape.com](http://www.medscape.com)

## ANTICOAGULATION

Ianitza Bankova, PharmD

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## Betrixaban (Bevyxxa®): Overview

- **FDA Approval:** June 2017
- **MOA:** Factor Xa inhibitor
- **Indication:** Prophylaxis of venous thromboembolism (VTE) in adult patients **hospitalized for an acute medical illness** who are at risk for thromboembolic complications
- **Manufacturer:** Portola Pharmaceuticals
- **Cost:** \$18 (per capsule); ~\$670 for 35 day course

Bevyxxa® [package insert]. San Francisco, CA: Portola Pharmaceuticals; 2017.  
UpToDate: Betrixaban. Accessed 13 Sept 2018.

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## Betrixaban: Efficacy

- Betrixaban (avg 36 days) vs. enoxaparin 40mg (avg 9 days)
  - 40 years of age, hospitalized for an acute medical illness, at risk for VTE due to moderate or severe immobility, and had additional risk factors for VTE
  - Composite primary endpoint: betrixaban superior, 95% CI, 0.75 (0.61, 0.91)
    - Asymptomatic proximal Deep Vein Thrombosis (DVT)
    - Symptomatic proximal or distal DVT
    - Non-fatal Pulmonary Embolism (PE)
    - VTE-related death
  - No difference in renal impairment group
    - Compared low-dose betrixaban to enoxaparin 20mg daily

Gibson CM, et al. Am Heart J. 2017 Mar; 185:93-100.  
Bevyxxa® [package insert]. San Francisco, CA: Portola Pharmaceuticals; 2017.

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## Betrixaban: Safety

- Overall rates of ADE, similar
  - Betrixaban: 54%
  - Enoxaparin: 52%
- Bleeding
  - Major bleeding: no difference (p=0.554)
    - GI bleeds double in betrixaban group (no CI or p-value)
  - Clinically relevant non-major bleeding: significantly higher in betrixaban group (p<0.001)
  - All bleeds: significantly higher in betrixaban group, 95% CI, 1.66 (1.17 - 2.35)
    - Betrixaban: 1.2%
    - Enoxaparin: 2.4%
  - No difference in bleeds in renal impairment group, low rate of events
    - Trend toward more bleeds in betrixaban

Gibson CM, et al. Am Heart J. 2017 Mar; 185:93-100.  
Bevyxxa® [package insert]. San Francisco, CA: Portola Pharmaceuticals; 2017.

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## Betrixaban: Dosing and Administration

- Dosing
  - 160mg on day 1, then 80mg daily thereafter for 35-42 days
  - With food
- Dosage Forms
  - 80mg capsule
  - 40mg capsule
- Dose adjustments
  - CrCl 15-30 mL/min (actual body weight): 80mg on day 1, then 40mg daily thereafter
  - Concomitant P-gp inhibitor: 80mg on day 1, then 40mg daily thereafter
  - Not studied in hepatic impairment, use not recommended

Bevyxxa® [package insert], San Francisco, CA: Portola Pharmaceuticals; 2017.

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## Betrixaban: Niche

Consider using betrixaban in patients hospitalized for an acute medical illness who are at risk for thromboembolic complications, have low risk of bleeding, and are unamenable to injectable therapy.



Image credit: <https://www.quickanddirtytips.com/education/grammar/how-do-you-pronounce-niche>

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## Betrixaban: Summary

- Factor Xa inhibitor approved for the prophylaxis of VTE in adult patients **hospitalized for an acute medical illness**
- First oral agent (DOAC) approved for this indication
- “Reduced VTE risk by 25% compared to enoxaparin”
- Clinically studied reduced dose for CrCl 15-30 mL/min
  - No difference compared to 20mg daily enoxaparin...?
- Higher rates of overall bleeding than enoxaparin

Gibson CM, et al. Am Heart J. 2017 Mar; 185:93-100.  
Bevyxxa® [package insert], San Francisco, CA: Portola Pharmaceuticals; 2017.

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## Andexanet Alfa (Andexxa®): Overview

- Coagulation factor Xa (recombinant), inactivated-zhzo
- **FDA Approval:** accelerated approval May 2018
- **MOA:** Binding to and sequestering Factor Xa inhibitors
- **Indication:** For patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding
- **Manufacturer:** Portola Pharmaceuticals
- **Cost:** ~\$60,000 (high-dose)

Andexxa® [package insert], San Francisco, CA: Portola Pharmaceuticals; 2018.  
UpToDate: Andexanet Alfa. Accessed 13 Sept 2018.

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## Andexanet Alfa: Efficacy

- Efficacy data comes from healthy volunteers, evaluating a surrogate endpoint
- Primary endpoint: Percent change in anti-FXa activity
  - 92.3% decrease in apixaban study (p <0.001)
    - n=31
  - 96.7% decrease in rivaroxaban study (p <0.001)
    - n=39
- ANNEXA-4: ongoing multinational, prospective, open-label study in patients w/ acute major bleeding having recently received a Fxa inhibitor
  - Interim results (n=185) show similar decrease in anti-FXa
  - Effective hemostasis achieved in 83% of patients

Siegel DM, et al. N Engl J Med. 2015 Dec 17; 373(25):2413-24.  
Connolly SJ, et al. N Engl J Med. 2016 Sept 22; 375(12):1131-41.  
Andexxa® [package insert], San Francisco, CA: Portola Pharmaceuticals; 2018.

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## Andexanet Alfa: Safety

- Most common adverse effects
  - UTI (≥5%)
  - Pneumonia (≥5%)
  - Infusion reactions (≥3%)
- ANNEXA-4: 30 day follow-up (n=185)
  - Deaths – 14%
  - 33 patients (17.8%) experienced 1 or more of the following
    - Deep venous thrombosis ischemic stroke, acute myocardial infarction, pulmonary embolism, cardiogenic shock, sudden death, congestive heart failure, acute respiratory failure, cardiac arrest, cardiac thrombus, embolic stroke, iliac artery thrombosis, and non-sustained ventricular tachycardia

Siegel DM, et al. N Engl J Med. 2015 Dec 17; 373(25):2413-24.  
Connolly SJ, et al. N Engl J Med. 2016 Sept 22; 375(12):1131-41.  
Andexxa® [package insert], San Francisco, CA: Portola Pharmaceuticals; 2018.

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## Andexanet Alfa: Dosing and Administration

- Dosage Forms
  - Lyophilized powder in single-use vials of 100 mg

FXa Inhibitor	FXa Inhibitor Last Dose	<8 hours or unknown	≥8 hours
Rivaroxaban	≤10mg	Low Dose	Low Dose
Rivaroxaban	>10mg or unknown	High Dose	
Apixaban	≤5mg	Low Dose	
Apixaban	>5mg or unknown	High Dose	

Dose	IV Bolus	Follow-on IV Infusion
Low Dose	400 mg, target rate of 30 mg/min	4 mg/min for up to 120 min
High Dose	800 mg, target rate of 30 mg/min	8 mg/min for up to 120 min

Andexxa\* [package insert], San Francisco, CA: Portola Pharmaceuticals, 2018.

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## Andexanet Alfa: Niche

Consider using andexanet alfa for reversal of anticoagulation in patients treated with apixaban or rivaroxaban if cost is of low concern and other options (4-factor PCC) are not ideal.




Image credit: <https://www.quickanddirtytips.com/education/grammar/how-do-you-pronounce-niche>

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## Andexanet Alfa: Summary

- Recombinant coagulation factor Xa that binds to and sequesters factor Xa inhibitors
- Only available efficacy data is via surrogate endpoints (percent change in anti-FXa activity)
- Per FDA accelerated approval requirements, phase 4 study looking at clinical outcomes expected to be complete in 2023
- Most common ADE are UTI, PNA, and infusion reactions
- Black box warning
  - Arterial and venous thromboembolic events
  - Ischemic events (myocardial infarction and ischemic stroke)
  - Cardiac arrest
  - Sudden deaths

Siegal DM, et al. N Engl J Med. 2015 Dec 17; 373(25):2413-24.  
 Connolly SJ, et al. N Engl J Med. 2016 Sept 22; 375(12):1131-41.  
 Andexxa\* [package insert], San Francisco, CA: Portola Pharmaceuticals, 2018.

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## Quiz Question!

JP is a 68 year old male admitted to your facility with intracranial hemorrhage. His wife is able to tell you that he takes rivaroxaban 20mg daily for atrial fibrillation and his last dose was this morning at 8am. It is now 2pm. Your team elects to proceed with anticoagulation reversal with andexanet alfa (because you work at a fancy hospital that has access to the medication already). Which dose would you recommend?

- A. 400 mg, target rate of 30 mg/min, then 4 mg/min for up to 120 min
- B. 400 mg, target rate of 30 mg/min, then 8 mg/min for up to 120 min
- C. 800 mg, target rate of 30 mg/min, then 4 mg/min for up to 120 min
- D. 800 mg, target rate of 30 mg/min, then 8 mg/min for up to 120 min

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## QUESTIONS?



Image credit: [https://blogs.bible.org/heartprints/suz\\_cilibrati/asking\\_questions\\_that\\_change\\_lives](https://blogs.bible.org/heartprints/suz_cilibrati/asking_questions_that_change_lives)

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## PAIN MANAGEMENT

Samantha Patton, PharmD

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## Erenumab-aooe (Aimovig®) : Overview

- First calcitonin gene-related peptide receptor (CGRP) antagonist
- MoA: human monoclonal antibody that binds and antagonizes CGRP receptor function
- FDA approved for the preventative treatment of migraine in adults (migraine prophylaxis)

Package insert: AIMOVIG, Amgen Inc. 2018.

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## Erenumab: Efficacy and Safety

- Study 1 and 2 – Episodic migraine
  - Erenumab 70 mg or 140 mg monthly vs. placebo x3-6 months
- Study 3 – Chronic migraine (Phase 2)
  - Erenumab 70 mg or 140 mg monthly vs. placebo x3 months
- Common Adverse effects
  - Injection site reactions (pain, erythema): 5 – 6%
  - Constipation: 1 – 3%
- Overall concluded both doses significantly reduced
  - Migraine frequency
  - Use of acute migraine-specific medication
  - Effects of migraines on daily activities

Goadsby, et al. N Engl J Med. 2017;377(23):2123-2132.  
 Dodick, et al. Cephalalgia. 2018;38(6):1026-1037.  
 Tepper, et al. Lancet Neurol. 2017;16(6):425-434.

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RESULTS	Study 1 (N = 955)	Study 2 (N = 570)	Study 3 (N = 667)
Change in monthly migraine days	70 mg: -3.2 days 140 mg: -3.7 days Placebo: -1.8 days <i>P</i> <0.001 *Baseline 8.3 days	Mean difference: -1.0 days (95% CI -1.6, -0.5) <i>P</i> <0.001	Mean difference: -2.5 days (95% CI -3.5, -1.4) <i>P</i> <0.0001
≥50% reduction in migraine days	70 mg: 43.3% 140 mg: 50% Placebo: 26.6% <i>P</i> <0.001	39.7% vs. 29.5% OR 1.59 <i>P</i> =0.010	N/A
Acute migraine medication use days	70 mg: 1.1 days 140 mg: 1.6 days Placebo: 0.2 days <i>P</i> <0.001	-0.6 days (95% CI -0.1, -0.2) <i>P</i> =0.002	N/A
Everyday activity scores	70 mg: 5.5 points 140 mg: 5.9 points Placebo: 3.3 points <i>P</i> <0.001	33% vs. 27.1% OR 1.33	N/A

Goadsby, et al. N Engl J Med. 2017;377(23):2123-2132. Dodick, et al. Cephalalgia. 2018;38(6):1026-1037. Tepper, et al. Lancet Neurol. 2017;16(6):425-434.

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## Erenumab: Dosing and Administration

	Migraine Prophylaxis	
Dosage	70 mg once monthly	<ul style="list-style-type: none"> <li>Some patients may benefit from 140 mg once monthly                             <ul style="list-style-type: none"> <li>Given as 2 consecutive 70 mg SQ injections</li> </ul> </li> <li>Administer missed dose ASAP, and schedule next dose in 1 month</li> <li>No adjustments available for renal or hepatic impairment (<i>not studied</i>)</li> </ul>
Dosage Form	70 mg/mL (1 mL) solution in single-dose prefilled syringe or SureClick® autoinjector	
Route	Subcutaneous: abdomen, thigh, or upper arm	
Storage	Store refrigerated in original carton to protect from light. Discard if stored at room temperature for >7 days.	
Comments	Intended for self-administration.	

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## Cost

	Dose/Day Supply	Price
Erenumab	Per 140 mg/mL dose	\$690.00
	1-year course	\$8,280
OnabotulinumtoxinA	Per 200 units	\$1,442
	1-year course	\$5,768
Propranolol	Per 80mg tab	\$0.97
	1-year course	\$708
Amitriptyline	Per 75mg tab	\$1.91
	1-year course	\$697

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## Erenumab: Summary

- Once monthly, *self-injection*, option for migraine prevention
- Well tolerated, injection site reaction and constipation
- Low potential for drug interactions
  - Studies show no impact on oral contraceptives and sumatriptan
- Consider alternatives prior to trial of therapy (no active comparator studies)
  - Beta-blockers
  - Antidepressants (TCA, SNRI)
    - Weak or insufficient evidence:*
      - ACE-I, ARB, alpha-agonist, ox/carbamazepine, gabapentin, CCB
  - Divalproex
  - Topiramate
  - Botox (OnabotulinumtoxinA)
- Not studied in renal or hepatic impairment
- Cost: \$345.00 per 70 mg/mL

Silberstein, et al. Neurology. 2012;78(17):1337-1345.  
 UpToDate: Migraine Prophylaxis. Accessed Aug 13, 2018.

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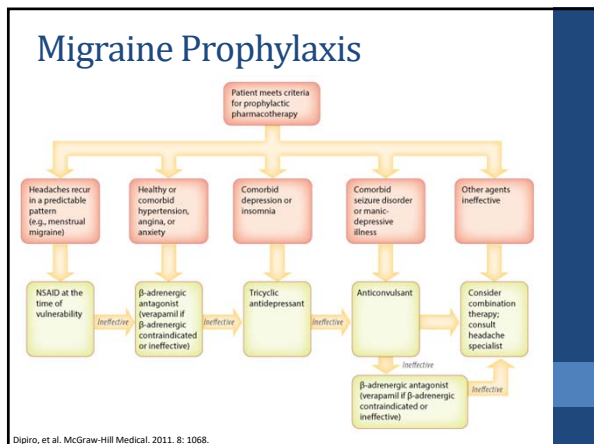
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### Lofexidine (Lucemyra®): Overview

- Central alpha-2 adrenergic agonist
- MOA:
  - Central alpha-2 adrenergic agonist that reduces the release of norepinephrine and sympathetic tone
- FDA approved
  - Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults
- Common adverse effects:
  - Bradycardia, hypotension

Package insert: LUCEMYRA. US WorldMed. LLC 2018.

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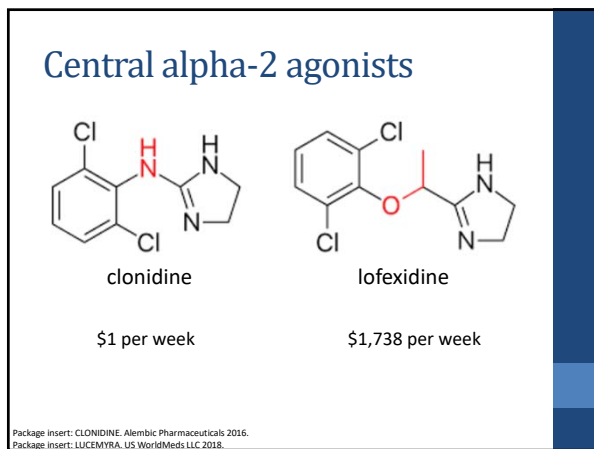
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## Lofexidine: Efficacy and Safety

- Study 1:
  - Lofexidine 0.54 mg q6h vs. 0.72 mg q6h vs. placebo
  - Days 1 – 7 inpatient (double-blind)
  - Days 8 – 14 inpatient or outpatient (open-label)
- Proportion of patients who completed Days 1 – 7:
  - Lofexidine 0.54 mg q6h (41%)
  - Lofexidine 0.72 mg q6h (40%)
  - Placebo (28%)
- Both groups associated with significant difference in mean SOWS-Gossop scores for days 1 – 7 compared to placebo
  - Lofexidine 0.54 mg q6h (mean difference -2.3)
  - Lofexidine 0.72 mg q6h (mean difference -2.7)

Package insert: LUCEMYRA, US WorldMeds LLC 2018.

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## Lofexidine: Efficacy and Safety

- Study 2: double-blind, randomized controlled trials
  - Days 1 – 5: Lofexidine 0.72 mg q6h vs. placebo
  - Days 6 – 7: Placebo
  - Withdrawal symptoms (SOWS): baseline and 3.5 hr after first morning dose on days 1 – 5
- Completed days 1 – 5:
  - Lofexidine (49%) vs. placebo (33%)
- Mean SOWS scores for days 1 – 5:
  - Lofexidine (7.0) vs. placebo (8.9)
  - Mean difference -1.9 (95% CI -3.2, -0.6)

Gorodetzky, et al. Drug and Alcohol Dependence. 2017;176(1):78-88.  
 Package insert: LUCEMYRA, US WorldMeds LLC 2018.

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## Dosing and Administration

	Lofexidine
<b>Formulation</b>	0.18 mg oral tablets
<b>Dosing</b>	Initial: 0.54 mg q5-6h x5-7 days Max dose: 0.72 mg/dose or 2.88 mg/day Discontinue: reduce by 0.18 mg/dose every 1-2 days
<b>Renal adjustment</b>	eGFR 30 – <90 ml/min: 0.36 mg 4 times daily eGFR < 30 ml/min, ESRD, dialysis: 0.18 mg 4 times daily
<b>Hepatic adjustment</b>	Moderate impairment (Child-Pugh class B): 0.36 mg 4 times daily Severe impairment (Child-Pugh class C): 0.18 mg 4 times daily
<b>Administration</b>	Lower doses may be appropriate as withdrawal symptoms improve

Package insert: LUCEMYRA, US WorldMeds LLC 2018.

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## Lofexidine: Summary

- Place in therapy remains unclear
- Lofexidine does not reduce blood pressure to the same extent as clonidine, but is otherwise similar in efficacy
  - Both are more effective than placebo for opioid withdrawal
- Renal and hepatic dose adjustments
- Drug interactions
  - Methadone, oral naltrexone, CNS depressants, CYP2D6 inhibitors
- Considerations:
  - QTc prolongation – DDIs
  - Hypotension
  - Bradycardia

Cochrane Database Syst Rev. 2016;5:CD000204.

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## Quiz Question!

PS is a 32 yof w/ chronic migraines w/ aura and usually experiences significant N/V. PMH also s/f allergic rhinitis and IBS-C. Labs and vitals WNL. She currently uses subQ sumatriptan at the onset of sx with some relief as well as propranolol for prophylaxis, but still experiences migraines 10-15 times per month that significantly interfere w/ her daily activities. She has tried numerous preventative agents in the past and has heard of a new medication to prevent migraines that she would like to try.

Which of the following statements is incorrect regarding use of erenumab?

- A. Erenumab-aooe may be appropriate in this patient since she experiences significant N/V and has trialed numerous preventative agents.
- B. PS should be counseled that erenumab may cause constipation.
- C. Inform PS that erenumab is used for the treatment of migraines and if initiated, it would replace the use of sumatriptan.
- D. Inform PS that erenumab may reduce migraine frequency, use of acute-migraine-specific medications, and will improve the effect of migraines on her daily activities.

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## QUESTIONS?



Image credit: [https://blogs.bible.org/heartprints/suzi\\_cilberti/asking\\_questions\\_that\\_change\\_lives](https://blogs.bible.org/heartprints/suzi_cilberti/asking_questions_that_change_lives)

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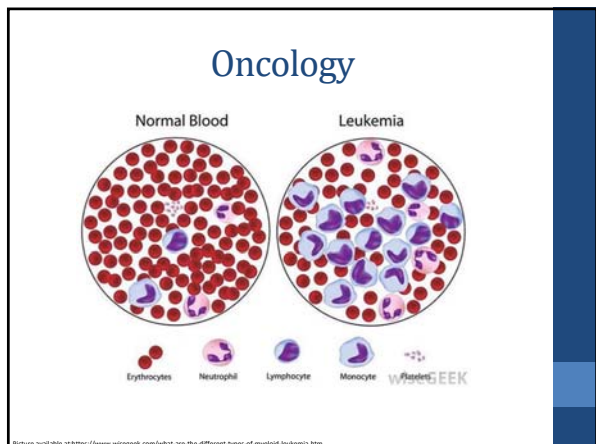
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**ENASIDENIB**  
Amanda Wright, PharmD

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**Enasidenib (Idhifa®)**

- Indications: relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation
- MOA: small molecule inhibitor of the IDH2 enzyme, targets specific mutations
  - Results in reduced 2-hydroxyglutarate (2-HG) levels, and induces differentiation of myeloid cells
- Dosing: 100 mg PO once daily with or without food
  - Given until progression of disease or unacceptable toxicity
- How Available: 50 mg and 100 mg tablets
- REMS – None
- Cost: \$29,846.40 for 30 tablets

Enasidenib (idhifa®) [package insert]. Summit, NJ: Celgene Corporation; 2017.  
Enasidenib, Lexi-Drugs; Lexicomp, Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: <http://online.lexi.com>

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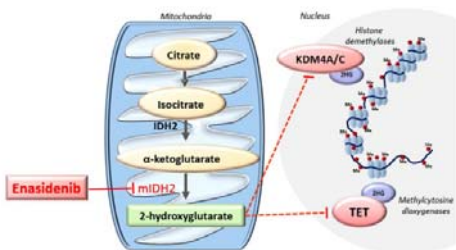
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## Enasidenib: Mechanism of Action



Blood. 2017 Aug 10;130(6):693-694. doi: 10.1182/blood-2017-06-790394.

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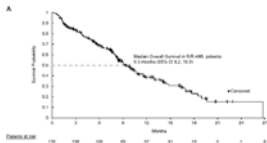
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## Enasidenib: Clinical Trial Information

- Open-label, single arm study completed at multiple centers with 2 cohorts
- Study Population
  - Adult patients with relapsed/refractory AML and an IDH2 mutation
- Study Results
  - Overall response rate: 40.3%
  - Median duration of response: 5.8 months
  - Median overall survival: 9.3 months
    - 19.7 months overall survival in those with complete remission



Blood. 2017 Aug 10;130(6):722-731. doi: 10.1182/blood-2017-04-779405. Epub 2017 Jun 6.

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## Enasidenib: Pearls

- Black Box Warning: Differentiation Syndrome
  - Fatal if not treated
  - Initiate corticosteroid therapy & hemodynamic monitoring until symptoms resolve
- Severe Adverse Reactions
  - Leukocytosis, tumor lysis syndrome, differentiation syndrome
- Adverse Reactions
  - Elevated bilirubin (81%), Hypocalcemia (74%), Nausea (50%), Diarrhea (43%), Hypokalemia (41%), Vomiting (34%), Decreased appetite (34%)
- Precaution: May cause fetal harm if administered during pregnancy
- Counseling Points
  - Swallow tablet whole with a glass of water
  - Moderate emetic potential, anti-emetics recommended
  - Monitor liver and renal function

Enasidenib (Idhifa®) [package insert]. Summit, NJ: Celgene Corporation; 2017.

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**IVOSIDENIB**  
Bryce Benson, PharmD

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**Ivosidenib (Tibsovo®)**

- Indication
  - Relapsed or refractory acute myeloid leukemia (AML) with isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test
- MOA
  - Small molecule inhibitor that targets the mutant (IDH1) enzyme resulting in decreased R-2-hydroxyglutarate, reduced histone hypermethylation and restored myeloid differentiation leading to apoptosis
- Dosing
  - 500mg once daily with or without food until progression or unacceptable toxicity
- Availability/Cost
  - 250mg tabs # 60- \$26,115.40 (AWP)

Tibsovo® (Ivosidenib) Prescribing Information. © July 2018. Array BioPharma.

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**Ivosidenib: Mechanism of Action**

Block in cellular differentiation, oncogenesis

2-HG 2-HG 2-HG 2-HG 2-HG

AG-120

Mutant IDH

Restoration of cell differentiation ability

Isocitrate → α-KG

ACS Med Chem Lett. 2018 Jan 19;9(4):300-305. doi: 10.1021/acsmchemlett.7b00421. eCollection 2018 Apr 12.

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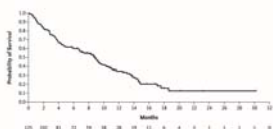
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## Ivosidenib: Clinical Trial

- Phase 1, multicenter, open-label, dose escalation and dose-expansion study
- 174 adult patients with relapsed/refractory AML and IDH1 mutation
- Study endpoints
  - Complete remission (CR) rate: 24.8%
  - Median duration of response: 8.2 months
  - Complete remission with partial hematological recovery
    - CRh: 8%
    - CR+CRh: 32.8%



N Engl J Med. 2018 Jun 21;378(25):2386-2398. doi: 10.1056/NEJMoa1716984. Epub 2018 Jun 2

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## Ivosidenib: Clinical Pearls

- Black Box Warning – Differentiation syndrome
- Severe Side-Effects
  - Leukocytosis, **differentiation syndrome**, QTc prolongation, Guillain-Barre Syndrome
- Common Side-Effects
  - Diarrhea (55%), febrile neutropenia (28.5%), nausea (27.9%), fatigue (25.7%) and dyspnea (24.6%)
- Counseling Points
  - Baseline EKG
  - CYP 3A4 metabolism- watch inhibitors or inducers
  - QTc elongation medications
  - Concentration increased by high fat meal

Tibsovo® (ivosidenib) Prescribing Information. © July 2018. Array BioPharma.

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## MIDOSTAURIN

Andrew Li, PharmD

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## Midostaurin (Rydapt®)

- Indications:
  - Acute myeloid leukemia (AML) with FLT3 mutation-positive
  - Myelodysplastic syndrome (MDS)
  - Advanced systemic mastocytosis
- Mechanism of Action:
  - Multi-targeted protein kinase inhibitor
- Dosing:
  - AML: 50 mg BID on days 8 to 21 of each induction cycle and consolidation cycle
  - Mast cell leukemia: 100 mg BID
  - Systemic mastocytosis: 100 mg BID
- Dosage Form:
  - 25 mg capsule (\$170.24 per capsule)

Midostaurin: Drug Information. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2018.

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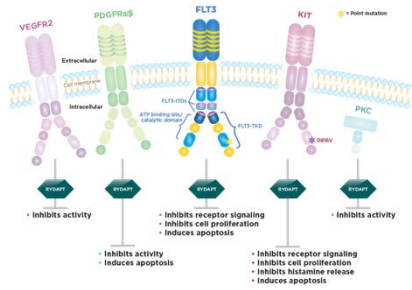
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## Midostaurin: Mechanism of Action



Rydapt [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.

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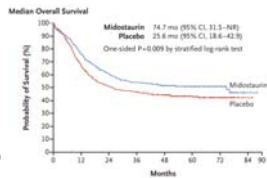
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## Midostaurin: Clinical Trial Information

Treatment-naïve FLT3+ AML patients (N = 717) were randomized to either midostaurin or placebo.

**Results:** Midostaurin had a significant improvement over placebo in:

- Overall survival (0.78, P = 0.009)
- Event-free survival (0.78, P = 0.002)



Outcome	Midostaurin	Placebo	Statistics
Median Overall Survival	74.7 months	25.6 months	P = 0.009
4-year Overall Survival Rate	51.4%	44.3%	N/A
Complete Remission	58.9%	53.5%	P = 0.15

N Engl J Med. 2017 Aug 3;377(5):454-464. doi: 10.1056/NEJMoa1614359. Epub 2017 Jun 23.

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## Midostaurin: Pearls

- Warnings and Precautions:
  - Embryo-fetal Toxicity
  - Pulmonary Toxicity: Interstitial lung disease, or pneumonitis
- Adverse Events (≥ 20%):
  - Febrile neutropenia, N/V, mucositis, **headache**, **petechiae**, epistaxis, musculoskeletal pain, **device-related infection**, hyperglycemia, and **upper respiratory tract infection**.
- Drug-drug interactions:
  - Midostaurin and its active metabolites are CYP3A4 substrates. CYP3A4 inducers and inhibitors may affect levels of exposure.
- Counseling Points:
  - Take with food

Blue denotes a 5% greater rate of midostaurin over placebo

Midostaurin (Rydapt®) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2017.

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## Quiz Question!

LH is a 46 y/o female who presents to the oncologist with a 10 month history of acute myeloid leukemia. She has swollen lymph nodes of the axilla, a sign of possible relapsed disease. She recently had labs drawn and was found to have relapsed AML. Genetic testing was completed and LH was found to have an IDH1 genetic mutation. Which of the following medications would LH be a candidate for?

- A. Ivosidenib
- B. Midostaurin
- C. Enasidenib
- D. Sunvalinib

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## FINAL QUESTIONS?

- Infectious Disease
- Ambulatory Care
  - Diabetes Mellitus
  - Women's Health
- Anticoagulation
- Pain Management
- Oncology
  - Acute Myeloid Leukemia (AML)




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