New Medications & FDA Updates 2018

A presentation for HealthTrust Members

October 15, 2019

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Speaker Disclosure

- Presenter has nothing to disclose

- Note: This program may contain the mention of suppliers, brands, products, services or drugs presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand, product, service or drug.

Pharmacist Objectives

- List the medications that were FDA-approved in 2018
- Describe the indications and mechanisms of action of the new medications
- Review adverse effects and patient safety information for these new medications
- Relate new medications FDA-approved in 2018 with those approved previously with similar indications
- Discuss important patient counseling and monitoring parameters for newly approved medications
- Identify drug safety warnings that were published by the FDA in 2018

Technician Objectives

- Review appropriate storage instructions for the newly approved medications
- Discuss unique preparation instructions for these new medications

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New Medications of 2018

- Aemcolo™ (rifamycin)
- Aimovig™ (erenumab-aooe)
- Ajovy® (fremanezumab-vfrm)
- Akynzeo® (netupitant-palonosetron)
- **Andexxa® (andexanet alfa)**
- Annovera™ (segesterone acetate-ethinyl estradiol)
- Asparlas™ (calaspargase pegol-mknl)
- Biktarvy® (bictegravir-emtricitabine-tenofovir alafenamide)
- Braftovi® (encorafenib)
- Copiktra™ (duvelisib)
- Crysvita® (burosumab-twza)
- Daurismo™ (glasdegib)
- Diacomit® (stiripentol)
- Doptelet® (avatrombopag)
- Elzonris™ (tagraxofusp-erzs)
- Emgality® (galcanezumab-gnlm)
- **Epidiolex® (cannabidiol)**
- Erleada™ (apalutamide)
- Firdapse® (amifampridine phosphate)
- Galafold™ (migalastat)
- Gamifant® (emapalumab-lzsg)

SOURCE: 2018 New Drug Therapy Approvals. Available at: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM629290.pdf. Accessed February 21, 2019.

New Medications of 2018

- Ilumya™ (tildrakizumab-asmn)
- Jivi® (antihemophilic factor (recombinant) PEGylated-aucl)
- **Krintafel® (tafenoquine)**
- Libtayo® (cemiplimab-rwlc)
- Lokelma™ (sodium zirconium cyclosilcate)
- Lorbrena® (lorlatinib)
- Lucemyra™ (lofexidine hydrochloride)
- Lumoxiti™ (moxetumomab pasudotox-tdfk)
- Lutathera® (lutetium Lu 177 dotatate)
- Mektovi® (binimetinib)
- Motegrity™ (prucalopride succinate)
- Moxidectin (moxidectin)
- Mulpleta® (lusutrombopag)
- Nuzyra™ (omadacycline)
- Olumiant® (baricitinib)
- **Omegaven® (fish oil triglycerides)**
- Onpattro™ (patisiran)
- Orilissa® (elagolix sodium)
- Oxervate™ (cenegermin-bkbj)
- Palynziq™ (pegvaliase-pqpz)

SOURCE: 2018 New Drug Therapy Approvals. Available at: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM629290.pdf. Accessed February 21, 2019.

New Medications of 2018

- Pifeltro™ (doravirine)
- Poteligeo® (mogamulizumab-kpkc)
- Revcovi™ (elapegademase-lvlr)
- Seysara™ (sarecycline)
- **Symdeko™ (tezacaftor-ivacaftor)**
- Takhzyro™ (lanadelumab)
- Talzenna® (talazoparib)
- Tavalisse™ (fostamatinib)
- Tegsedi™ (inotersen)
- Tibsovo® (ivosidenib)
- **Tpoxx® (tecovirimat)**
- Trogarzo™ (ibalizumab-uiyk)
- Ultomiris™ (ravulizumab-cwvz)
- Vitrakvi® (larotrectinib)
- Vizimpro® (dacomitinib)
- Xerava™ (eravacycline)
- **Xofluza™ (baloxavir marboxil)**
- Xospata® (gilteritinib)
- **Yupelri™ (revefenacin)**
- Zemdri™ (plazomicin)

SOURCE: 2018 New Drug Therapy Approvals. Available at: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM629290.pdf. Accessed February 21, 2019.

Andexxa® (andexanet alfa)

- **Approval date**
  - May 3, 2018
- **FDA approved indications**
  - Reversal of anticoagulation due to life-threatening or uncontrolled bleeding in patient treated with apixaban or rivaroxaban
- **Mechanism of action**
  - Binds and sequesters the FX_a inhibitors, rivaroxaban and apixaban
  - Binds to and inhibits the activity of Tissue Factor Pathway Inhibitor which leads to increase in tissue factor-initiated thrombin generation
- **Adverse reactions**
  - Urinary tract infections
  - Pneumonia
  - Thromboembolic and ischemic events

SOURCE: Andexxa® (andexanet alfa). Prescribing Information. San Francisco, CA. 2018.

Andexxa® (andexanet alfa)

Dose	Initial IV Bolus	Follow-On IV Infusion	Total Number of 200 mg vials
Low Dose	400 mg at 30 mg/min	4 mg/min for 120 mins (480 mg)	5
High Dose	800 mg at 30 mg/min	8 mg/min for 120 mins (960 mg)	9

FX_a Inhibitor	FX_a Inhibitor Last Dose	< 8 Hours or Unknown	≥ 8 Hours
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
	> 10 mg or Unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	
	> 5 mg or Unknown	High Dose	

SOURCE: Andexxa® (andexanet alfa). Prescribing Information. San Francisco, CA. 2018.

Andexxa® (andexanet alfa)

- **Interactions**
  - None
- **Monitoring**
  - Signs and symptoms of arterial and venous thromboembolic events, ischemic events or cardiac arrest
- **Dosage forms available**
  - 200 mg vials
- **Storage / stability**
  - Unopened vial
    - Refrigerated
  - Reconstituted vial
    - Room temperature up to 8 hours; refrigerated up to 24 hours
  - Reconstituted IV bag
    - Room temperature up to 8 hours
- **Counseling points**
  - Increases risk of thromboembolic events

SOURCE: Andexxa® (andexanet alfa). Prescribing Information. San Francisco, CA. 2018.

ANNEXA-A & ANNEXA-R Trials

	Apixaban	Rivaroxaban
Treatment Groups	• Andexanet 400 mg IV bolus (part 1) • Andexanet 400 mg IV bolus + 480 mg IV infusion (part 2) • Placebo	• Andexanet 800 mg IV bolus (part 1) • Andexanet 800 mg IV bolus + 960 mg IV infusion (part 2) • Placebo
Primary End Point	• Percent change in anti-factor Xa activity from baseline to nadir	
Results	• After bolus: 94±2% vs 21±9% (P< 0.001) • After bolus + infusion: 92±3% vs 33±6% (P< 0.001)	• After bolus: 92±11% vs 18±15% (P<0.001) • After bolus + infusion: 97±2% vs 45±12% (P<0.001)
Adverse Effects	• No serious or severe adverse events • Mild events: constipation, flushing, urticaria • No development of factor X or factor Xa antibodies	

SOURCE: Siegal DM, Curnutte JT, Connolly SJ, et al. *N Engl J Med* 2015;373:2413-24.

ANNEXA-4 Trial

Treatment Group	• Apixaban or rivaroxaban > 7 hours: 400 mg IV bolus + 480 mg IV infusion • Enoxaparin, edoxaban, rivaroxaban ≤ 7 hours: 800 mg IV bolus + 960 mg IV infusion	
Primary End Point	• Percent change from baseline in anti-factor Xa activity after andexanet treatment • Percentage of patients with excellent or good hemostatic efficacy 12 hours after andexanet infusion	
Results	**Anti-factor Xa Activity** • Apixaban*: 92%, 32%, 34%, 38% reduction • Rivaroxaban*: 92%, 42%, 48%, 62% reduction	**Hemostatic Efficacy** • Excellent or good: 82%

Adverse Effects	• 10% of patients had thrombotic event during 30-day follow-up
	  ○ Myocardial infarction: 7 patients
	  ○ Ischemic stroke: 14 patients
	  ○ Deep vein thrombosis: 13 patients
	• 2 patients had infusion reactions
	• No patients developed antibodies to factor X or Xa	

*time points at end of bolus and 4, 8 and 12 hours after andexanet infusion, respectively

SOURCE: Connolly SJ, Crowther M, Eikelboom JW, et al. *N Engl J Med* 2019;380:1326-35.

Epidiolex® (cannabidiol)

- **Approval date**
  - June 25th, 2018
- **Controlled Substance**
  - Schedule V
- **FDA approved indications**
  - Treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) or Dravet Syndrome (DS) in patients 2 years of age and older
- **Mechanism of action**
  - Unknown
- **Adverse reactions**
  - Hepatocellular injury
  - Sedation / somnolence
  - Suicidal behavior and ideation
  - Decreased weight

SOURCE: Epidiolex® (cannabidiol). Prescribing Information. Carlsbad, CA. 2018.

Dosing

	Starting Dosage	Maintenance Dosage	Maximum Recommended Dosage
Normal Hepatic Function	2.5 mg/kg twice daily (5 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)	10 mg/kg twice daily (20 mg/kg/day)
Mild Hepatic Impairment	2.5 mg/kg twice daily (5 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)	10 mg/kg twice daily (20 mg/kg/day)
Moderate Hepatic Impairment (Child-Pugh B)	1.25 mg/kg twice daily (2.5 mg/kg/day)	2.5 mg/kg twice daily (5 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)
Severe Hepatic Impairment (Child-Pugh C)	0.5 mg/kg twice daily (1 mg/kg/day)	1 mg/kg twice daily (2 mg/kg/day)	2 mg/kg twice daily (4 mg/kg/day)

SOURCE: Epidiolex® (cannabidiol). Prescribing Information. Carlsbad, CA. 2018.

Epidiolex® (cannabidiol)

- **Interactions**
  - Moderate or strong inhibitors of CYP3A4 or CYP2C19
  - Strong inducers of CYP3A4 or CYP2C19
  - Clobazam
  - Valproate
- **Monitoring**
  - Liver function tests
  - Mental status
  - Therapeutic response
- **Dosage forms available**
  - 100 mg/mL oral solution – 100 mL glass bottle
- **Storage / stability**
  - Unopened bottle
    - Room temperature
  - Opened bottle
    - Room temperature for 12 weeks
- **Counseling points**
  - Do not abruptly stop taking medication

SOURCE: Epidiolex® (cannabidiol). Prescribing Information. Carlsbad, CA. 2018.

Clinical Trials

	Dravet Syndrome Study	Lennox-Gastaut Syndrome Study
Treatment Groups	• Cannabidiol titrated to 20 mg/kg/day • Placebo	• Cannabidiol 10 mg/kg/day • Cannabidiol 20 mg/kg/day • Placebo
Primary End Point	Percent change per 28 days in convulsive seizure frequency	Percent change from baseline in frequency of drop seizures
Results	• Cannabidiol: 38.9% reduction • Placebo: 13.3% reduction	• Cannabidiol 10 mg/kg/day: 37.2% reduction • Cannabidiol 20 mg/kg/day: 41.9% reduction • Placebo: 17.2% reduction
Adverse effects	Vomiting, fatigue, decreased appetite, diarrhea, somnolence	

SOURCES: Devinsky O, Cross H, Laux L, et al. *N Engl J Med* 2017;376:2011-20.
Devinsky O, Pate; A, Cross H et al. *N Engl J Med* 2018;378:1888-97.

Krintafel® (tafenoquine)

- **Approval date**
  - July 20th, 2018
- **FDA approved indications**
  - Radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients aged 16 years and older who are receiving appropriate antimalarial therapy
- **Mechanism of action**
  - 8-aminoquinoline antimalarial; active against the liver stages including the hypnozoite of *P. vivax*
- **Dosing**
  - Single dose of 300 mg
- **Adverse reactions**
  - Hemolytic anemia
  - Methemoglobinemia
  - Psychiatric effects
  - Hypersensitivity reactions

SOURCE: Krintafel® (tafenoquine). Prescribing Information. Research Triangle Park, NC. 2018.

Krintafel® (tafenoquine)

- **Interactions**
  - Organic cation transporter-2 (OCT2) and multidrug and toxin extrusion (MATE) substrates
- **Monitoring**
  - Signs/symptoms of hemolysis, hypersensitivity reaction, methemoglobinemia, and psychiatric effects
- **Dosage forms available**
  - 150 mg tablet
- **Storage / stability**
  - Unopened bottle
    - Room temperature
  - Opened bottle
    - In original container for 3 months
- **Counseling points**
  - Take with food to increase absorption
  - Swallow tablets whole

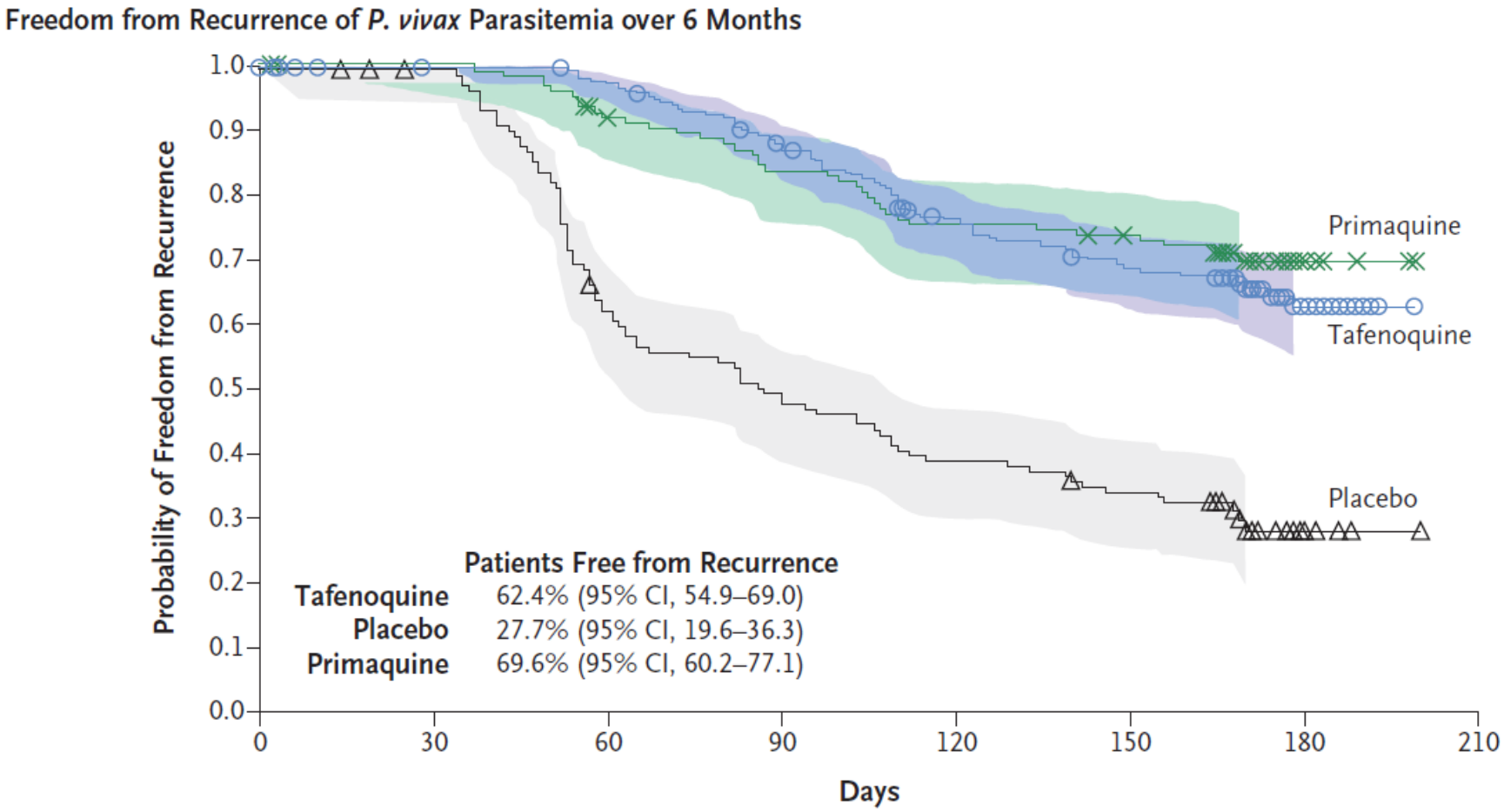
SOURCE: Krintafel® (tafenoquine). Prescribing Information. Research Triangle Park, NC. 2018.

DETECTIVE Trial

- Phase III, multicenter, double-blind, double-dummy, parallel group, randomized, placebo-controlled trial
  - All patients received chloroquine 600 mg on day 1 & 2, then 300 mg on day 3 plus one of the following
    - Tafenoquine 300 mg PO once on day 1 or 2
    - Primaquine 15 mg PO once daily x 14 days
    - Placebo – tafenoquine and primaquine matched
- Primary efficacy outcome
  - Percentage of patients who were free from recurrence at 6 months
- Safety assessment
  - Nature and frequency of adverse events
  - Abnormal EKG

SOURCE: Lacerda MVG, Llanos-Cuentas A, Krudsood S, et al. *N Engl J Med* 2019;380:215-28.

Results – Efficacy



SOURCE: Lacerda MVG, Llanos-Cuentas A, Krudsood S, et al. *N Engl J Med* 2019;380:215-28.

Results – Safety

	Tafenoquine (N = 260)	Placebo (N = 133)	Primaquine (N = 129)
	Number of patients (percent)		
Pruritus	29 (11.2)	17 (12.8)	14 (10.9)
Dizziness	22 (8.5)	4 (3.0)	8 (6.2)
Nausea	16 (6.2)	9 (6.8)	7 (5.4)
Vomiting	15 (5.8)	7 (5.3)	9 (7.0)
Hemoglobin decreased	14 (5.4)	2 (1.5)	2 (1.6)
Headache	12 (4.6)	9 (6.8)	5 (3.9)
Diarrhea	10 (3.8)	4 (3.0)	3 (2.3)
Upper abdominal pain	8 (3.1)	9 (6.8)	6 (4.7)
ALT increased	6 (2.3)	6 (4.5)	3 (2.3)

SOURCE: Lacerda MVG, Llanos-Cuentas A, Krudsood S, et al. *N Engl J Med* 2019;380:215-28.

Omegaven® (fish oil triglycerides)

- **Approval date**
  - July 27th, 2018
- **FDA approved indications**
  - Indicated as source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC)
- **Mechanism of action**
  - Provides biologically utilizable source of calories and essential fatty acids
- **Dosing**
  - 1 g/kg/day
- **Adverse reactions**
  - Hypersensitivity reactions
  - Risk of infections
  - Hypertriglyceridemia
  - Aluminum toxicity

SOURCE: Omegaven® (fish oil triglycerides). Prescribing Information. Graz, Austria. 2018.

Omegaven® (fish oil triglycerides)

- **Interactions**
  - Antiplatelet agents and anticoagulants
- **Monitoring**
  - Triglycerides
  - Liver and kidney function
  - Coagulation parameters
- **Dosage forms available**
  - 5 g/50 mL and 10 g/100 mL (0.1 g/mL) bottles
- **Storage / stability**
  - Unopened bottle
    - Room temperature
  - Once connected to infusion set (Y-connector)
    - Use immediately and complete infusion within 12 hours
  - Admixture
    - 6 hours room temperature / 24 hours refrigerated
    - Complete infusion within 24 hours after removal from storage
- **Counseling points**
  - Monitor for hypersensitivity reactions

SOURCE: Omegaven® (fish oil triglycerides). Prescribing Information. Graz, Austria. 2018.

Clinical Trials

	NCT00910104	NCT00738101
Treatment Groups	Pediatric patients who developed cholestasis while receiving parenteral nutrition	2 weeks to 6 months of age with increased conjugated bilirubin requiring parenteral nutrition for 28 days
Results	• Median total bilirubin and direct bilirubin improved significantly from baseline values of 7.9 and 5.4 mg/dL to 0.5 and 0.2 mg/dL • Decreased LDL, VLDL, cholesterol and serum triglycerides	• Resolution of hyperbilirubinemia and survival to hospital discharge occurred in 47 infants • Median number of days to resolution of cholestasis was 35 • Non-survivors showed a trend towards being more premature than survivors at birth • Infants with higher conjugated bilirubin at initiation of therapy had longer time to resolution • Time to resolution correlated inversely with gestational age at birth and directly to time to receive 100% calories enterally • No infants developed liver failure after initiation

SOURCE: Le HD, de Meijer VE, Robinson E, et al. *Am J Clin Nutr* 2011;94:749-58.
Premkumar MH, Carter BA, Hawthorne KM, et al. *J Pediatr* 2013;162:793-8.

Symdeko™ (tezacaftor-ivacaftor)

- **Approval date**
  - February 12th, 2018
- **FDA approved indications**
  - Treatment of patients with cystic fibrosis age 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene
- **Mechanism of action**
  - Tezacaftor: increases the amount of mature CFTR protein that is delivered to the cell surface
  - Ivacaftor: increases chloride transport by potentiating the channel-open probability of the CFTR protein on the cell surface
- **Dosing**
  - Tezacaftor 100 mg/Ivacaftor 150 mg PO every morning and Ivacaftor 150 mg PO every evening
  - Hepatic impairment
    - Moderate and Severe (Child-Pugh Class B and C): no ivacaftor 150 mg dose in the evening
- **Adverse reactions**
  - Transaminase elevations
  - Cataracts

SOURCE: Symdeko™ (tezacaftor-ivacaftor). Prescribing Information. Boston, MA. 2018.

Symdeko™ (tezacaftor-ivacaftor)

- **Interactions**
  - Strong CYP3A inducers
  - Moderate and strong CYP3A inhibitors
  - Grapefruit juice
- **Monitoring**
  - Liver function tests
  - Ophthalmology exam
- **Dosage forms available**
  - Co-packaged tezacaftor 100 mg/ivacaftor 150 mg fixed-dose combination tablet with ivacaftor 150 mg tablet
- **Storage / stability**
  - Unopened / opened bottle
    - Room temperature until expiration on package
- **Counseling points**
  - Take with fat containing meal/snack
  - Avoid medications that interact

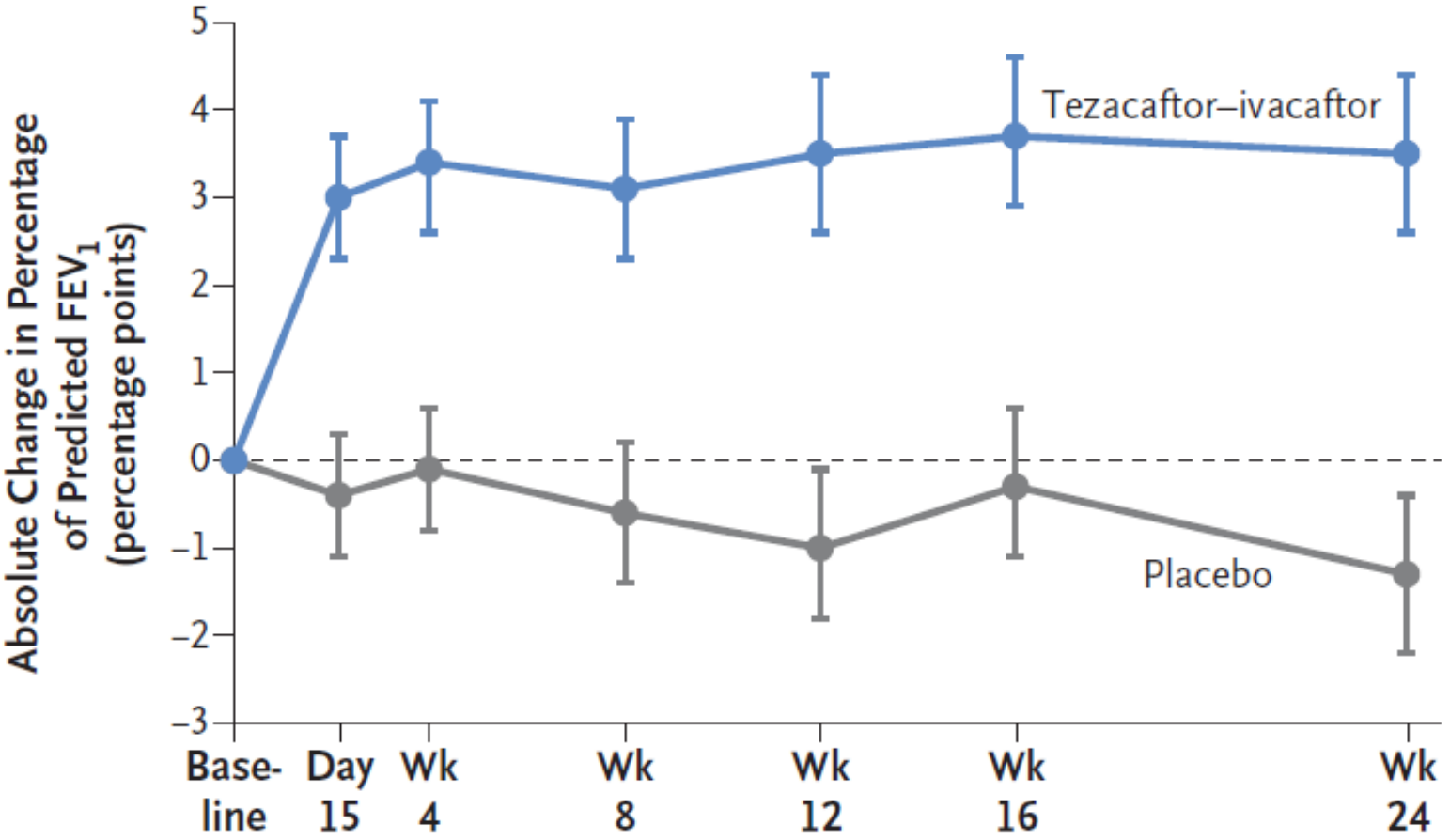
SOURCE: Symdeko™ (tezacaftor-ivacaftor). Prescribing Information. Boston, MA. 2018.

EVOLVE Trial

- Phase III, randomized, double-blind, multicenter, placebo-controlled, parallel-group trial
  - Tezacaftor 100 mg/ivacaftor 150 mg PO daily + ivacaftor 150 mg daily
  - Matched placebo
- Primary efficacy end point
  - Absolute change in the percentage of the predicted FEV_1 from baseline through week 24
- Safety assessment
  - Adverse events
  - Clinical laboratory values
  - EKG
  - Vital signs
  - Spirometry

SOURCE: Taylor-Cousar JL, Munck A, McKone EF, et al. *N Engl J Med* 2017;377:2013-23.

Results – Efficacy



SOURCE: Taylor-Cousar JL, Munck A, McKone EF, et al. *N Engl J Med* 2017;377:2013-23.

Results – Safety

	Tezacaftor-Ivacaftor Group (N = 251)	Placebo Group (N = 258)
	Number of patients (percent)	
Infective pulmonary exacerbation of CF	75 (29.9)	96 (37.2)
Cough	66 (26.3)	84 (32.6)
Headache	44 (17.5)	37 (14.3)
Nasopharyngitis	42 (16.7)	39 (15.1)
Increased sputum production	36 (14.3)	42 (16.3)
Pyrexia	28 (11.2)	32 (12.4)
Hemoptysis	26 (10.4)	35 (13.6)
Oropharyngeal pain	22 (8.8)	29 (11.2)
Fatigue	16 (6.4)	31 (12.0)

SOURCE: Taylor-Cousar JL, Munck A, McKone EF, et al. *N Engl J Med* 2017;377:2013-23.

Tpoxx® (tecovirimat)

- **Approval date**
  - July 13th, 2018
- **FDA approved indications**
  - Treatment of human smallpox disease caused by variola virus
- **Mechanism of action**
  - Inhibits the activity of the orthopoxvirus VP37 protein and blocks its interaction with cellular Rab9 GTPase and TIP47, which prevents cell-to-cell and long-range dissemination of virus
- **Dosing**
  - 13 kg to less than 25 kg: 200 mg PO twice daily x 14 days
  - 25 kg to less than 40 kg: 400 mg PO twice daily x 14 days
  - 40 kg and above: 600 mg PO twice daily x 14 days
- **Adverse reactions**
  - Hypoglycemia when co-administered with repaglinide
  - Headache
  - Nausea

SOURCE: Tpoxx® (tecovirimat). Prescribing Information. Corvallis, OR. 2018.

Tpoxx® (tecovirimat)

- **Interactions**
  - Repaglinide
  - Midazolam
- **Monitoring**
  - Blood glucose
- **Dosage forms available**
  - 200 mg capsules
- **Storage / stability**
  - Unopened / opened bottle
    - Original container at room temperature until expiration date
- **Counseling points**
  - Take within 30 minutes of a moderate to high fat meal
  - Efficacy is based on animal models alone
  - Let prescriber know if also taking repaglinide

SOURCE: Tpoxx® (tecovirimat). Prescribing Information. Corvallis, OR. 2018.

Pharmacokinetic and Safety Trial

- Placebo-controlled pharmacokinetic and safety study
  - Tecovirimat 600 mg PO twice daily x 14 days
  - Placebo

Table 3. Adverse Events That Occurred or Worsened during Receipt of Tecovirimat or Placebo in the Overall Summary Safety Population.

Type of Event*	Placebo (N=90)		Tecovirimat (N=359)		Total (N=449)	
	No. of Participants (%)	No. of Events	No. of Participants (%)	No. of Events	No. of Participants (%)	No. of Events
Any event	30 (33.3)	68	134 (37.3)	318	164 (36.5)	386
Event related to the trial agent	15 (16.7)	32	71 (19.8)	176	86 (19.2)	208
Event leading to discontinuation of trial agent	2 (2.2)	3	6 (1.7)	16	8 (1.8)	19
Serious events and events leading to death	0	0	1 (0.3)†	1	1 (0.2)	1

* The adverse events considered here included any newly occurring event or previous condition that increased in severity or frequency since administration of the first dose of tecovirimat or placebo.
† The death was due to a pulmonary embolus that was judged by the investigators not to be related to tecovirimat.

SOURCE: Grosenbach DW, Honeychurch K, Rose EA, et al. *N Engl J Med* 2018:379:44-53.

Xofluza™ (baloxavir marboxil)

- **Approval date**
  - October 24th, 2018
- **FDA approved indications**
  - Treatment of acute uncomplicated influenza in patients 12 years of age and older
- **Mechanism of action**
  - Inhibits endonuclease activity of the polymerase acidic protein, an influenza virus-specific enzyme in the viral RNA polymerase complex required for vial gene transcription, resulting in inhibition of virus replication
- **Dosing**
  - 40 kg to less than 80 kg: single dose of 40 mg PO
  - Greater than 80 kg: single dose of 80 mg PO
- **Adverse reactions**
  - Diarrhea
  - Bronchitis
  - Nausea
  - Headache

SOURCE: Xofluza™ (baloxavir marboxil). Prescribing Information. Osaka, Japan. 2018.

Xofluza™ (baloxavir marboxil)

- **Interactions**
  - Polyvalent cation-containing products
- **Monitoring**
  - Secondary bacterial infections
- **Dosage forms available**
  - 20 mg tablet
  - 40 mg tablet
- **Storage / stability**
  - Room temperature in original blister package
- **Counseling points**
  - Avoid co-administration with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids or oral supplements
  - Consult healthcare professional before receiving a live attenuated influenza vaccine after taking this medication

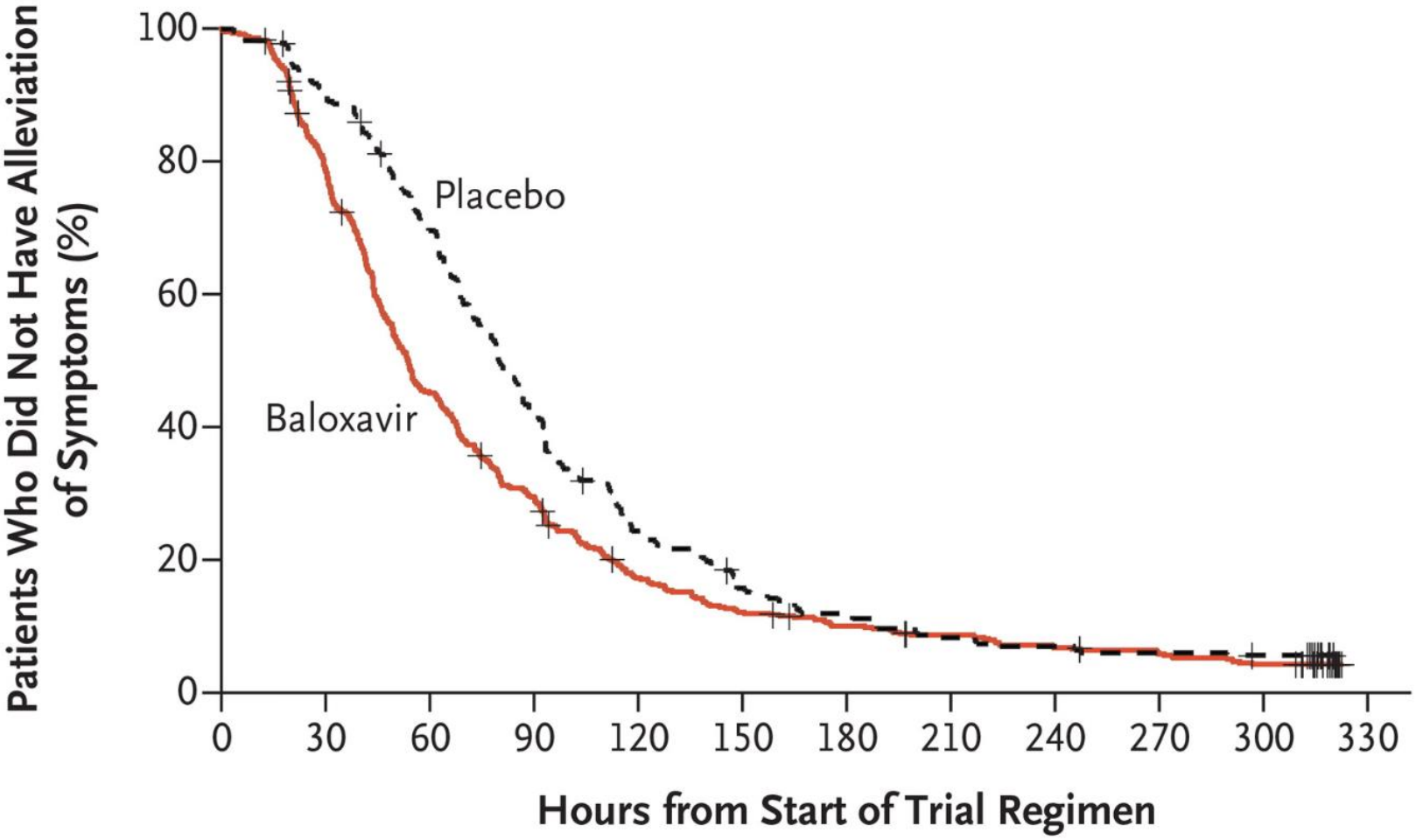
SOURCE: Xofluza™ (baloxavir marboxil). Prescribing Information. Osaka, Japan. 2018.

CAPSTONE - 1 Trial

- Phase III, double-blind, placebo- and oseltamivir-controlled, randomized trial
  - Baloxavir
    - Patients < 80 kg: 40 mg PO once
    - Patients ≥ 80 kg: 80 mg PO once
  - Oseltamivir 75 mg PO twice daily x 5 days
  - Matching placebos
- Primary efficacy end point
  - Time to alleviation of symptoms: from start until when all symptoms rated as absent or mild for 21.5 hours
- Safety end points
  - Adverse events

SOURCE: Hayden FG, Sugaya N, Hirotsu N, et al. *N Engl J Med* 2018;379:913-23.

Results – Efficacy



SOURCE: Hayden FG, Sugaya N, Hirotsu N, et al. *N Engl J Med* 2018;379:913-23.

Results – Safety

	Baloxavir (%)	Placebo (%)	Oseltamivir (%)
Any adverse event	20.7	24.6	24.8
Adverse event considered related to trial regimen	4.4	3.9	8.4
Adverse event related to trial regimen and reported in ≥ 1% patients			
Diarrhea	1.8	1.3	1.4
Nausea	0.3	0.6	1.6
Serious adverse event	0.3	0	0
Adverse event leading to discontinuation of trial	0.3	0.3	0.4

SOURCE: Hayden FG, Sugaya N, Hirotsu N, et al. *N Engl J Med* 2018;379:913-23.

Yupelri™ (revefenacin)

- **Approval date**
  - November 9th, 2018
- **FDA approved indications**
  - Maintenance treatment of patients with chronic obstructive pulmonary disease (COPD)
- **Mechanism of action**
  - Long-acting muscarinic antagonist (anticholinergic)
- **Dosing**
  - 175 mcg nebulized once daily
- **Adverse reactions**
  - Paradoxical bronchospasm
  - Narrow-angle glaucoma
  - Urinary retention
  - Hypersensitivity reactions

SOURCE: Yupelri™ (revefenacin). Prescribing Information. Morgantown, WV. 2018.

Yupelri™ (revefenacin)

- **Interactions**
  - Other anticholinergic-containing medications
  - OATP1B1 and OATP1B3 inhibitors
- **Monitoring**
  - Pulmonary function tests
  - Liver function tests at baseline
  - Signs and symptoms of narrow-angle glaucoma, urinary retention and hypersensitivity reactions
- **Dosage forms available**
  - 175 mcg/3 mL nebulizer solution
- **Storage / stability**
  - Room temperature in protective foil pouch
  - Protect from light and excessive heat
  - Use immediately after removing from foil pouch
- **Counseling points**
  - Remove from foil pouch immediately before administration
  - Only administer via a standard jet nebulizer connected to an air compressor with adequate airflow and a mouthpiece
  - Not to be used for acute symptoms
  - Do not mix with other medications

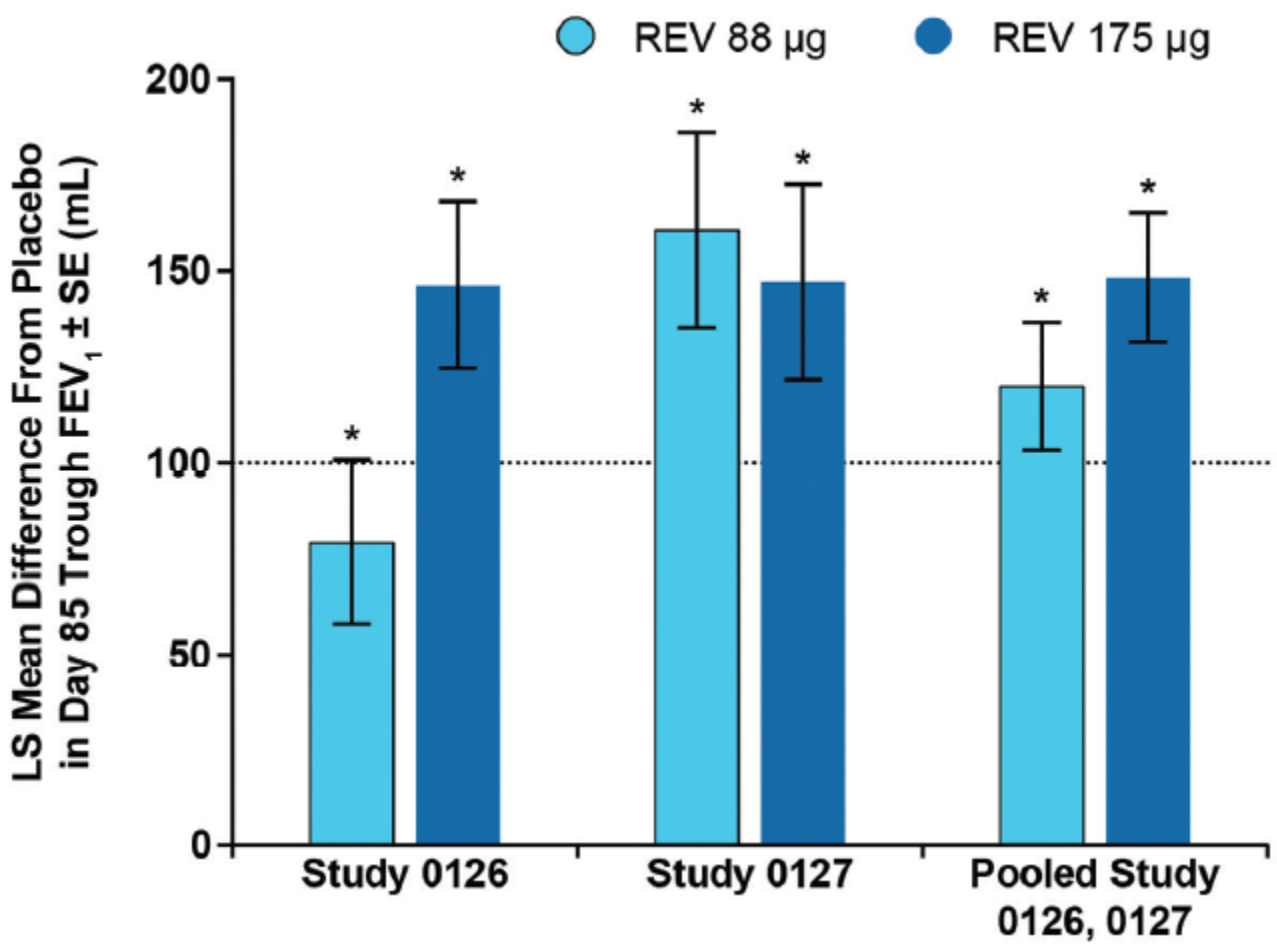
SOURCE: Yupelri™ (revefenacin). Prescribing Information. Morgantown, WV. 2018.

Two Replicate Phase III Clinical Trials

- Phase III, randomized, double-blind, placebo-controlled, multiple-dose, parallel-group studies
  - Revefenacin 88 mcg nebulized once daily x 12 weeks
  - Revefenacin 175 mcg nebulized once daily x 12 weeks
  - Matching placebo
- Primary efficacy end point
  - Change from baseline in trough FEV_1 on day 85
- Safety assessment
  - Adverse events
  - Clinical laboratory measurements
  - EKG
  - Vital signs
  - Physical examination

SOURCE: Ferguson GT, Feldman G, Pudi KK, et al. *Chronic Obstr Pulm Dis* 2019;6(2):154-165.

Results – Efficacy



* P < 0.001 versus placebo

SOURCE: Ferguson GT, Feldman G, Pudi KK, et al. *Chronic Obstr Pulm Dis* 2019;6(2):154-165.

Results – Safety

Patients with an adverse event, n (%)	Study 0126			Study 0127		
	REV 88 mcg (N = 212)	REV 175 mcg (N = 198)	Placebo (N = 209)	REV 88 mcg (N = 205)	REV 175 mcg (N = 197)	Placebo (N = 209)
Any AE	**110 (51.9)**	**101 (51.0)**	**108 (51.7)**	**116 (56.6)**	**102 (51.8)**	**98 (46.9)**
Patients with an SAE, n (%)						
Any SAE	**10 (4.7)**	**10 (5.1)**	**14 (6.7)**	**11 (5.4)**	**5 (2.5)**	**7 (3.3)**
COPD	0	4 (2.0)	2 (1.0)	8 (3.9)	1 (0.5)	4 (1.9)
Chest Pain	1 (0.5)	1 (0.5)	0	1 (0.5)	0	0
Cellulitis	1 (0.5)	0	0	1 (0.5)	0	1 (0.5)
Acute myocardial infarction	1 (0.5)	1 (0.5)	0	0	0	0
Upper GI hemorrhage	1 (0.5)	1 (0.5)	0	0	0	0
Noncardiac chest pain	0	1 (0.5)	1 (0.5)	0	0	0
Acute respiratory failure	0	0	0	2 (1.0)	0	0
Respiratory failure	0	0	1 (0.5)	1 (0.5)	0	0
Patients with an antimuscarinic-related AE, n (%)						
Constipation	1 (0.5)	2 (1.0)	0	2 (1.0)	0	1 (0.5)
Dry mouth	0	2 (1.0)	0	1 (0.5)	1 (0.5)	0
Dysuria	0	0	0	2 (1.0)	0	0

AE = adverse event; REV = revefenacin; SAE = serious adverse event; COPD = chronic obstructive pulmonary disease; GI = gastrointestinal

SOURCE: Ferguson GT, Feldman G, Pudi KK, et al. *Chronic Obstr Pulm Dis* 2019;6(2):154-165.

Question 1 – Pharmacists

Which of the following has the correct brand name matched with the correct generic name?

A. Krintafel® (cannabidiol)
B. Tpoxx® (tezacaftor-ivacaftor)
C. Yupelri™ (revefenacin)
D. Omegaven® (tafenoquine)

Response 1 – Pharmacists

Which of the following has the correct brand name matched with the correct generic name?

A. Krintafel® (cannabidiol)
B. Tpoxx® (tezacaftor-ivacaftor)
C. Yupelri™ (revefenacin)
D. Omegaven® (tafenoquine)

Question 2 – Pharmacists

The following medication inhibits influenza virus replication by inhibiting the endonuclease activity of the polymerase acidic protein, an influenza virus-specific enzyme required for viral gene transcription

A. Andexxa® (andexanet alfa)
B. Xofluza™ (baloxavir marboxil)
C. Symdeko™ (tezacaftor-ivacaftor)
D. Krintafel ® (tafenoquine)

Response 2 – Pharmacists

The following medication inhibits influenza virus replication by inhibiting the endonuclease activity of the polymerase acidic protein, an influenza virus-specific enzyme required for viral gene transcription.

A. Andexxa® (andexanet alfa)
B. Xofluza™ (baloxavir marboxil)
C. Symdeko™ (tezacaftor-ivacaftor)
D. Krintafel® (tafenoquine)

Question 3 – Pharmacists

The following medication has a black box warning for thromboembolic risks, cardiac arrest and sudden death

A. Yupelri™ (revefenacin)
B. Epidiolex® (cannabidiol)
C. Omegaven® (fish oil triglycerides)
D. Andexxa® (andexanet alfa)

Response 3 – Pharmacists

The following medication has a black box warning for thromboembolic risks, cardiac arrest and sudden death

A. Yupelri™ (revefenacin)
B. Epidiolex® (cannabidiol)
C. Omegaven® (fish oil triglycerides)
D. Andexxa® (andexanet alfa)

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Question 4 – Pharmacists

Unlike other medications in its class, Yupelri™ (revefenacin) is manufactured as the following dosage form

A. Dry powder inhaler
B. Multi-dose inhaler
C. Nebulization
D. All of the above
E. None of the above

Response 4 – Pharmacists

Unlike other medications in its class, Yupelri™ (revefenacin) is manufactured as the following dosage form:

A. Dry powder inhaler
B. Multi-dose inhaler
C. Nebulization
D. All of the above
E. None of the above

Question 5 – Technicians

The following medication must be stored securely due to its controlled substance status

A. Tpoxx® (tecovirimat)
B. Epidiolex® (cannabidiol)
C. Symdeko™ (tezacaftor-ivacaftor)
D. Xofluza™ (baloxavir marboxil)

Response 5 – Technicians

The following medication must be stored securely due to its controlled substance status:

A. Tpoxx® (tecovirimat)
B. Epidiolex® (cannabidiol)
C. Symdeko™ (tezacaftor-ivacaftor)
D. Xofluza™ (baloxavir marboxil)

Question 6 – Technicians

The following medication requires reconstitution and then further dilution prior to dispensing:

A. Krintafel® (tafenoquine)
B. Andexxa® (andexanet alfa)
C. Omegaven® (fish oil triglycerides)
D. Yupelri™ (revefenacin)

Response 6 – Technicians

The following medication requires reconstitution and then further dilution prior to dispensing:

A. Krintafel® (tafenoquine)
B. Andexxa® (andexanet alfa)
C. Omegaven® (fish oil triglycerides)
D. Yupelri™ (revefenacin)

Question 7 – Pharmacists

Patient counseling for which of the following medications should include that it should be taken with food to help increase absorption:

A. Symdeko™ (tezacaftor-ivacaftor)
B. Tpoxx® (tecovirimat)
C. Krintafel® (tafenoquine)
D. All of the above
E. None of the above

Response 7 – Pharmacists

Patient counseling for which of the following medications should include that it should be taken with food to help increase absorption:

A. Symdeko™ (tezacaftor-ivacaftor)
B. Tpoxx® (tecovirimat)
C. Krintafel® (tafenoquine)
D. All of the above
E. None of the above

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FDA Updates 2018

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Prescription Opioid Cough and Cold Medicines: Labeling Changes

- January 11, 2018
- FDA is restricting the use of codeine and tramadol medicines in children
  - Codeine and tramadol now contraindicated in children less than 12 years of age
  - Tramadol is now contraindicated in children less than 18 years of age to treat pain after surgery to remove the tonsils and/or adenoids
  - Recommendation against their use in adolescents between 12 and 18 years of age
  - Recommendation against their use in breastfeeding mothers
- Recommendation
  - Health care professionals
    - Be aware that FDA is changing the age range for which prescription opioid cough and cold medicines are indicated
    - Reassure parents that cough due to a cold or upper respiratory infection is self-limited and generally does not need to be treated
    - Recommend other products such as dextromethorphan or benzonatate
  - Patients
    - Be aware that opioid cough and cold medicines that include codeine or hydrocodone should not be used in children
    - Read labels on prescription bottles and talk to healthcare professional to ensure that child's medication does not contain codeine or hydrocodone

SOURCE: FDA Drug Safety Communication: Prescription Opioid Cough and Cold Medicines: Drug Safety Communication – FDA Requires Labeling Changes. Available at: https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm592053.htm. Accessed February 22, 2019.

Clarithromycin: Potential Increased Risk of Health Problems or Death in Patients with Heart Disease

- February 22, 2018
- FDA is advising caution before prescribing the antibiotic clarithromycin to patients with heart disease because of a potential increased risk of heart problems or death that can occur years later
  - CLARICOR trial observed an unexpected increase in deaths among patients with coronary heart disease who received a two-week course of clarithromycin
  - FDA is unable to determine why the risk of death is greater for patients with heart disease
  - FDA added a new warning about this increased risk of death in patients with heart disease
- Recommendation
  - Health care professionals
    - Be aware of these significant risks and weigh the benefits and risks of clarithromycin before prescribing to any patient
  - Patients
    - Tell your health care professionals if you have heart disease
    - Don’t stop take medications without speaking with health care professional

SOURCE: FDA Drug Safety Communication: Clarithromycin (Biaxin): Drug Safety Communication – Potential Increased Risk of Heart Problems or Death in Patients with Heart Disease. Available at: https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm597862.htm. Accessed February 22, 2019.

Lamictal: Serious Immune System Reaction

- April 25, 2018
- FDA is warning that lamotrigine can cause a rare but serious reaction that excessively activates the body's infection fighting immune system – hemophagocytic lymphohistiocytosis (HLH)
  - New warning asked to be added to the prescribing information
- Recommendation
  - Health care professionals
    - Prompt recognition and early treatment is important for improving HLH outcomes and decreasing mortality
    - Evaluate patients who develop fever or rash promptly and discontinue lamotrigine if HLH is suspected
  - Patients
    - Contact health care professionals right away if they are experiencing symptoms of HLH (fever, enlarged liver, skin rashes, yellow skin, unusual bleeding)

SOURCE: FDA Drug Safety Communication: Lamictal (Lamotrigine): Drug Safety Communication – Serious Immune System Reaction. Available at: https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm605628.htm. Accessed February 22, 2019.

Fluoroquinolone Antibiotics: FDA Requires Labeling Changes

- July 10th, 2018
- FDA is strengthening the current warnings regarding fluoroquinolones causing significant decreases in blood sugar and certain mental health side effects
  - Add warning that low blood sugars can lead to coma
  - Make mental health side effects more prominent and consistent across the drug class
- Recommendation
  - Health care professionals
    - Be aware of potential risk of hypoglycemia, especially in the elderly and those taking an oral hypoglycemic or insulin
    - Have patients more carefully monitor blood glucose levels
    - Inform patients about risk of psychiatric adverse reactions
    - Do not prescribe fluoroquinolones in patients who have other treatment options
  - Patients
    - Tell your health care professionals if you are taking a diabetes medication
    - Monitor blood sugar more often while taking a fluoroquinolone

SOURCE: FDA Drug Safety Communication: Fluoroquinolone Antibiotics: FDA Requires Labeling Changes Due to Low Blood Sugar Levels and Mental Health Side Effects. Available at: https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm612979.htm. Accessed February 22, 2019.

Zithromax: Increased Risk of Cancer Relapse with Long-term Use After Donor Stem Cell Transplant

- August 3, 2018
- FDA is warning that azithromycin can cause increased rate of relapse in cancers affecting blood and lymph nodes when given to patients who underwent a donor stem cell transplant
  - Studied for treatment of bronchiolitis obliterans syndrome

- Recommendation
  - Health care professionals
    - Do not give azithromycin for long-term prevention of bronchiolitis obliterans syndrome in patients who underwent a donor stem cell transplant
  - Patients
    - Do not stop taking medication without speaking with health care professional first

SOURCE: FDA Drug Safety Communication: Zithromax, Zmax (Azithromycin): FDA Warning – Increased Risk of Cancer Relapse with Long-Term Use After Donor Stem Cell Transplant. Available at: https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm615738.htm. Accessed February 22, 2019.

Conclusion

- In 2018 …
  - 59 novel drugs approved
    - 19 first in class
    - 34 to treat rare diseases
    - 14 designated as breakthrough therapies
  - 16 new medications for cancer
  - 11 new medications to treat infectious diseases
  - Multiple FDA updates

Question 8 – Pharmacists

The following medication now has added labeling regarding its risk of causing hemophagocytic lymphohistiocytosis (HLH)

A. Tramadol
B. Zithromax® (azithromycin)
C. Clarithromycin
D. Lamictal® (lamotrigine)

Response 8 – Pharmacists

The following medication now has added labeling regarding its risk of causing hemophagocytic lymphohistiocytosis (HLH)

A. Tramadol
B. Zithromax® (azithromycin)
C. Clarithromycin
D. Lamictal® (lamotrigine)

Thank you!

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