Keeping Up with FDA Drug Approvals: 60 New Drugs in 60 Minutes

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April 10, 2019

Program Objectives

By the end of the presentation, the pharmacist or pharmacy technician participant will be able to:

- Identify orphan drugs and first-in-class medications approved by the FDA in 2018.
- List five new drugs and their indications.
- Identify the place in therapy for three novel monoclonal antibodies.
- Discuss at least two new medications that address public health concerns.

Dr. Shlom does not have any conflicts of interest in regard to this presentation.

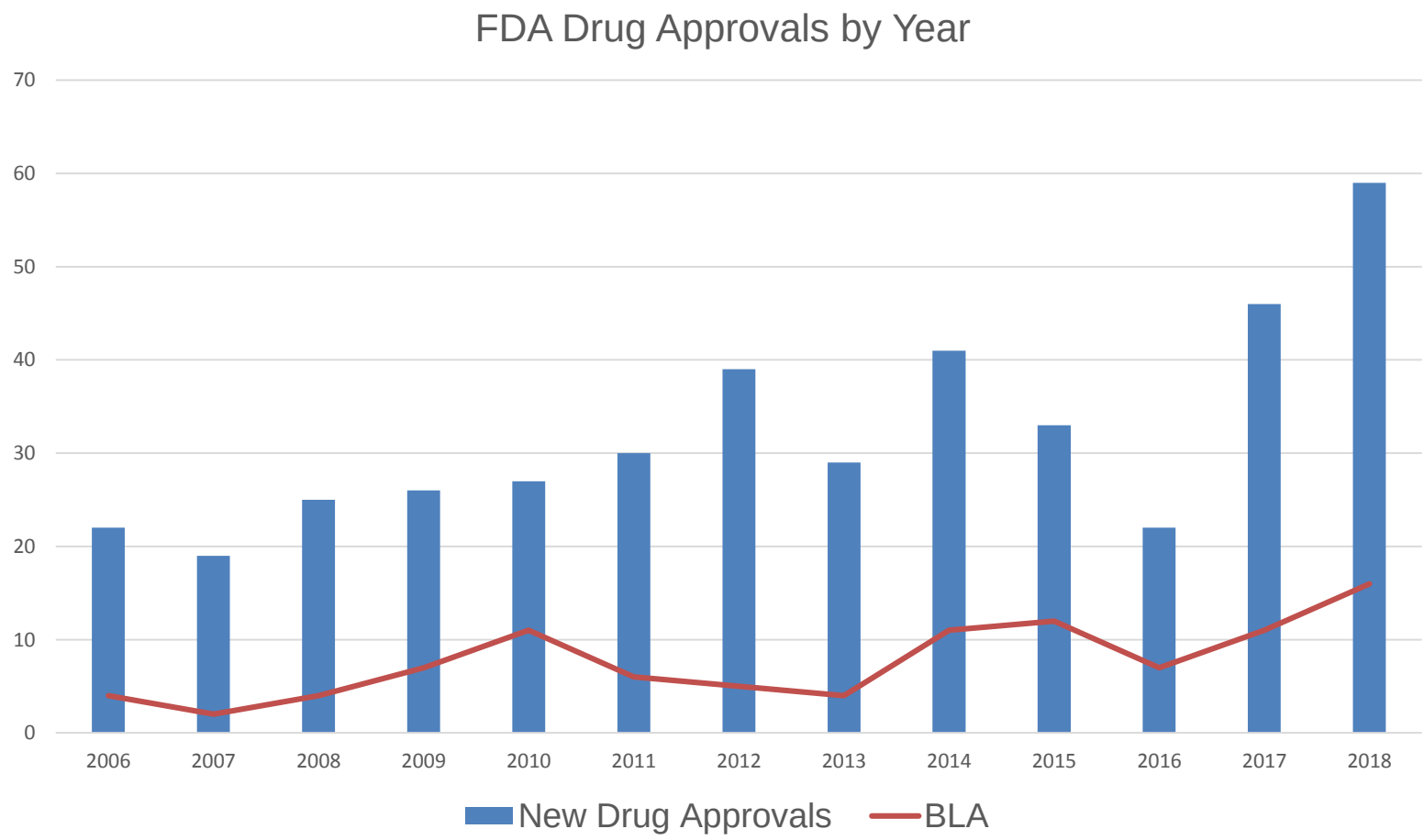
Both trade names and generic names will be discussed throughout the presentation

2018 NDA Approvals (NMEs/BLAs)

- Lutathera (lutetium Lu 177 dotatate)
- Biktarvy (bictegravir, emtricitabine, tenofovir, alafenamide)
- Symdeko (tezacaftor, ivacaftor)
- Erleada (apalutamide)
- Trogarzo (ibalizumab-uiyk)
- Ilumya (tildrakizumab-asmn)
- Tavalisse (fostamatinib disodium)
- Crysvita (burosumab-twza)
- Akynzeo (fosnetupitant, palonosetron)
- Lucemyra (lofexidine)
- Aimovig (erenumab-aooe)
- Lokelma (sodium zirconium cyclosilicate)
- Doptelet (avatrombopag maleate)
- Palynziq (pegvaliase-pqpz)
- Olumiant (baricitinib)
- Moxidectin (moxidectin)
- Epidiolex (cannabidiol)
- Zemdri (plazomicin)
- Mektovi (binimetinib)
- Braftovi (encorafenib)
- TPOXX (tecovirimat)
- Tibsovo (ivosidenib)
- Krintafel (tafenoquine)
- Orilissa (elagolix sodium)
- Omegaven (fish oil triglycerides)
- Mulpleta (lusutrombopag)
- Poteligeo (mogamulizumab-kpkc)
- Onpattro (patisiran)
- Annovera (segesterone acetate, ethinyl estradiol)
- Galafold (migalastat)
- Diacomit (stiripentol)
- Oxervate (cenegermin-bkbj)
- Takhzyro (lanadelumab)
- Xerava (eravacycline)
- Pifeltro (doravirine)
- Lumoxiti (moxetumomab pasudotox-tdfk)
- Ajovy (fremanezumab-vfrm)
- Copiktra (duvelisib)
- Emgality (galcanezumab-gnlm)
- Vizimpro (dacomitinib)
- Libtayo (cemiplimab-rwic)
- Seysara (sarecycline)
- Nuzyra (omadacycline)
- Revcovi (elapegademase-lvir)
- Tegsedi (inotersen)
- Talzenna (talazoparib)
- Xofluza (baloxavir marboxil)
- Lorbrena (lorlatinib)
- Yupelri (revefenacin)
- Aemcolo (rifamycin)
- Gamifant (emapalumab-lzsg)
- Daurismo (glasdegib)
- Vitrakvi (larotrectinib)
- Firdapse (amifampridine)
- Xospata (gilteritinib)
- Motegrity (prucalopride)
- Asparlas (calaspargase pegol-mknl)
- Elzonris (tagraxofusp-erzs)
- Ultomiris (ravulizumab-cwvz)

History of FDA Approvals

- 2018 – 59 new drug approvals
- 16 monoclonal antibodies
- 19 (32%) first-in-class medications
- 34 (58%) for orphan diseases
  - 1983 to 2009: average of 8 orphan drugs per year
  - 2009 to 2015: 37% of drug approvals were orphan drugs
- 17 new oncology medications in 2018



Kesselheim AS, Treasure CL, Joffe S. Biomarker-defined subsets of common diseases:: Policy and economic implications of orphan drug act coverage. PLoS Med 2017;14(1):e1002190

FDA Approval Designations

ORPHAN DRUG

Designation for a drug or biological product to treat a rare disease or condition

Prevalence of 200,000 or fewer patients

ACCELERATED APPROVAL

Regulations allowing drugs for serious conditions that fill an unmet medical need to be approved based on a surrogate endpoint

BREAKTHROUGH THERAPY

Process designed to expedite the development and review of drugs that may demonstrate substantial improvement over available therapies

PRIORITY REVIEW

Designation meaning that the FDA's goal is to take action on an application within 6 months vs. 10 months with standard review

FAST TRACK

Process to facilitate development and expedite review of drugs to treat serious conditions and fill an unmet medical need

https://www.fda.gov/ForPatients/Approvals/Fast/default.htm
https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM629290.pdf

Anti-Infectives

Antibiotics

- Aminoglycoside
  - Zemdri™ (plazomicin)
- Tetracyclines
  - Xerava™ (eravacycline)
  - Nuzyra™ (omadacycline)
  - Seysara™ (sarecycline)

HIV medications

- Biktarvy® (bictegravir, emtricitabine, tenofovir alafenamide)
- Trogarzo™ (ibalizumab-uiyk)
- Pifeltro™ (doravirine)

Anti-viral medications

- Tpoxx ® (tecovirimat)
- Xofluza™ (baloxavir marboxil)

Anti-malarial medication

- Krintafel® (tafenoquine)

Antihelmintic

- Moxidectin® (moxidectin)

Antibiotics

New aminoglycoside - **Zemdri™ (plazomicin)**

- Complicated urinary tract infections in adults (including pyelonephritis)
  - Once-daily administration: 15 mg/kg IV every 24 hours (CrCl ≥ 60 mL/min)
    - Dosing in renal impairment: 10mg/kg Q 24hrs (CrCl 30-60), 10mg/kg Q 48h(CrCl 15-30)
    - Administer over 30 min diluted in normal saline or lactated ringers
  - PK monitoring: if serum trough levels >3 mcg/mL, prolong dosing interval by 1.5 times
  - Effective against enterobacteriaceae (*E. coli, K. pneumoniae, P. mirabilis, E. cloacae*) including those resistant to carbapenems and other aminoglycosides
    - Additional data needed to demonstrate efficacy against *P. aeruginosa* and Staph spp (including MRSA) (*J Antimicrob Chemother, 2018;73(12):3346–3354; Pharmacotherapy 2019;39(1):77-93*)

Boxed warning: nephrotoxicity, ototoxicity, neuromuscular blockade, fetal harm

Antibiotics – New Tetracyclines

Xerava™ (Eravacycline)

- Fully synthetic fluorocycline
- **Complicated intra-abdominal infections**
  - First- or second-line antibiotic
  - Coverage: some highly resistant gram negatives (e.g., CRE and Acinetobacter), MRSA, VRE and anaerobes
- Two trials showed lack of efficacy for complicated UTI
- 1 mg/kg IV every 12 hours
  - 4-14 day treatment
  - Cost approx. $200 per day

Nuzyra™ (Omadacycline)

- Semi-synthetic aminomethylcycline
- **Community-acquired pneumonia** and **acute bacterial skin/skin structure infections**
  - Coverage: gram positives, anaerobes, gram negatives, and atypicals (e.g. *C. pneumoniae, L. pneumophilia, M. pneumoniae)*
- 200 mg IV LD, 100 mg IV QD, or 300 mg PO QD
- ADEs >5%: nausea (21%), vomiting (11%), infusion site reactions (5%)

Seysara™ (Sarecycline)

- **Mod-severe acne vulgaris**
  - Patients ≥ 9 years
- Once daily oral dosing
  - 60 mg (weight: 33-54 kg)
  - 100 mg (weight: 55-84 kg)
  - 150 mg (weight: 85-136 kg)
- Drug interactions:
  - Avoid concomitant use with oral retinoids or penicillin
  - Separate dosing from antacids
- 22% therapy success vs. 13% with placebo after 12 weeks

Warnings in last half of pregnancy, infants and children up to age 8 : Permanent tooth discoloration, tooth enamel hypoplasia and inhibition of bone growth

Anti-Viral medications

- First drug to treat smallpox -**Tpoxx® (tecovirimat)** **First-in-Class** **Orphan Drug**
  - WHO: global eradication of smallpox in 1980
  - FDA – priority status as a “Material Threat Medical Countermeasure”
    - “Animal Rule” permits efficacy testing on animals when not feasible for human trials
    - Developed by Siga Technologies in conjunction with U.S. Biomedical Adv Res and Dev Authority
    - Added to national stockpile
  - Dosing for adults and children ≥13 kg: 1-3 capsules twice daily x 14 days
- **Xofluza™ (baloxavir marboxil)** **First-in-Class**
  - New antiviral medication class – endonuclease inhibitor – for treatment of acute, uncomplicated influenza infection < 48 hours duration
  - Single oral dose (ages ≥12 years): 40 mg for patients weighing 40 to < 80 kg; 80mg for ≥80 kg
  - Awaiting study data in patients with CrCl < 50 mL/min and with concomitant diseases (asthma, diabetes, CV disease, etc.)

New Medications for HIV

Trogarzo™ (Ibalizumab-uiyk)

- **HIV-1 infection in heavily treatment-experienced & MDR patients**
- MOA: CD4-directed post-attachment HIV-1 inhibitor (first-in-class)
- Dose: 2,000 mg IV loading dose then 800 mg IV every 2 weeks
  - Admin in infusion center
  - Used in combination with other antiretrovirals
  - Salvage therapy
- ADEs ≥5%: diarrhea (8%), dizziness (8%), nausea (5%), rash (5%)
- 43% HIV suppression after 24 weeks
- Cost: $1,135 per 200 mg vial (WAC)

First-in-Class | Orphan Drug | Breakthrough Status

Biktarvy®

- **HIV-1 infection in treatment-naïve or experienced patients**
- Dose: one tablet once daily
  - 50 mg of bictegravir
  - 200 mg of emtricitabine
  - 25 mg of tenofovir alafenamide
- 11th product on market as complete one-pill, once-daily regimen for HIV
- Boxed warning: exacerbation of hepatitis B infections
- ADEs ≥5%: diarrhea (6%), nausea (6%), and headache (5%)

Pifeltro™ (Doravirine)

- **HIV-1 infection (tx-naïve)**
- MOA: non-nucleoside reverse transcriptase inhibitor (NNRTI)
  - Active against some drug-resistant HIV strains
- Dose: 100 mg tab once daily
- Contraindicated with strong CYP3A inducers

Delstrigo™ (#60)

- **HIV-1 infection (tx-naïve)**
- Dose: one tablet once daily
  - 100 mg doravirine
  - 300 mg lamivudine
  - 300 mg tenofovir disoproxil fum
- Not with CrCl < 50 mL/min

New Anti-Infectives for Tropical Diseases

- **Krintafel® (tafenoquine) for Prevention of Malaria Relapse**
  - 300 mg single oral dose for patients ≥16 years old
    - Administered at same time as treatment for *Plasmodium vivax* malaria infections
    - 6 month malaria recurrence reduced from 66% with placebo to 33% with tafenoquine
  - Contraindicated with G6PD deficiency or unknown G6PD status

Orphan Drug

Breakthrough Status

- **Moxidectin for Onchocerciasis aka "*River Blindness*"**
  - Parasitic worm, *Onchocerca volvulus,* transmitted by black flies is common in tropical areas with rapidly flowing rivers (Africa, Middle East, Central and South America)
    - Moxidectin significantly reduced parasitic worm microfilariae skin density vs. ivermectin at 1, 6 and 12 months
  - 8 mg single oral dose – mean half-life 23 days; for use in patients ≥12 years old
  - Will replace ivermectin in annual community protection programs when a donation sponsor is named

Orphan Drug

Blood Disorders

- Treatments for thrombocytopenia
  - Tavalisse™ (fostamatinib disodium hexahydrate)
  - Doptelet® (avatrombopag)
  - Mulpleta® (lusutrombopag)
- Orphan Diseases
  - X-linked hypophosphatemia
    - Crysvita® (burosumab-twza)
  - Primary hemophagocytic lymphohistiocytosis
    - Gamifant® (emapalumab-izsg)
  - Paroxysmal nocturnal hemoglobinuria
    - Ultomiris™ (ravulizumab -cwvz)

- Treatment for Hyperkalemia
  - Lokelma™ (Sodium zirconium cyclosilicate)

Treatments for Thrombocytopenia

Tavalisse™ (fostamatinib disodium hexahydrate)

Chronic Immune Thrombocytopenia (adults)

- 2nd/3rd line treatment – reduces antibody-mediated platelet destruction — Orphan Drug
- Oral agent targeting spleen tyrosine kinase (SYK) — First-in-Class
- 100 mg twice daily
  - Titrate dose to treatment goal: platelets ≥ 50 x 10^9/L
  - Discontinue after 12 weeks if insufficient response
  - Monitor/adjust dose for ADEs (incre. BP, LFTs, diarrhea, neutropenia)
- Clin trials: 16-18% response vs 0-4% with placebo

Doptelet® (avatrombopag) & Mulpleta® (lusutrombopag)

Thrombocytopenia with chronic liver disease – for patients scheduled to undergo a procedure with low/mod/high bleeding risk

- 64-84% incidence of thrombocytopenia with cirrhosis or fibrosis
- MOA: oral thrombopoietin receptor agonists – stimulating bone marrow production of platelets

Doptelet	Mulpleta
Dose based on platelet count: <40 x 10^9/L → 60 mg QD x 5 days 40 to < 50 x 10^9/L → 40 mg QD x 5 days	Dose: 3 mg QD x 7 days
Start: 10-13 days prior to procedure	Start: 8-14 days prior to procedure
Procedure: 5-8 days after last dose	Procedure:2-8 days after last dose
Cost: 40 mg dose $9000; 60 mg dose $14,500	Cost: $8500

- Clinical trials for both demonstrated statistically significant reduction in platelet transfusions or rescue procedures for bleeding with procedures

New Monoclonal Antibodies for Orphan Disease Blood Disorders

First-in-Class

Breakthrough Status

Crysvita® (burosumab-twza) for X-linked hypophosphatemia (XLH)

What is X-linked hypophosphatemia?

Hereditary or de novo mutation hypophosphatemia resulting in abnormal bone growth and rickets; resistant to Vitamin D administration

- Prevalence: 1/20,000
- Leads to small stature, bone pain, repeated surgeries for bone deformities
- Treatments: phosphate supplements, high-dose calcitriol, growth hormone, corrective surgeries

MOA:
human immunoglobulin that blocks fibroblast growth factor 23 (FGF23) -- restoring normal reabsorption of phosphate in kidneys and increasing 1,25 dihydroxyvitamin D serum concentrations

Dosing:

- SC; adjust to obtain serum phosphate level 3.5-5.0 mg/dL
- Pediatrics (1-18 years): start at 0.8 mg/kg q 2 weeks; adjust to max dose of 90 mg q 2 weeks
- Adults: start at 1 mg/kg q 4 weeks; adjust to max dose of 90 mg q 4 weeks

Clinical trials: significant improvement in fracture healing (adults), rickets response (children), increase in serum phosphate to desired range in 94% of patients
ADEs: >40% of pediatric patients had headache, pyrexia, injection site reactions, vomiting, and injection site reactions; adult subjects had back pain (15%), headache (13%), tooth infection (13%), dizziness (10%)

New Monoclonal Antibodies for Orphan Disease Blood Disorders Gamifant® (emapalumab-lzsg) for primary hemophagocytic lymphohistiocytosis (HLH)

First-in-Class

Breakthrough Status

What is hemophagocytic lymphohistiocytosis? (HLH)

Primary HLH is an inherited condition (autosomal recessive) in which the body's immune cells are overactive, leading to inflammation that can damage the liver, brain, and bone marrow

- Incidence: 1/100,000 children
- Presentation: fever, pancytopenia, multi-organ involvement, serum ferritin > 500 ng/mL
- Treatments: immunosuppressants (steroids, cyclosporine, methotrexate), bone marrow transplantation

MOA:

binds and neutralizes interferon gamma, which is hyper-secreted in HLH

Dosing:

- 1 mg/kg IV infusion twice a week – administered over 60 minutes
- Dexamethasone is administered concomitantly
- May increase dose to 10 mg/kg based on lack of response and patient factors
- Continue treatment until bone marrow transplant or toxicity requires discontinuation

Phase 2 trial: 27 pediatric patients (up to 13 years old) with 63% overall response, 26% complete response (normalization of HLH abnormalities)
ADEs occurring >20%: infections, hypertension, infusion-related reactions, and pyrexia

New Monoclonal Antibodies for Orphan Disease Blood Disorders
Ultomiris™ (ravulizumab-cwvz) for paroxysmal nocturnal hemoglobinuria

What is paroxysmal nocturnal hemoglobinuria (PNH)?

PNH is an acquired stem cell disorder leading to rupture or destruction of red blood cells that is triggered by stresses such as exercise or infection

- Prevalence: 1-5 cases per million in world
- Presentation: clinical triad of hemolytic anemia, bone marrow failure, and propensity for thromboembolism; life-threatening condition
- Other treatments: eculizumab (Soliris®); stem cell transplantation

MOA: inhibits terminal complement-mediated intravascular hemolysis in patients with PNH

Dosing:

- IV loading dose (LD) then IV maintenance dosing starting 2 weeks after LD, then every 8 weeks
  - Eculizumab is admin every 2 weeks IV
- Weight-based dosing: 40-<60 kg, 60-<100 kg, >100 kg

REMS: due to meningococcal infection/sepsis risk, vaccination required prior to ravulizumab administration

Clinical trials: ravulizumab non-inferior to eculizumab (standard of care) in avoiding hemolysis or transfusions in treatment-naïve patients (n=246) and eculizumab-experienced patients (n=195)

ADEs similar to eculizumab: upper respiratory tract infections (39%), headache (32%), <10% D/N/V

Lokelma™ for Hyperkalemia

- Non-absorbed potassium binder for hyperkalemia in adults
  - Increases fecal elimination of potassium
  - Not for emergency treatment of life-threatening hyperkalemia
- Starting Dose: 10 grams 3 times a day – for up to 48 hours
  - Maintenance Dose: 10 grams once daily
  - Dissolve powder in water
- Drug interactions – separate administration of other oral meds by 2 hours, before and after

Brand	Lokelma	Veltassa	Kayexalate
Generic	Sodium zirconium cyclosilicate	Patiromer calcium sorbitex	Sodium polystyrene sulfonate
Dose	10 g TID x 48 hours, then 5 g, 10 g or 15 g daily	8.4 g once daily; max 25.2 g/day	15 g 1-4 times a day
Onset	1-6 hours	7-48 hours	2-6 hours
Duration	6-24 hours	12-24 hours	6-24 hours
Affinity for potassium	Highly selective; also binds ammonium	Selective, also binds magnesium	Non-selective, also binds calcium and magnesium
Sodium content	1,000 mg per 10 g dose	None	1,500 mg per 15 g dose
Sorbitol content	None	4 g per 8.4 g dose	20 g per 15 g dose

Beccari MV, Meaney CJ. Core Evid 2017;12:11-24

Endocrine and Metabolic Disorders

- Cystic fibrosis
  - Symdeko® (ivacaftor and tezacaftor)
- Phenylketonuria
  - Palynziq™ (pegvaliase-pqpz)
- Fabry disease
  - Galafold® (migalastat)
- Amyloidosis polyneuropathy
  - Onpattro™ (patisiran)
  - Tegsedi™ (inotersen)
- Endometriosis pain
  - Orilissa® (elagolix sodium)
- Contraceptive
  - Annovera™ (segesterone acetate & ethinyl estradiol)

Endocrine and Metabolic Disorders

- **Symdeko® (tezacaftor, ivacaftor) for Cystic Fibrosis** Orphan Drug Breakthrough Status
  - For CF patients ≥12 years and with two *F508del* mutations or one mutation responsive to tezacaftor/ivacaftor
  - Tezacaftor is a CFTR modulator similar to lumacaftor (in Orkambi®) – both available in combination with ivacaftor, which potentiates the CFTR protein brought to the cell surface
  - Dose: one tablet (tezacaftor 100 mg/ivacaftor 150 mg) every morning + one tablet (ivacaftor 150 mg) every evening,12 hours apart
    - Dose reductions with mod/sev hepatic impairment or mod/strong CYP3a inhibitors
- **Palynziq™ (pegvaliase-pqpz) for Phenylketonuria (PKU)** Orphan Drug First-in-Class
  - PKU screening of newborns: incidence is 1 in 13,500-19,000 newborns; elevated phenylalanine blood levels lead to irreversible brain damage and neurological complications
  - MOA: a PEGylated enzyme that converts phenylalanine to ammonia and *trans*-cinnamic acid
  - Dose: started at 2.5 mg SC once weekly x 4 then titrated to achieve 20% blood phenylalanine reduction with once-daily dosing; adjust dietary protein and phenylalanine intake;
  - **REMS: for dosing adjustments; risk of anaphylaxis (must carry epinephrine at all times)**

Endocrine and Metabolic Disorders

Orphan Drug | First-in-Class

Galafold® (migalastat)

For adults with Fabry disease and amenable galactosidae alpha gene variant based on in vitro test (list avail in PI)

MOA: "Oral Chaperone Therapy" stabilizing certain dysfunctional alpha-Gal A, and restoring its activity

Dosing: 123 mg tablet once every other day

Clinical trials: >50% reduction in disease-causing glycolipid accumulation vs. 45% reduction with placebo

ADEs >10%: headache, nasopharyngitis, UTI, nausea, pyrexia

What is Fabry Disease?

Rare x-linked lysosomal storage disorder due to deficient activity of alpha-galactosidase A (alpha-Gal A) enzyme and leads to build-up of glycolipids

- Prevalence: 1/40,000-60,000
- Presentation:
  - Begins as pain/burning in hands and feet, cloudy vision, hearing loss, joint pain
  - Progressive organ dysfunction especially affecting the heart and kidneys at age 30-45 years
- Other treatment:
  - Enzyme replacement - agalsidase beta (Fabrazyme®) 1 mg/kg IV every 2 weeks

Endocrine and Metabolic Disorders

Onpattro™ (patisiran)

- Small interfering ribonucleic acid (siRNA) treatment encased in a nanoparticle to travel directly to liver; alters or stops the production of disease-causing proteins
- Dose: 0.3 mg/kg every 3 weeks by IV infusion
- 18-month improvement in quality of life, 10-meter walk test and neuropathy impairment scores

First-in-Class Breakthrough Status

Tegsedi™ (inotersen)

First-in-Class

- Transthyretin-directed antisense oligonucleotide
- Dose: 284 mg SC once weekly
- Boxed warnings: thrombocytopenia, glomerulonephritis; REMS for distribution

Orphan Disease

What is Polyneuropathy of Amyloidosis?

Deposition of amyloid protein affecting peripheral sensory, motor, or autonomic nerves and leads to degeneration and dysfunction of the nerves.
Inherited as mutation in transthyretin (TTR) gene

- Prevalence: 1/100,000 (U.S.); most common in Portugal, Sweden, and Japan
- Presentation:
  - symptoms start in adulthood; progress slowly
  - less likely to feel pain or heat, have trouble walking, carpal tunnel syndrome, weight loss
- Treatments: liver transplant to remove source of amyloid; medications to slow amyloid growth; changes in diet to help ease symptoms

Endocrine and Metabolic Disorders

First-in-Class

- **Orilissa® (elagolix sodium) for moderate to severe endometriosis pain**
  - 1 in 10 women of reproductive age have endometriosis lesions that develop on ovaries, fallopian tubes, bladder, intestines, etc., from retrograde menstruation
  - MOA: first oral gonadotropin-releasing hormone (GnRH) receptor antagonist – decreasing estradiol and progesterone
  - Dose: 150 mg once daily for up to 24 months or 200 mg twice daily for up to 6 months
    - Moderate hepatic impairment – dose is 150 mg once daily for up to 6 months
    - Dose-dependent decrease in bone mineral density; contraindicated in patients with known osteoporosis or severe hepatic failure
    - Reduced efficacy with estrogen-containing contraceptives
  - ADEs >10%: hot flushes, night sweats, headache, nausea
  - Clinical trials demonstrated significant reduction in dysmenorrhea and non-menstrual pelvic pain
- **Annovera™ (segesterone acetate & ethinyl estradiol) for contraception**
  - First vaginal ring - left in place for 21 days, removed for 7 days, repeated for 13 cycles
  - Segesterone acetate is a new progestin
  - 17 clinical trials demonstrated contraceptive efficacy of 97.3%

Gastrointestinal Disorders

- Cholestasis in pediatric patients on parenteral nutrition
  - Omegaven® (fish oil triglycerides)
- Traveler's diarrhea
  - Aemcolo™ (rifamycin)
- Chronic idiopathic constipation
  - Motegrity™ (prucalopride)

Immune Disorders

- Plaque psoriasis
  - Ilumya™ (tildrakizumab-asmn)
- Rheumatoid arthritis
  - Olumiant® (baricitinib)
- Hereditary angioedema
  - Takhzyro™ (lanadelumab)
- Severe combined immune deficiency
  - Revcovi™ (elapegademase-lvir)
- Lambert-Eaton Myasthenic Syndrome
  - Firdapse® (amifampridine)

Gastrointestinal Disorders

Omegaven® (Fish oil TG)

- **Pediatric patients with parenteral nutrition-associated cholestasis**
  - Provides calories and essential fatty acids – especially EPA and DHA
  - When conj. bilirubin ≥2 mg/dL
- Dose: 1 g/kg/day IV infusion at a max rate of 0.15 g/kg/hr
  - Monitor and adjust based on serum triglycerides
- ADEs >20%: vomiting, agitation, bradycardia, apnea
- Clinical trials; effectiveness based on 82 pediatric patients (3-42 weeks old)

Orphan Drug

Aemcolo™ (Rifamycin)

- **Traveler's diarrhea**
  - Use only if no fever, bloody stool or pathogens other than noninvasive strains of *E.coli.*
- MOA: antibiotic
- Dose: 388 mg (two tablets) twice daily for three days
- ADEs <1%: abdominal pain, pyrexia
- Clinical cure:
  - Definition: ≤2 soft stools and minimal enteric symptoms at beginning of 24-hour period
  - 81% vs. 57% with placebo in 264 patients with travelers diarrhea in Guatemala, India, Ecuador, and Mexico (statistically significant improvement)

Motegrity™ (Prucalopride)

- **Chronic idiopathic constipation in adults**
- MOA: selective serotonin-4 (5-HT_4) receptor agonist – stimulates colonic peristalsis, increasing bowel motility
  - New generation with high affinity to 5-HT_4 receptors – not associated dysfunction of cardiac HERG K+ channel
- Dose: 2 mg once daily
  - 1 mg once daily if CrCl <30 mL/min
- Clinical trials – statistically signif increase in ≥3 complete spontaneous bms/week in 5 trials (each@12 weeks duration)

Immune Disorders

Olumiant® (baricitinib)

- Indication: Rheumatoid arthritis – mod to sev and inadequate response to at least one TNF antagonist (infliximab, adalimumab, etc.)
- MOA: Janus kinase (JAK) inhibitor
  - Tofacitinib (Xeljanz®) is also a JAK inhibitor for RA
- Dose: 2 mg orally once daily
  - Dosing guided by lymphocyte count, ANC, and hemoglobin levels
  - Avoid with CrCl <60 mL/min
- 24-week clinical trials – signif higher ACR20 response vs placebo/DMARD

Boxed Warnings: patients are at risk for serious infections; lymphoma and serious malignancies can develop; increased incidence of thrombosis (DVT, PE)

Ilumya™ (tildrakizumab-asmn)

- Indication: Plaque psoriasis – moderate to severe disease in adults
- MOA: interleukin-23 antagonist; IL-23 is a cytokine involved in inflammatory and immune responses
  - Other IL-23 mabs: guselkumab (Tremfya) approved Jul 2017 and IL-12/23 mab ustikinumab (Stelara®)
- Dose: 100 mg SC once at weeks 0, 4 and every 12 weeks thereafter; admin by healthcare provider
- Clinical trials: 68% with sustained skin clearance versus 22% with placebo after 3 years
- Institute for Clinical and Economic Review (ICER) reports IL-23 inhibitors preferred over Anti-TNF agents for plaque psoriasis

New Monoclonal Antibodies for Immune Disorders

Takhzyro™ (lanadelumab) for Hereditary Angioedema

Orphan Drug

Breakthrough Status

What is Hereditary Angioedema?

Autosomal dominant disease – deficiency in functional C1 inhibitor (C1INH) leading to uncontrolled increases in kallikrein activity

- Prevalence: 1/50,000
- Leads to recurrent attacks of severe swelling of skin and mucous membranes
- 85% Type 1 – gene mutation leads to low plasma C1INH and low C1INH function
- 15% Type 2 – gene mutation leads normal levels but dysfunctional C1INH
- Meds available for treatment and prevention of acute attacks

Takhzyro is indicated for Type 1 and Type 2 hereditary angioedema in patients ≥12 years

MOA: plasma kallikrein inhibitor – acts to prevent kallikrein's proteolytic activity which leads to swelling attacks

Dosing: 300 mg SC every 2 -4 weeks; self-administered by patient

Clinical trials: Significant reduction in HAE attacks, attacks requiring acute treatment, and number of moderate or severe attacks over 6 months, compared to placebo

ADEs (>10%): injection site reactions, upper resp tract infections, headache, rash

New Monoclonal Antibodies for Immune Disorders

Orphan Drug

Revcovi™ (elapegademase-lvlr) for Severe Combined Immune Deficiency

What is Severe Combined Immune Deficiency?

Inherited primary immunodeficiency disorders with lack of functional peripheral T lymphocytes

- Prevalence: 1/50,000 live births
- Presents in first months of life; leads to failure to thrive, severe infections, severe thrush, chronic diarrhea, absent lymph nodes; without treatment – death by age 2
- Treatments:
  - bovine enzyme replacement (Adagen®)
  - HSCT provides > 90% long-term survival
  - One-shot gene therapy available in Italy

For treatment of severe combined immune deficiency associated with adenosine deaminase deficiency (ADA-SCID) AKA “Bubble Boy Disease”

MOA: ADA replacement therapy with recombinant adenosine deaminase

Dosing: 0.2 mg/kg IM once or twice weekly, titrated based on measured ADA activity

Clinical trials: two trials with total of 10 patients – treatment increased ADA levels, reduced toxic metabolites; improved total lymphocyte counts
Most common ADEs: cough (50%), vomiting (33%)

Firdapse® (amifampridine)
for Lambert-Eaton Myasthenic Syndrome

Orphan Drug

Breakthrough Status

What is Lambert-Eaton Myasthenic Syndrome?

Autoimmune disease in which the system attacks calcium channels on nerve endings, required to release acetylcholine. Lower levels of acetylcholine result in muscle weakness

- Prevalence: 1/100,000 (400 known cases in U.S.)
  - 60% association with small cell lung cancer and onset around age 60 years
  - 40% of unknown cause; onset around 35 years
- Presentation:
  - difficulty walking due to weakness in upper legs and hip
  - weakness in upper arms and shoulders
  - milder weakness in eye muscles and those involved in talking, swallowing, and chewing

For treatment of Lambert-Eaton myasthenic syndrome in adults; to help relieve symptoms of the disease (e,g., arm and leg weakness)

MOA: potassium channel blocker that increases release of acetylcholine

Dosing: 15-30 mg PO daily in divided doses (3-4 times per day); titrate to max total daily dose of 80 mg

Pivotal trials based on improvement in scoring tools MD-rated QMG (Quantitative Myasthenia Gravis) and patient-rated SGI (Subject Global Impression)
Under development for 20 years in U.S.
Media complaints over $375,000 annual cost

CNS and Neurological Disorders

- Dravet's syndrome
  - Epidiolex® (cannabidiol)
  - Diacomit® (stiripentol)
- Migraine headache prevention
  - Aimovig™ (erenumab-aooe)
  - Ajovy® (fremanezumab-vfrm)
  - Emgality® (galcanezumab-gnim)
- Prevention of chemotherapy-induced nausea and vomiting
  - Akynzeo® injection (fosnetupitant/palonosetron)
- Opioid withdrawal
  - Lucemyra™ (lofexidine)

Two New Drugs for Dravet's Syndrome

Orphan Disease

What is Dravet's Syndrome?

Severe form of epilepsy thought to be due to gene mutation coding for sodium ion channel (SCN1A gene)

- Prevalence: 1/15,700
- Represents 0.17% of all epilepsies
- Average age of seizure onset is 5.2 months
- Hyperthermia/overwarming is the most common seizure trigger
- No cure – treatments are focused on reducing symptoms
- Avoid drugs that block the sodium channel: carbamazepine, oxcarbazine, lamotrigine, vigabatrin, rufinamide, and chronic use of phenytoin or fosphenytoin

Epidiolex® (cannabidiol) (Schedule V)

- For treatment of seizures with Dravet syndrome or Lennox-Gastaut in patients $\geq$ 2 years old
- Highly purified, plant-derived cannabidiol (CBD) – doesn't provide a "high"; MOA unknown
- Oral solution administered twice daily
- ADEs: somnolence, decreased appetite, diarrhea

Diacomit® (stiripentol)

- For add-on treatment of seizures with Dravet syndrome in patients $\geq$2 years old who are taking clobazam
- MOA: inhibition of $GABA_A$ receptors and inhibition of CYP450, increasing clobazam levels
- Oral dosing 2-3 times daily – capsules or powder mixed in water

Migraine Prevention

New Class of Medications: Calcitonin gene-related peptide (CGRP) antagonists (monoclonal antibodies); CGRP levels have been shown to increase with migraines

Brand	Aimovig™ **(First-in-Class)**	Ajovy®	Emgality®
Generic	Erenumab-aooe	Fremanezumab-vfrm	Galcanezumab-gnlm
MOA	Binds to CGRP receptor and antagonizes CGRP receptor function	Binds to CGRP ligand and blocks its binding to receptor	Binds to CGRP and prevents its binding to CGRP receptor
Dose	70 mg or 140 mg SC monthly	225 mg SC monthly or 675 mg SC every 3 months	LD: 240 mg SC (2 injections) MD: 120 mg SC monthly

- American Headache Society position statement (*Headache 2019;59:1-18*)
  - Reserve CGRP inhibitors for adult patients with moderate migraine disability who don't tolerate or respond adequately to 6-week trials of at least 2 oral medications (e.g., topiramate, beta-blocker, divalproex sodium, etc.) or at least 2 quarterly injections of onabotulinum toxin A

Prevention of chemotherapy-induced nausea and vomiting (CINV)

- Akynzeo®
  - Formulations
    - Injection: 235 mg fosnetupitant/0.25 mg palonosetron per single dose vial
    - Oral approved in 2014: 300 mg netupitant/0.5 mg palonosetron per cap
  - MOA
    - Acute phase N&V prevention with netupitant - selective antagonist of human substance P/neurokinin 1 (NK-1) receptors
    - Delayed N&V prevention with palonosetron - 5-HT_3 receptor antagonist
  - 96 hour half-life
  - Avoid with strong CYP3A4 inducers
  - 90% complete response with cisplatin-based highly emetogenic chemotherapy

Treatment regimens:

	Day 1		Days 2-4
Highly Emetogenic Chemotherapy			
PO	300 mg/0.5 mg capsule	1 hour prior to chemo	Dexametha-sone 8 mg once daily
	Dexamethasone 12 mg	30 min prior to chemo	
Inj	235 mg/0.25 mg vial	Infuse over 30 min starting 30 min prior to chemo	Dexametha-sone 8 mg once daily
Non-Highly Emetogenic Chemotherapy			
PO	300 mg/0.5 mg capsule	1 hour prior to chemo	None
	Dexamethasone 12 mg	30 min prior to chemo	

New Drug for Opioid Withdrawal

First-in-Class

- **Lucemyra™ (lofexidine hydrochloride)**
  - **MOA:** central alpha-2 adrenergic agonist – reduces release of norepinephrine
    - First non-opioid treatment for management of opioid withdrawal symptoms (clonidine is used off-label for this indication)
  - **Dose:** 3 tabs (0.18 mg each) PO 4 times daily up to 14 days based on symptoms; dose is tapered off when discontinued
  - **Warnings:** potentiation of CNS depressant drugs; increased risk of opioid overdose if resume opioid use; risk of hypotension, bradycardia and syncope; risk of QT prolongation
  - **Clinical trials**
    - 866 adults with DSM-III opioid dependence undergoing abrupt opioid discontinuation
      - Randomized, double-blind, placebo-controlled trials
      - Outcomes: significantly reduced scores on Short Opiate Withdrawal Scale of Gossop rating withdrawal symptoms
  - FDA is requiring post-marketing studies (animal and human) on long-term use, gradual opioid taper, and additional safety information

New FDA Approvals for Other Disorders

- Neurotropic keratitis
  - Oxervate™ (cenegermin-bkbj)
- COPD
  - Yupelri™ (revefenacin)

Oxervate™ (cenegermin-bkbj) for Neurotropic Keratitis

What is Neurotropic Keratitis?

Degenerative disease with reduced sensitivity, spontaneous epithelial breakdown and impaired healing of the cornea; due to impairment in trigeminal nerve conduction

- Prevalence: 1-5/10,000
- Presentation:
  - Most common in adults
  - Starts as red-eye, blurred vision, decreased acuity
  - Progresses to epithelial defects and corneal ulcers, scarring and astigmatism
- Treatments:
  - Artificial tears, lubricant ointment
  - Corneal-scleral contact lenses
  - Surgery for refractory or severe cases

First-in-Class | Orphan Drug | Breakthrough Status

Ophthalmic solution of cenegermin-bkbj 0.002% for treatment of neurotrophic keratitis

MOA: recombinant human nerve growth factor that acts through nerve growth receptors in the eye to improve corneal innervation and integrity

Dosing: 1 drop in affected eye 6 times per day at 2-hour intervals for 8 weeks

Clinical trials: 8 week placebo-controlled trials (N=151) with 65-72% corneal healing vs. 16%-33% with placebo; 14%-20% of those healed had recurrences

Most common ADE: eye pain (16%)

Yupelri™ (revefenacin) for COPD

- **MOA:** long-acting muscarinic agent (LAMA) anticholinergic inhalation solution for maintenance treatment of patients with chronic obstructive lung disease
- **Dose:** 175 mg once daily by inhalation
- **ADEs** in less than 5% of patients (cough, nasopharyngitis, headache)
- **Clinical trials**
  - 1,229 adults with mod-severe COPD, smoking history ≥10 pack years, $FEV_1/FVC \leq 0.7$
    - 12-week randomized, double-blind, placebo-controlled, multi-dose, parallel-group trials
    - Outcomes: significant improvement in lung function compared to placebo
    - 52-week open-label active control trial demonstrated long-term safety; LABA or LABA/ICS therapy was used concomitantly in 50% of patients
- Considerations:
  - First approved once-daily LAMA inhalation through standard jet nebulizers
  - Medicare Part B coverage vs. other inhalers covered through Medicare Part D

Oncology

Trade Name	Generic Name	Indication
Lutathera® **(F, O)**	Lutetium Lu 177 dotatate	Gastroentero-pancreatic neuroendocrine tumors
Erleada™	Apalutamide	Prostate cancer
Braftovi™ **(O)**	Encorafenib	Melanoma
Mektovi® **(O)**	Binimetinib	Melanoma
Tibsovo® **(F, O)**	Ivosidenib	Melanoma
Poteligeo® **(F, O)**	Mogamulizumab -kpkc	Mycosis fungoides
Lumoxiti™ **(O)**	Moxetumomab pasudotox-tdfk	Hairy cell leukemia
Copiktra™ **(O)**	Duvelisib	CLL, lymphoma

Trade Name	Generic Name	Indication
Vizimpro® **(O)**	Dacomitinib	Non-small cell lung cancer
Libtayo® **(B)**	Cemiplimab-rwlc	Cutaneous squamous cell carcinoma
Talzenna®	Talazoparib	Breast cancer
Lorbrenna® **(O, B)**	Lorlatinib	Non-small cell lung cancer
Daurismo™ **(O)**	Glasdegib	AML in elderly
Viktrakvi® **(F, O, B)**	Larotrectinib	Solid tumors
Xospata® **(O)**	Gilteritinib fumarate	AML
Elzonris™ **(F, O, B)**	tagraxofusp-erzs	Dendritic cell neoplasm

F = First in Class; O = Orphan Drug; B = Breakthrough Drug

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