



Overview of Selected Novel Drugs Approved in 2018

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Abstract

2018 was a record setting year for new drug approvals by the FDA. This article highlights some of the drugs that have new mechanisms of action or have indications that have not previously been available. For example, Trogarzo is an IgG4 monoclonal antibody for the treatment of multidrug-resistant HIV. Xofluza, is a polymerase acidic endonuclease inhibitor that can be used to treat influenza by blocking a different step in the influenza lifecycle than previous flu medications, such as oseltamivir. Although smallpox has been declared eradicated for almost 40 years, TPOXX was approved for the treatment of smallpox in the event it is ever used as a bioterrorist agent. Epidiolex just became the first FDA-approved medication to contain an active ingredient derived from marijuana, and is the first medication approved for the treatment of Dravet syndrome. Three new medications for preventative migraine treatment were also approved. These agents (Aimovig, Ajovy, and Emgality) are calcitonin gene-related peptide receptor antagonists, which has been shown to be involved in migraine attacks.





The FDA set a record in novel drug approvals this past year. A total of 59 new molecular entities (NMEs) were approved in 2018, which surpassed the previous record of 53 NMEs from 22 years prior in 1996.¹ This record follows 46 NMEs approved in 2017.¹ In addition, there has been a recent spike in the number of drugs approved since 2016 when only 22 NMEs were approved.¹ The 59 NMEs approved cover a myriad of more common indications such as cancer, human immunodeficiency virus (HIV), migraines, influenza, and COPD, as well as rare conditions such as paroxysmal nocturnal hemoglobinuria and Lambert-Eaton Myasthenic syndrome.¹ Out of the 59 novel drugs approved, cancer drugs came out on top with the most approvals and included NMEs for a variety of both blood and solid tumors.¹ Unlike past years, there were no NMEs approved for hepatitis C.¹ Because there were drugs approved for numerous conditions, the remainder of the paper highlights drugs approved for several different indications.

Trogarzo™ (ibalizumab-uiyk)

Although most patients with HIV can be treated using a combination of two or more antiretroviral drugs, there are some patients who have developed multidrug-resistant HIV.² This greatly limits treatment options for these individuals and also puts them at a higher risk for complications, such as infections and cancer, and a higher risk for death.² Therefore, current research has its focus on drugs with new mechanisms of action (MOA) for multidrug-resistant HIV. One newly approved drug, Trogarzo, is indicated for multidrug-resistant HIV-1, and it is the first HIV therapy with a new MOA approved in more than ten years.^{3,4} Trogarzo is a humanized IgG4 monoclonal antibody

that targets the second extracellular domain of the CD4+ T-cell receptor inhibiting the viral entry process by preventing the binding of HIV to the cell.^{3,5} The binding site of ibalizumab is distant from the major histocompatibility complex II binding sites.^{3,5} This allows MHC class II molecules to still interact with CD4, and thus does not inhibit CD4-mediated immune functions so it does not cause immunosuppression.⁵ Trogarzo is approved for use in combination with other antiretroviral medications.³ In clinical trials, 33 of 40 patients (83%) treated with Trogarzo experienced a significant decrease in human immunodeficiency virus (HIV)-RNA levels after one week of adding Trogarzo to their failing antiretroviral therapies.⁴ After 24 weeks of initiating Trogarzo, 43% of the patients achieved HIV RNA suppression.⁴ It is administered as an IV infusion by a health care professional every two weeks.^{3,6} The first dose is 2,000 mg, and every dose thereafter is 800 mg.^{3,6} The infusion takes 15-30 minutes to perform.^{3,6} The most common side effects include dizziness, nausea, and rash.^{3,6}

Xofluza™ (baloxavir marboxil)

According to the Centers for Disease Control and Prevention (CDC), on average each year, 5-20% of the U.S. population contracts the flu.⁷ In addition, tens of thousands are hospitalized and thousands die from flu-related illnesses each year.⁷ Therefore, having effective treatment alternatives readily available is crucial. If treatment with antiviral drugs is started within 48 hours of symptoms appearing, it can lessen the time the patients feel sick.⁸ However, because flu viruses can become resistant to drugs, researching drugs with different MOAs is critical. Xofluza is the only treatment for the flu with a new MOA

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that has been approved in almost twenty years.⁸

Xofluza is indicated for patients 12 years of age and older who have acute uncomplicated influenza and who have been symptomatic for no more than 48 hours.^{9,10} Xofluza works differently than oseltamivir (Tamiflu), which is used to prevent and treat influenza by inhibiting a viral enzyme neuraminidase.⁶ Unlike oseltamivir, Xofluza is a polymerase acidic endonuclease inhibitor which inhibits viral replication early in the influenza lifecycle.⁹ The CAPSTONE-1 clinical trials compared Xofluza to placebo and oseltamivir.^{10,11} Xofluza significantly reduced the duration of flu symptoms compared to placebo.^{10,11} The median time to alleviation of symptoms was 53.7 hours with Xofluza compared to 80.2 values with placebo ($p < 0.001$).

Xofluza is administered orally as a single dose.^{6,9} It is recommended that patients 40-80kg take a single dose of 40 mg and patients over 80 kg should take a single dose of 80 mg.^{6,9} It is important to avoid taking Xofluza with polyvalent cation-containing laxatives or oral supplements, dairy products or other beverages containing calcium.^{6,9} Adverse reactions that were common in the CAPSTONE-1 Trial include diarrhea (3%), bronchitis (2%), headache (1%), nausea (1%), and nasopharyngitis (1%).^{6,9}

TPOXX™ (tecovirimat)

Before 2018, there were no drugs indicated for the treatment of smallpox; only vaccines for prevention of smallpox were available.¹² Almost 40 years ago in 1980, the World Health Assembly declared smallpox eradicated.¹² However, in the United States, smallpox research still continues as a

protective measure in the event that it is used as an agent for bioterrorism.¹²

TPOXX is the only drug approved for the treatment of smallpox disease in adults and children weighing at least 13 kg.^{6,13,14} It is the only product to receive a Material Threat Medical Countermeasure priority review voucher from the FDA.¹⁴ This allows priority review from the FDA for medical products, including drugs, for conditions associated with biological, chemical, nuclear, or radiological threats.¹⁴ TPOXX works by inhibiting the orthopox virus VP37 envelope wrapping protein which is needed for the production of extracellular virus (variola virus).^{6,14} By inhibiting this process, the virus cannot leave an infected cell. Therefore, the spread of the virus in the body is prevented. To establish efficacy, clinical trials were conducted in animals that were infected with viruses that are closely related to the virus that causes smallpox.¹⁵ Outcomes measured survival at the conclusion of the study, and more animals treated with TPOXX lived compared to animals who received placebo.¹⁵ To establish safety, TPOXX was administered to over 350 healthy human patients.¹⁵ The most common adverse reactions (>2%) were headache, nausea and vomiting, and abdominal pain.¹⁵ TPOXX is given orally twice a day for 14 days within 30 minutes after a full meal containing fat.^{6,13}

Epidiolex™ (cannabidiol)

It is important to recognize that certain active ingredients found in marijuana can have medical benefits, such as cannabidiol (CBD).¹⁶ In 2018, Epidiolex became the first medication that contains a substance derived from marijuana to be approved by the FDA.¹⁶ CBD is not known to cause the psychoactive or euphoric effects

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found in marijuana, which are instead related to the chemical tetrahydrocannabinol (THC).¹⁶ THC is not present in Epidiolex and therefore does not create the same “high” feeling as marijuana.¹⁶

Epidiolex is FDA approved for the treatment of two severe, but rare, forms of epilepsy in patients age 2 and older.¹⁶ Lennox-Gastaut syndrome is a multi-seizure disorder that begins in early childhood and can cause frequent tonic seizures in 3 to 5 year olds.¹⁶ This disorder can lead to developmental problems such as delayed motor skills (walking or crawling), and learning or intellectual disability.¹⁶ Epidiolex also became the first FDA-approved drug for the treatment of Dravet syndrome.¹⁶ Dravet syndrome usually appears during the first year of life as febrile seizures, but can later evolve to all types of seizures.¹⁶ This can potentially cause a child to go into status epilepticus, which requires emergency care and is life-threatening.¹⁶ Both of these syndromes are difficult to control and have a significant impact on a patient’s quality of life.¹⁶ Epidiolex was studied in different randomized, double-blind, placebo-controlled clinical trials involving patients with either syndrome.¹⁷ These patients were currently not controlled on their seizure medications. Epidiolex was shown to be effective at reducing the number of convulsive seizures compared to placebo.¹⁷ Epidiolex decreased seizure frequency by 37-44%, whereas placebo only showed a 13-22% decrease.¹⁷

Epidiolex is only available in a liquid solution form, and is taken twice daily based on weight.^{6,17,18} The dosing is the same for children and adults with an initial dose of 2.5 mg/kg twice daily for the first week. It should then be titrated to 5 mg/kg twice daily for the

minimum maintenance dose.^{6,18} Epidiolex can be titrated weekly up to a 10 mg/kg twice daily max dose, but should not be discontinued immediately without proper titration down.^{6,18} It should be taken via a syringe and it does not need to be taken with or without food, but the patient should be consistent.⁶ Liver function should be assessed prior to treatment and monitored periodically as increased serum alanine aminotransferase >3x ULN has been shown in patients (13-17%).^{6,18} Daily doses need to be decreased in patients with moderate to severe hepatic impairment.^{6,18} Some common side effects a patient may experience include fatigue, weight loss, anemia, lack of appetite, diarrhea, or difficulty sleeping.^{6,18} The patient should notify their doctor immediately upon any signs of liver problems, signs of depression and mood changes, or signs of infection.^{6,18} Epidiolex is a moderate CYP2C19 inhibitor, so the majority of drug interactions invoke increasing the serum concentration of CYP2C19 substrates.⁶

Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists

Migraines affect more than 10% of people worldwide, and can be very painful or debilitating.¹⁹ In 2018, the FDA approved 3 new medications for a new class of preventative migraine treatment.¹⁹ This class blocks the activity of CGRP, which is known to be involved in migraine attacks.¹⁹ These new medications are all monoclonal antibodies and include Aimovig™ (erenumab-aooe), Emgality™ (galcanezumab-gnlm), and Ajovy™ (fremanezumab-vfrm).¹⁹





All 3 of these medications are subcutaneous injections that are to be given monthly (Ajoyv has an every 3 month option).^{6,20-22} These medications are only indicated for adults (18 years and older), and do not require any dosage adjustments for renal or hepatic impairment, or geriatric patients.^{6,20-22} All of these medications come in a prefilled syringe in the typical monthly dose.^{6,20-22} Each medication should be stored in the refrigerator, but taken out 30 minutes before administration to allow it to reach room temperature.^{6,20-22} The syringe should not be shaken. To use, the syringe can be injected into the abdomen, thigh, or upper arm.^{6,20-22} For doses that need more than 1 injection, (Emagily has a loading dose of 2 injections, and Ajoyv 3-month dosing takes 3 injections) the injections should be given on the same location on the body, but not in the exact same spot.^{6,20-22} Ajoyv must be used within 24 hours from becoming room temperature, but Emagily and Aimovig are good for 7 days outside of the refrigeration.^{6,20-22}

Emagily and Ajoyv should be used cautiously in patients with cardiovascular disease, as those patients were excluded from all clinical trials.^{6,21,22} The most notable side effect is injection site reactions (pain, swelling, or redness).^{6,20-22} Aimovig also had side effects of constipation and muscle cramps or spasms.^{6,20} Finally, Emgality and Aimovig should be avoided in patients on belimumab, as they can increase the adverse or toxic effects of belimumab.^{6,20,22}



Knowledge Check: Multiple Choice
Xufluz is indicated for patients 12 years of age and older who have acute uncomplicated influenza and who have been symptomatic for no more that how many hours?

- A. 12
- B. 24
- C. 36
- D. 48

Answer: D

Conclusion

2018 provided U.S. citizens treatment options for not only a variety of disease states, but also the first treatment options for several rare disease states as well. Above are just a few novel medications from 2018. The full list of FDA approved medications in 2018 can be viewed here: <https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm592464.htm>





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