
*Abstract: In 2018, the FDA approved several new drugs for use in primary care. This article highlights the following new drugs: bictegravir, emtricitabine, and tenofovir alafenamide (Biktarvy); doxylamine succinate and pyridoxine hydrochloride (Bonjesta); erenumab-aooe (Aimovig); lofexidine hydrochloride (Lucemyra); tezacaftor and ivacaftor (Symdeko); and tildrakizumab-asmn (Ilumya).*

**By Cortney Mospan, PharmD, BCACP, BCGP; Geoffrey Mospan, PharmD, BCPS; Emily Byland; William Blake Whitaker; Linda Xiong; Jordan Dunlap; and Katherine Canupp**



## ▼ HIV-1 infection

# Bictegravir, emtricitabine, and tenofovir alafenamide (Biktarvy)

In the US, 39,782 individuals were newly diagnosed with HIV in 2016.[1] HIV infects the immune system and destroys CD4 cells, which help to fight infections. Current therapy regimens to treat HIV involve combining multiple antiretroviral therapy (ART) medications.[2] Bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF), a three-drug combination medication, was approved by the FDA in February 2018 as a complete regimen for treating HIV-1 infection.[3] BIC/FTC/TAF is manufactured by Gilead Sciences.[4]

### Indications

BIC/FTC/TAF is indicated for adults as initial therapy for those who have not previously taken ART.[4] Additionally,

**Keywords: CF, cystic fibrosis, drug approvals, FDA, HIV, migraine, nausea and vomiting of pregnancy, new drugs, NVP, opioid withdrawal, plaque psoriasis**

BIC/FTC/TAF is indicated to replace a current ART regimen in stable adult patients who have an HIV-1 RNA of less than 50 copies/mL for at least 3 months with no history of treatment failure and no resistance to any component of the drug.[4]

## Mechanism of action

BIC/FTC/TAF is a three-drug combination of bictegravir, emtricitabine, and tenofovir alafenamide. Bictegravir is an integrase strand inhibitor, whereas emtricitabine is a nucleoside reverse transcriptase inhibitor and tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor, all of which prevent replication of the HIV virus.[4]

## Dosing and administration

BIC/FTC/TAF is available as a once-daily fixed-dose combination tablet with bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg that can be taken with or without food.[4] BIC/FTC/TAF is not recommended in patients who have a creatinine clearance less than 30 mL/min or those with severe hepatic impairment (Child-Pugh class C).[4]

***BIC/FTC/TAF is indicated for adults as initial therapy for those who have not previously taken ART.***

## Contraindications

The package insert lists administration of BIC/FTC/TAF with dofetilide or rifampin as contraindications due to altering serum concentrations with potential for adverse reactions.[4]

## Warnings and precautions

BIC/FTC/TAF has a boxed warning for posttreatment acute exacerbation of hepatitis B.[4] Severe exacerbations resulting in liver decompensation or liver failure have occurred in patients who are coinfected with HIV and the hepatitis B virus after discontinuing products containing emtricitabine and tenofovir.[4] Therefore, patients should be tested for the hepatitis B virus before initiation of BIC/FTC/TAF.[4]

Prescribers should also be aware of immune reconstitution syndrome, also known as immune recovery syndrome. This is a condition in which the immune system begins to recover, but a residual opportunistic infection leads to an inflammatory response that may require treatment.[4] Finally, patients should be monitored for new or worsening kidney impairment, lactic acidosis, and hepatotoxicity.[4]

## Adverse reactions

Patients undergoing 48 weeks of treatment with BIC/FTC/TAF in randomized controlled trials showed that the most common adverse reactions included diarrhea, nausea, headache, fatigue, abnormal dreams, dizziness, and insomnia.[4,5]

## Pharmacokinetics

As a coformulated tablet, the pharmacokinetics of BIC/FTC/TAF do not differ in comparison with each agent being administered separately.[4] BIC is 99% bound to plasma proteins, metabolized by CYP3A enzymes and hepatic glucuronidation, and is mostly excreted in the feces.[4] FTC is not significantly metabolized and is excreted through the urine.[4] TAF is approximately 80% bound to plasma proteins, metabolized by hydrolysis, and excreted mainly through the feces.[4]

## Clinical pearls

- There is insufficient data on the use of BIC/FTC/TAF in pregnancy or lactation.[4] Consult the prescribing information for additional information related to pregnancy.
- Several medications may interact with BIC/FTC/TAF, leading to loss of efficacy or increased toxicities. Analyze concomitant medications for potential interactions.[4]
- Antacids and iron supplements may decrease the serum concentration of BIC/FTC/TAF. The prescribing information recommends taking BIC/FTC/TAF 2 hours prior to antacids or supplements that contain cations.[4]
- Monitoring parameters include CD4 count, HIV RNA plasma levels, serum creatinine, creatinine clearance, urine glucose concentration, urine protein concentration, and hepatic function tests.[4]
- Safety of BIC/FTC/TAF in pediatric patients younger than 18 years has not been established.[4]
- Patients age 65 and older were underrepresented in clinical trials; therefore, safety and effectiveness in this patient population is unknown.[4,5]

### REFERENCES

1. Centers for Disease Control and Prevention. HIV Surveillance Reports. 2018. www.cdc.gov/hiv/library/reports/hiv-surveillance.html.

2. Centers for Disease Control and Prevention. HIV basics. 2018. www.cdc.gov/hiv/basics/index.html.
3. U.S. Food and Drug Administration. Drug Trials Snapshot: BIKTARVY. 2018. www.fda.gov/drugs/informationondrugs/ucm597572.htm.
4. Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) [Package Insert]. Foster City, CA: Gilead Sciences, Inc; 2018.
5. Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet*. 2017;390(10107):2073-2082.

## ▼ Nausea & vomiting of pregnancy

# Doxylamine succinate and pyridoxine hydrochloride (Bonjesta)

Morning sickness, also known as nausea and vomiting of pregnancy (NVP), affects up to 80% of pregnant women.[1] NVP usually begins before week 9 of pregnancy and can last up until delivery, having the potential to negatively affect activities of daily living, work, and quality of life (QoL).[1,2] Bonjesta, a two-drug combination product, was approved by the FDA in November 2016 for treating NVP.[3] The two active ingredients in Bonjesta, doxylamine succinate and pyridoxine hydrochloride, are recommended by the American College of Obstetricians and Gynecologists as first-line treatment for NVP if diet and lifestyle modifications have failed.[2] Doxylamine succinate and pyridoxine hydrochloride is manufactured by Duchesnay Inc. The medication was first available in the US in April 2018.[4]

### Indications

Doxylamine and pyridoxine is indicated for the treatment of NVP in women who do not respond to conservative management.[5]

### Mechanism of action

The mechanism of action of doxylamine and pyridoxine for treating NVP is unknown; however, doxylamine is known to compete with histamine-1 receptor sites.[5,6] This activity blocks the chemoreceptor trigger zone and diminishes vestibular stimulation.[6] The delayed-release characteristics allow the medication to be dosed at night to decrease adverse reactions and to counteract increased symptoms that are more common in the morning hours.[7]

### Dosing and administration

Doxylamine and pyridoxine is a combination extended-release tablet containing 20 mg of doxylamine and 20 mg of pyridoxine. On day 1, patients are instructed to take one tablet at bedtime on an empty stomach with a glass of water.[5] If one dose adequately controls symptoms, the patient may continue to take this dose at bedtime.[5] If symptoms are not adequately controlled on day 2, the dose may be increased to a maximum of one tablet in the morning and one tablet at bedtime.[5] Doxylamine and pyridoxine should be taken every day and not on an as-needed basis.[5] As the pregnancy progresses, the prescriber should evaluate the appropriateness of continuing the drug.[5]

### Contraindications

Doxylamine and pyridoxine is contraindicated in women with hypersensitivity to any active or inactive ingredients of the product and in women taking a monoamine oxidase inhibitor (MAOI).[5]

### Warnings and precautions

Doxylamine, one of the active ingredients in Bonjesta, is an antihistamine and may cause somnolence because of its anticholinergic properties.[5] Somnolence may be more pronounced if doxylamine and pyridoxine is taken with alcohol or other central nervous system (CNS) depressants, and therefore the drug is not recommended for use in combination with alcohol or CNS depressants.[5] Pregnant women should be advised to avoid alcohol during pregnancy.

> ***Morning sickness, also known as nausea and vomiting of pregnancy, affects up to 80% of pregnant women.***

Women with asthma, increased intraocular pressure, narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal or urinary bladder-neck obstruction should use doxylamine and pyridoxine with caution due to its anticholinergic properties.[5]

### Adverse reactions

To date, there have not been any safety or efficacy trials conducted with the new fixed-dose combination drug, Bonjesta. However, single-dose and multiple-dose crossover clinical trials demonstrated Bonjesta was bioequivalent to 10 mg of doxylamine and 10 mg of pyridoxine.[5] Thus, adverse reactions are based on clinical trials involving the effects of 10 mg of doxylamine

and 10 mg of pyridoxine, which showed somnolence occurring at a greater incidence in the treatment group compared with the placebo group.[5]

### Pharmacokinetics

The absorption of doxylamine and pyridoxine is delayed and reduced when taken with a high-fat or high-calorie meal.[5] Doxylamine is biotransformed in the liver by N-dealkylation, and its metabolites are excreted by the kidneys.[5] Pyridoxine is a prodrug primarily metabolized in the liver.[5] The elimination half-life of doxylamine is 11.9 hours and only 0.4 hours for pyridoxine.[5]

### Clinical pearls

- Women should not breastfeed while taking doxylamine and pyridoxine, as both drugs can pass through the breast milk to the infant.[5]
- The safety and efficacy of doxylamine and pyridoxine has not been established in women younger than 18 years.[5]
- Doxylamine and pyridoxine has not been studied in women with hyperemesis gravidarum.[5]
- Reports of false-positive urine screen tests for methadone, opioids, and phencyclidine phosphate have been documented with doxylamine and pyridoxine use.[5]
- There are currently no hepatic or renal adjustments recommended because of the lack of pharmacokinetic studies in these specific patient populations.[5]
- Women should be advised to avoid engaging in activities requiring mental alertness, such as driving or operating heavy machinery, because of the risk of somnolence when taking the drug.[5]


**REFERENCES**

1. Lee NM, Saha S. Nausea and vomiting of pregnancy. *Gastroenterol Clin North Am*. 2011;40(2):309-334.
2. ACOG Practice Bulletin No. 189: Nausea and Vomiting of Pregnancy. *Obstet Gynecol*. 2018;131(1):e15-e30.
3. Department of Health and Human Services. Center for Drug Evaluation and Research. 2016. www.accessdata.fda.gov/drugsatfda_docs/nda/2016/209661Orig1s000TOC.cfm.
4. Duchesnay USA. Duchesnay USA Announces Availability of Bonjesta® (doxylamine succinate, pyridoxine hydrochloride) in the United States. 2018. www.duchesnayusa.com/en/press-room/329-duchesnay-usa-announces-availability-of-bonjesta-doxylamine-succinate-pyridoxine-hydrochloride-in-the-united-states.
5. Bonjesta (doxylamine succinate and pyridoxine hydrochloride) [package insert]. Bryn Mawr, PA: Duchesnay USA, Inc.; 2018.
6. Bonjesta. Lexicomp Online. http://online.lexi.com. Accessed September 18, 2018.
7. Koren G, Clark S, Hankins GD, et al. Maternal safety of the delayed-release doxylamine and pyridoxine combination for nausea and vomiting of pregnancy; a randomized placebo controlled trial. *BMC Pregnancy Childbirth*. 2015;15:59.


## ▼ Migraine prevention

# Erenumab-aooe (Aimovig)

Migraine headaches affect 14.2% of adults age 18 years and older in the US and disproportionately affect females compared with males.[1,2] Migraines are the fourth-leading cause of ED visits, with many patients having reoccurring attacks triggered by environmental factors.[1,2] Erenumab-aooe, a novel preventive treatment, is an immunoglobulin G2 monoclonal antibody designed to reduce the number of days patients experience migraines.[2,3] Manufactured by Amgen, erenumab-aooe is available as a subcutaneous injection and was approved by the FDA in May 2018.[2,3]

### Indications

Erenumab-aooe is currently indicated for the prevention of migraines in adults.[3] In clinical trials, erenumab-aooe has been studied in difficult-to-treat patient populations who have failed two to four therapies previously.[4] Other currently available treatment options are often associated with poor tolerability and lack of efficacy.[5] Currently, erenumab-aooe is best utilized in patients who have failed standard migraine prevention treatments but may emerge as first-line treatment because of low discontinuation rate and sustained migraine prevention.[4]

### Mechanism of action

Erenumab-aooe is a human monoclonal antibody designed to selectively block the calcitonin gene-related peptide (CGRP) receptor, which is thought to play a critical role in migraine activation.[3,4] The exact role of CGRP in migraine pathology is unclear; however, it is thought to contribute to a proinflammatory state and sensitization of trigeminal ganglion neurons.[6] Erenumab-aooe binds to the CGRP receptor and antagonizes its function to reduce inflammation and sensitization.[3]

### Dosing and administration

Erenumab-aooe is formulated as a 1 mL single-dose prefilled syringe or prefilled autoinjector containing 70 mg of the drug.[3] The recommended dosage is one subcutaneous injection (70 mg) once monthly; however, some patients may require two consecutive injections (140 mg total dosage) once monthly. If a dose is missed, it should be administered as soon as possible.[3]

The Erenumab-aooe injection schedule should then be adjusted to monthly from the date of the last dose.[3]

Patients may self-administer the subcutaneous injections after training. Erenumab-aooe is administered into the upper arm, abdomen, or thigh at a 90-degree angle with the autoinjector and a 45- to 90-degree angle with the prefilled syringe.[3] Areas that are bruised, tender, red, or hard should not be used as an injection site.[3] Erenumab-aooe should be stored in the refrigerator and allowed to reach to room temperature by sitting out for at least 30 minutes prior to administration.[3]

Store erenumab-aooe in the refrigerator at 36° F to 46° F (2° C to 8° C), in the original carton, to protect the autoinjectors and syringes from light.[3] Erenumab-aooe can be removed from the refrigerator and kept at room temperature (up to 77° F [25° C]) in the original carton.[3] The autoinjectors and syringes must be discarded if not used within 7 days after reaching room temperature.[3] The autoinjector and syringes should be kept out of sunlight and should not be shaken.[3] The administration with the autoinjector is complete when the window turns yellow.[3]

## Contraindications

No contraindications are currently listed within the manufacturer's prescribing information.[3]

## Warnings and precautions

Portions of the erenumab-aooe caps contain dry natural rubber, which may cause allergic reactions in patients with a latex allergy.[3]

## Adverse reactions

The most commonly observed adverse reactions in phase III clinical trials were pain, erythema, and itching at the injection site and constipation.[3] Some patients may experience muscle cramping.[3] In clinical trials, discontinuation of erenumab-aooe was only 1.3%, showing high tolerability.[3] Approximately 6.2% of patients taking 70 mg and 2.6% of patients taking 140 mg of erenumab-aooe developed antibodies to erenumab-aooe, but these did not appear to have any effects on efficacy or safety.[3] However, data are currently too limited to determine clinical significance.[3]

## Pharmacokinetics

After a single dose of erenumab-aooe, the median time to peak serum concentration is 6 days.[3] Steady state is reached after 3 months of dosing.[3] Bioavailability is approximately 82% following subcutaneous administration. At low concentrations, the drug is eliminated via saturable binding to the target receptor (CGRP receptor), whereas at high concentrations, it is eliminated primarily through a nonspecific, nonsaturable proteolytic pathway.[3]

## Clinical pearls

- Although erenumab-aooe has not been studied in renal or hepatic insufficiency, it is not expected to have differing pharmacokinetics or dose adjustments.[3]
- There are no data about the use of erenumab-aooe in pregnant women, presence in breast milk, impact on breast-fed infants, or its effects on milk production.[3]
- Erenumab-aooe can safely be used in combination with sumatriptan.[3]

***Erenumab-aooe, a novel preventive treatment, is designed to reduce the number of days patients experience migraines.***

- Erenumab-aooe is not metabolized by CYP450 enzymes; therefore, interactions with medications that are substrates, inducers, or inhibitors of CYP450 enzymes are unlikely.[3]
- In clinical trials, erenumab-aooe reduced the number of days patients experienced migraine, decreased patient use of acute migraine medication, and improved patient physical functioning.[7]

### REFERENCES


1. Burch RC, Loder S, Loder E, Smitherman TA. The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies. *Headache.* 2015;55(1):21-34.
2. U.S. Food and Drug Administration. FDA approves novel preventive treatment for migraine. 2018. www.fda.gov/newsevents/newsroom/pressannouncements/ucm608120.htm.
3. Aimovig (erenumab-aooe) [package insert]. Thousand Oaks, CA: Amgen Inc; 2018.
4. Novartis. Novartis reports erenumab met all primary and secondary endpoints in unique Phase IIIb study in episodic migraine patients who have failed multiple prior preventative treatments. 2018. www.novartis.com/news/media-releases/novartis-reports-erenumab-met-all-primary-and-secondary-endpoints-unique-phase-iiib-study-episodic-migraine-patients-who-have-failed-multiple-prior-preventive.
5. Blumenfeld AM, Bloudek LM, Becker WJ, et al. Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study (IBMS-II). *Headache.* 2013;53(4):644-655.
6. Durham PL, Vause CV. Calcitonin gene-related peptide (CGRP) receptor antagonists in the treatment of migraine. *CNS Drugs.* 2010;24(7):539-548.
7. Rosenberg J. Amgen, Novartis announce positive results of erenumab trial for episodic migraines. 2018. www.ajmc.com/newsroom/amgen-novartis-announce-positive-results-of-erenumab-trial-for-episodic-migraine.

▼ Opioid withdrawal symptoms

## Lofexidine hydrochloride (Lucemyra)

The opioid epidemic continues to devastate the US, claiming an average of 115 lives in the US daily.[1] Treating opioid use disorder often begins with medically supervised withdrawal, also known as detoxification, for patients physically dependent on opioids.[2] Lofexidine was approved by the FDA in May 2018 as the first nonopioid for the management of opioid withdrawal symptoms in adults.[3] Lofexidine is manufactured by US WorldMeds.[4]

### Indications

Lofexidine has been approved for the mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults.[4]

### Mechanism of action

Lofexidine is an alpha-2 adrenergic agonist that binds to receptors in the central nervous system (CNS) to decrease the release of norepinephrine.[4] Decreased release of norepinephrine decreases sympathetic tone.[4] During opioid withdrawal, an increase in sympathetic tone occurs and is responsible for many of the symptoms (for example, excessive sweating, muscle aches, restlessness, runny nose, watery eyes).[5]

*Treating opioid use disorder often begins with medically supervised withdrawal for patients physically dependent on opioids.*

### Dosing and administration

The recommended starting dose of lofexidine is three 0.18 mg tablets taken orally four times daily, with 5 to 6 hours between each dose.[4] Lofexidine should be initiated when opioid withdrawal symptoms are at their peak, and the dosage may be increased or decreased based on withdrawal symptoms or adverse reactions experienced.[4] The maximum total daily dose should not exceed 2.88 mg (16 tablets), and the maximum single dose should not exceed 0.72 mg (four tablets).[4] Lofexidine may be used for up to 14 days.[4] Patients with renal or hepatic impairment must be prescribed lower dosages based on their degree of impairment.[4] Lofexidine may be taken with or without food.[4] Because lofexidine can cause discontinuation symptoms itself, dosages of lofexidine should be tapered over 2 to 4 days after opioid withdrawal symptoms have ceased.[4]

### Contraindications

No contraindications are currently listed in the manufacturer's prescribing information.[4]

### Warnings and precautions

Because of the pharmacologic effects of lofexidine, hypotension, orthostatic hypotension, and bradycardia can occur, which may lead to syncope.[4] Patients with BP lower than 90/60 mm Hg were excluded from a phase III clinical trial of lofexidine.[6] However, the drug's prescribing information does not list a specific BP measurement as a contraindication to therapy.[4] If a patient develops hypotension or bradycardia while on lofexidine therapy, the next dose should be reduced, delayed, or skipped.[4]

It is recommended to avoid using lofexidine in patients with coronary insufficiency, recent myocardial infarction, cerebrovascular disease, chronic renal failure, and in those with marked bradycardia.[4] Lofexidine has also been shown to prolong the QT interval, and patients with risk factors for QT prolongation should be monitored accordingly.[4] Lofexidine potentiates the CNS depressive effects of benzodiazepines, and may potentiate the CNS depressive effects of alcohol, barbiturates, and other sedating drugs. Providers need to question patients about the use of sedating drugs and alcohol and advise patients to avoid using these while taking lofexidine.[4]

Finally, patients who discontinue use of opioids are at risk for a fatal overdose due to decreased tolerance if they resume opioid use.[4]

### Adverse reactions

Adverse reactions observed during a phase III trial for lofexidine occurred more frequently than in patients taking placebo. These adverse reactions included insomnia, orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth. As with clonidine, there is a risk of rebound hypertension upon discontinuation due to the mechanism of action for patients taking lofexidine.[4] Other adverse reactions that may occur

after discontinuing lofexidine include diarrhea, insomnia, anxiety, chills, hyperhidrosis, and extremity pain.[4] If these discontinuation symptoms develop, the patient should receive the same dose of lofexidine that was most recently given followed by a gradual taper.[4]

### Pharmacokinetics

After oral ingestion of a lofexidine tablet, approximately 72% of the dose reaches the plasma, and the peak plasma concentration occurs 3 to 5 hours after administration.[4] Lofexidine is metabolized in the liver by CYP2D6, CYP1A2, and CYP2C19.[4] At steady state, the terminal half-life is 17 to 22 hours.[4] The kidneys are responsible for 93.5% of drug excretion.[4]

### Clinical pearls

- The safety of lofexidine during pregnancy and lactation has not been established.[4]
- Clinically significant drug interactions with lofexidine include other medications that may decrease heart rate or BP, concomitant QT-prolonging agents, CNS depressants including alcohol, oral naltrexone, and CYP2D6 inhibitors, such as paroxetine.[4]
- Lofexidine has not been evaluated in pediatric patients.[4]
- Although structurally similar to clonidine, lofexidine may cause less hypotension compared with clonidine.[5]
- In a Phase III clinical trial, lofexidine use resulted in decreased opioid withdrawal symptoms compared with placebo, and patients were more likely to complete the study protocol.[6]


**REFERENCES**

1. Centers for Disease Control and Prevention. Understanding the epidemic. 2017. www.cdc.gov/drugoverdose/epidemic/index.html.
2. Substance Abuse and Mental Health Services Administration. Medications for opioid use disorder for healthcare and addiction professional, policymakers, patients, and families. 2018. www.store.samhsa.gov/shin/content/SMA18-5063FULLDOC/SMA18-5063FULLDOC.pdf.
3. U.S. Food and Drug Administration. FDA approves the first non-opioid treatment for management of opioid withdrawal symptoms in adults. 2018. www.fda.gov/newsevents/newsroom/pressannouncements/ucm607884.htm.
4. Lucemyra (lofexidine) [package insert]. Louisville, KY: US WorldMeds, LLC; 2018.
5. Yu E, Miotto K, Akerele E, et al. A phase 3 placebo-controlled, double-blind, multi-site trial of the alpha-2-adrenergic agonist, lofexidine, for opioid withdrawal. *Drug Alcohol Depend.* 2008;97(1-2):158-168.
6. Gorodetzky CW, Walsh SL, Martin PR, Saxon AJ, Gullo KL, Biswas K. A phase III, randomized, multi-center, double blind, placebo controlled study of safety and efficacy of lofexidine for relief of symptoms in individuals undergoing inpatient opioid withdrawal. *Drug Alcohol Depend.* 2017;176:79-88.


## ▼ Cystic fibrosis

# Tezacaftor and ivacaftor (Symdeko)

Cystic fibrosis (CF) currently affects over 30,000 individuals in the US. It is characterized by viscous mucus buildup in the lungs, reproductive tract, pancreas, and gastrointestinal tract caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[1-3] Over 1,500 mutations of the CFTR gene have been identified, with 46% of patients being homozygous for the F508del mutation.[2] Symdeko, a novel product coformulation of tezacaftor and ivacaftor, is manufactured by Vertex Pharmaceuticals and was approved by the FDA in February 2018.[4]

### Indications

Tezacaftor and ivacaftor is indicated for the treatment of CF in patients who are homozygous for the F508del mutation or who have at least a single copy of one of the 26 CFTR mutations that respond to tezacaftor and ivacaftor.[3,5] It should not be used in patients under 12 years of age or when the genotype is unknown.[4] Tezacaftor and ivacaftor greatly expands the number of individuals who could benefit from CFTR therapy, which treats the underlying cause of CF.[3]

### Mechanism of action

Both tezacaftor and ivacaftor are CFTR modulators that work synergistically to target specific defects in the CFTR protein to restore function. Tezacaftor is a CFTR corrector, responsible for aiding in protein processing to increase the numbers of functional CFTR at the cell surface.[5,6] Ivacaftor is a CFTR potentiator that increases the probability of the chloride channel opening, increasing the ability to allow water to flow out of the cell and lower the viscosity of mucus in patients with CF.[5,7]

### Dosing and administration

Symdeko is copackaged as tezacaftor 100 mg and ivacaftor 150 mg fixed-dose combination tablets (yellow) and ivacaftor 150 mg single-entity tablets (blue).[5] Patients should be instructed to take the combination tezacaftor and ivacaftor tablet in the morning and the single-entity ivacaftor tablet in the evening with a fat-containing food. Doses should be separated by approximately 12 hours.[5] If a dose is missed and more than 6 hours have passed, that dose should be skipped; if less than 6 hours have

passed, the missed dose should be taken immediately.[5] Patients with moderate and severe liver impairment (Child-Pugh class B and C) should only take the morning tezacaftor and ivacaftor dose and should not take the ivacaftor evening dose.[5] Tezacaftor and ivacaftor has not been studied in patients with moderate or severe kidney impairment. No dose adjustments are recommended for patients with mild or moderate kidney impairment. However, caution is recommended when prescribing tezacaftor and ivacaftor in patients with severe kidney impairment or end-stage renal disease.[5]

*Tzacaftor and ivacaftor are CFTR modulators that work synergistically to target specific defects in the CFTR protein to restore function.*

## Contraindications

No contraindications to tezacaftor and ivacaftor are currently listed within the manufacturer's prescribing information.[5]

## Warnings and precautions

Elevated transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) may occur. ALT and AST levels should be monitored prior to initiating therapy every 3 months during the first year of therapy, then annually thereafter.[5] Therapy should be held when ALT and AST levels are elevated greater than five times the upper limit of normal (ULN) or greater than three times ULN with bilirubin greater than twice the ULN.[5] CYP3A inducers may significantly decrease systemic concentrations, reducing efficacy. It is recommended to avoid concomitant use of CYP3A inducers.[5] Cataracts have been observed in pediatric patients in clinical trials. Other risk factors for cataract development were present, but risk attributable to tezacaftor and ivacaftor cannot be ruled out. Thus, baseline and regular ophthalmologic follow-up exams are recommended for pediatric patients.[5]

## Adverse reactions

The most commonly observed adverse reactions in phase III clinical trials for tezacaftor and ivacaftor were infectious pulmonary exacerbations, cough, hemoptysis, and headache, which are common clinical manifestations of CF.[5-7] Additional adverse reactions that can be anticipated include nausea, sinus congestion, and dizziness.[5]

## Pharmacokinetics

Upon oral administration, tezacaftor reaches steady-state concentrations within 8 days, but ivacaftor reaches steady state between 3 to 5 days.[5] Pharmacokinetics are similar between patients with CF and healthy adults.[5] Tezacaftor and ivacaftor is extensively metabolized by CYP3A4 and CYP3A5, and both drugs have active metabolites.[5] Tezacaftor and ivacaftor is eliminated primarily through feces.[5] Doses should be taken with a fatty food because ivacaftor absorption is three times higher when taken with a fat-containing food compared with a fasting state. Tezacaftor absorption does not change from fasting to a fed state.[5]

## Clinical pearls

- The safety of tezacaftor and ivacaftor during pregnancy and lactation is unkown.[5]
- CYP3A inducers (for example, St. John's wort and rifampin) decrease tezacaftor and ivacaftor concentrations and should not be coadministered.[5]
- Dose reductions of tezacaftor and ivacaftor are necessary when moderate or strong CYP3A inhibitors (for example, clarithromycin, fluconazole, or ketoconazole) are coadministered with tezacaftor and ivacaftor; consult the prescribing information or a drug information reference before coadministering.[5]
- Patients should avoid foods containing grapefruit or Seville oranges because of CYP3A inhibition.[5]
- Phase III clinical trials have found significant improvement in lung function, including exacerbations and QoL, with tezacaftor and ivacaftor. The drug produces greater improvement in lung function in heterozygous F508 del than ivacaftor alone.[6,7]

### REFERENCES


1. Sorscher EJ. Cystic fibrosis. In: Kasper D, et al., eds. *Harrison's Principles of Internal Medicine*. 19th ed. New York, NY: McGraw-Hill; 2014.
2. Dodge JA. A millennial view of cystic fibrosis. *Dev Period Med.* 2015;19(1):9-13.
3. Cystic Fibrosis Foundation. FDA approves new CFTR modulator treatment for cystic fibrosis. 2018. www.cff.org/News/News-Archive/2018/FDA-Approves-New-CFTR-Modulator-Treatment-for-Cystic-Fibrosis/.
4. U.S. Food and Drug Administration. Drug Trials Snapshots: SYMDEKO. 2018. www.fda.gov/Drugs/InformationOnDrugs/ucm598699.htm.
5. Symdeko (tezacaftor/ivacaftor) [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; 2018.
6. Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor-ivacaftor in residual-function heterozygotes with cystic fibrosis. *N Engl J Med.* 2017;377(21):2024-2035.
7. Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del. *N Engl J Med.* 2017;377(21):2013-2023.

## ▼ Plaque psoriasis

# Tildrakizumab-asmn (Ilumya)

Psoriasis is the most common autoimmune disease, occurring in 7.5 million individuals in the US, with plaque psoriasis being the most common form.[1] The hallmark symptom of plaque psoriasis is erythematous plaques with silvery scales.[2] Tildrakizumab-asmn is a monoclonal antibody and an interleukin-23 (IL-23) antagonist.[3] It was approved in March 2018 by the FDA for moderate-to-severe plaque psoriasis and is manufactured as a subcutaneous injection by Merck Sharp and Dohme.[3]

### Indication

Tildrakizumab-asmn is indicated for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.[3]

### Mechanism of action

Tildrakizumab-asmn is a humanized IgG1/k monoclonal antibody that binds selectively to the p19 subunit of IL-23 to block its interaction with the IL-23 receptor. This results in the inhibition of the release of proinflammatory cytokines and chemokines to decrease inflammatory and immune responses in plaque psoriasis.[3]

### Dosing and administration

Tildrakizumab-asmn is formulated as a 1 mL single-dose, preservative-free, prefilled syringe containing 100 mg of the drug. The recommended dosing is one injection (100 mg) given at weeks 0 and 4, then every 12 weeks thereafter. If a dose is missed, an appointment should be scheduled as soon as possible to administer the dose, and the regular dosing schedule should be resumed.[3]

Tildrakizumab-asmn should only be administered by a healthcare provider. It should be administered subcutaneously to clear, unbruised, easily accessible skin, such as the thighs, upper arms, or abdomen. It should not be administered within 2 in (5 cm) around the naval, into scars or stretchmarks, or where skin is tender, indurated, erythematous, or affected by psoriasis.[3] Tildrakizumab-asmn should be stored in the refrigerator. Prior to administration, the prefilled syringe should be taken out of the refrigerator for 30 minutes to reach room temperature. Once taken out of the refrigerator, the medication should not be placed back in the refrigerator because it will remain stable for up to 30 days at room temperature.[3]

### Contraindications

Tildrakizumab-asmn is contraindicated in patients who have had previous hypersensitivity reactions to tildrakizumab or any of the excipients in the injection, such as angioedema or urticaria.[3]

### Warnings and precautions

Patients taking tildrakizumab-asmn should be aware of the increased risk of infection. In clinical trials, tildrakizumab-asmn had a greater risk of infection than placebo, but the increased risk is low.[3] Patients with clinically important active infections should not start tildrakizumab-asmn until the infection resolves or has been adequately treated.[3] Patients should be counseled to report infections that do not respond to standard treatment.[3]

Before administration of tildrakizumab-asmn, patients must be screened for tuberculosis (TB) infection. Tildrakizumab-asmn should not be administered to patients with active infection, and patients with latent TB must complete treatment before tildrakizumab-asmn is started. Additionally, patients should receive all recommended immunizations prior to treatment. Live vaccines should be avoided after tildrakizumab-asmn is started because of a weakening of immune response with tildrakizumab-asmn use.[3]

*Tildrakizumab-asmn should be administered subcutaneously to clear, unbruised, easily accessible skin.*

### Adverse reactions

The most common adverse reactions in phase III clinical trials were upper respiratory infections, injection site reactions, and diarrhea.[3-5] Approximately 6.5% of patients in clinical trials developed antibodies to tildrakizumab-asmn, with 40% of these classified as neutralizing, which can lower concentration and efficacy.[3]

### Pharmacokinetics

Tildrakizumab-asmn has a bioavailability of 73% to 80% when injected into the skin. Peak concentration after a single dose of tildrakizumab-asmn is reached in

approximately 6 days. Steady state after multiple doses is reached at 16 weeks of treatment. The exact mechanism of degradation is unknown, but the drug is thought to be broken down into small peptides and amino acids.[3]

## Clinical pearls

- Data are limited about the use of this drug during pregnancy, and there are no data about its use during lactation. Human immunoglobulin G antibodies cross the placental barrier and are found in breast milk, so tildrakizumab-asmn may be transferred from mother to fetus or infant.[3]
- Live vaccinations should be avoided in combination with tildrakizumab-asmn because of an increased risk of infection.[3]
- Tildrakizumab-asmn has not been studied in patients younger than 18 years; therefore, it is not currently indicated in the pediatric population.
- In clinical trials, tildrakizumab-asmn was shown to be more efficacious compared with placebo and etanercept in achieving "clear" or "minimal" psoriatic involvement of the skin.[4,5] NP

### REFERENCES


1. National Psoriasis Society. Statistics. 2018. www.psoriasis.org/content/statistics.
2. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. *J Am Acad Dermatol.* 2011;65(1):137-174.
3. Ilumya (tildrakizumab-asmn) [package insert]. Whitehouse Station, NJ: Merck Sharp and Dohme Corporation; 2018.
4. PR Newswire. Sun Pharma announces US FDA approval of Ilumya (tildrakizumab-asmn) for the treatment of moderate-to-severe plaque psoriasis [news release]. 2018. www.prnewswire.com/news-releases/sun-pharma-announces-us-fda-approval-of-ilumya-tildrakizumab-asmn-for-the-treatment-of-moderate-to-severe-plaque-psoriasis-300617454.html.
5. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet.* 2017;390(10091):276-288.


Consult the manufacturer's prescribing label for the complete prescribing information including dose recommendations and any dose adjustments for each drug.


Cortney Mospan is an assistant professor of pharmacy at Wingate University, Levine College of Health Sciences, Wingate, N.C.

Geoffrey Mospan is an assistant professor of pharmacy at Wingate University, Levine College of Health Sciences, Wingate, N.C.

Emily Byland is a PharmD candidate at Wingate University, School of Pharmacy, Wingate, N.C.

William Blake Whitaker is a PharmD candidate at Wingate University, School of Pharmacy, Hendersonville, N.C.

Linda Xiong is a PharmD candidate at Wingate University, School of Pharmacy, Wingate, N.C.

Jordan Dunlap is a PharmD candidate at Wingate University, School of Pharmacy, Wingate, N.C.

Katherine Canupp is a PharmD candidate at Wingate University, School of Pharmacy, Wingate, N.C.


The authors and planners have disclosed no potential conflicts of interest, financial or otherwise.

DOI-10.1097/01.NPR.0000547548.63764.6b