



**Magellan Rx**  
MANAGEMENT<sup>SM</sup>

Magellan Medicaid  
Administration

# Washington Pharmacy Advisory Committee Meeting

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# Agenda Topics

Overview of Disease  
State

Indications

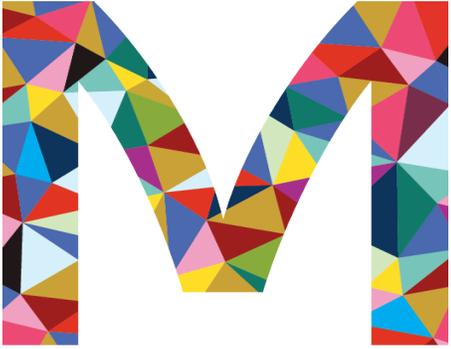
Dosage & Formulations

Guideline Updates



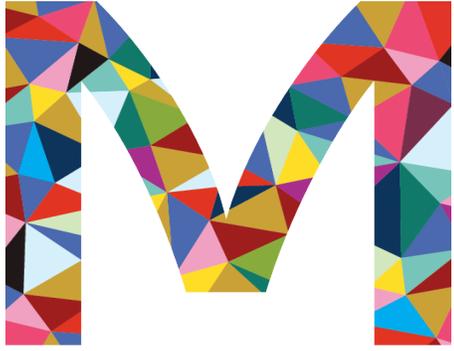
# Antihyperlipidemics: Microsomal Triglyceride Transfer Protein (MTP) Inhibitor





# Antihyperlipidemics: PCSK-9 Inhibitors





# Antivirals: HIV



# Overview of Disease State – HIV Agents

- Human Immunodeficiency Virus (HIV) infection is a complex disease that results in destruction of the immune system of HIV-infected individuals
- There are 2 major subtypes of HIV:
  - HIV-1
    - Considered most responsible for the Acquired Immune Deficiency Syndrome (AIDS) epidemic
    - More common worldwide
  - HIV-2
    - Less virulent and less transmissible; however, both are known to cause AIDS and are transmitted by sexual contact, through blood, and from mother to child
    - More concentrated in West Africa
- HIV retrovirus establishes infection by killing the CD4+ T cells that are crucial to a healthy immune system
  - These T cells are also called “T-helper cells” because they also signal other cells in the immune system to perform their functions
  - Research has shown that most infecting strains of HIV use a co-receptor molecule called CCR5, in addition to the CD4 molecule, to enter the T cells and take over the cellular machinery for viral replication
  - Without these CD4+ T cells, the immune system is vulnerable to infection
    - A healthy uninfected person usually has 800 to 1,200 CD4+T cells per cubic millimeter ( $\text{mm}^3$ ) of blood
    - Once infected, the number of T cells declines. This decline may be swifter than previously believed in the absence of early treatment. If the T cell count falls below  $200/\text{mm}^3$ , then the condition is classified as AIDS
    - The individual then becomes even more vulnerable to the opportunistic infections (OIs) and cancers that are associated with this end stage of HIV disease

# Overview of Disease State – HIV Agents

- Nine therapeutic classes represent the drug treatment options for HIV/AIDS:
  - Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)
  - Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
  - Protease inhibitors (PIs)
  - Integrase inhibitors (INSTIs)
  - Attachment inhibitor
  - CCR5 antagonists
  - Fusion inhibitors
  - Pharmacokinetic enhancers
  - Monoclonal antibody, ibalizumab-uiyk (Trogarzo)
- Initial regimen selection should be guided by patient characteristics, including comorbidities, drug-drug interaction possibilities, toxicity risk, regimen complexity, and virologic efficacy

# Treatment Guidelines

- Department of Health and Human Services, 2019

- Guidelines state that clinical trials have shown that using effective ART to consistently suppress plasma **HIV RNA levels to < 200 copies/mL** prevents transmission of HIV to sexual partners
  - Thus, the guidelines recommend that inform patients that maintaining HIV RNA levels < 200 copies/mL with ART prevents HIV transmission to sexual partners
  - Patients should also use an **alternative form of prevention** with sexual partners for at least the first 6 months of treatment and until an HIV RNA level of < 200 copies/mL have been documented, and many experts recommend confirming sustained suppression prior to assuming that there is no risk of sexual HIV transmission
  - Furthermore, healthcare providers should inform patients that maintaining an HIV RNA level of < 200 copies/mL does not prevent acquisition or transmission of other sexually transmitted infections
- Recommend that **CD4 counts be measured every 3 to 6 months during the first 2 years of therapy**, if viremia develops while patient is on antiretroviral therapy, if ART initiation is delayed, if there are ART modifications, and if CD4 count reaches < 300 cells/mm<sup>3</sup>
  - Testing is then **recommended every 12 months after 2 years** on ART with a consistently suppressed viral load
  - **Drug-resistance testing is recommended at entry** into care regardless of whether therapy will be initiated immediately or deferred
  - Guidelines also recommend **mutation testing** for reverse transcriptase (RT), protease (PR) genes, and INSTIs if needed
  - Resistance testing is also recommended in the setting of virologic failure while the patient is taking the drug or within 4 weeks after discontinuing therapy
- Notably, patients should be **screened for both hepatitis B or C virus** at entry into care, as having the co-infection may impact the initiation of ART
- A portion of the published recommended laboratory schedule is outlined in the HIV TCR

# Treatment Guidelines

- Department of Health and Human Services, 2019

- Guidelines provide recommendations to consider before initiating dolutegravir (DTG) and other INSTIs as initial therapy
- **Pregnancy testing** should be performed in those of childbearing potential prior to initiation of ART
  - The latest data has shown that prevalence of neural tube defects (NTDs) is lower than initially reported
- Based on new data, the guidelines have revised **dolutegravir** recommendations in pregnant patients by recommending that providers discuss the benefits and risks with persons of **childbearing potential** and allow them to make informed decisions
  - They further state that dolutegravir may be used as an alternative ARV for patients who are of childbearing potential and trying to conceive and those who are sexually active and not using contraception
  - For individuals who are using effective contraception, dolutegravir may be used as a recommended option
- In addition, in patients who are pregnant, **bictegravir is not recommended due to insufficient safety data**, and **elvitegravir/cobicistat is not recommended** due to reportedly low elvitegravir plasma concentrations during the second and third trimesters
- Lastly, there is **limited raltegravir data during the first trimester** in the US
- Currently, it is **not known whether the link between DTG and NTDs represents a class effect**; however, this potential risk should be discussed with patients of childbearing potential who prefer an INSTI-containing regimen

# Treatment Guidelines

- International Antiviral Society, 2018
  - Initial Antiretroviral Treatment of Adults (IAS)

## Initial Antiretroviral Treatment of Adults (IAS)

\*Generally recommended initial regimens. Other regimens listed are for individuals for whom these generally recommended regimens are not available or are not an option.

INSTI plus 2 NRTIs	NNRTI plus 2 NRTIs	Ritonavir-boosted protease inhibitor plus 2 NRTIs
bictegravir + tenofovir alafenamide (TAF) + emtricitabine*	efavirenz + TDF + emtricitabine	darunavir + cobicistat + TAF (or TDF) + emtricitabine
dolutegravir + abacavir + lamivudine*	rilpivirine + TAF (or TDF) + emtricitabine (if pretreatment HIV RNA level is < 100,000 copies/mL and CD4 cell count is > 200/ $\mu$ L)	darunavir + ritonavir + TAF (or TDF) + emtricitabine
dolutegravir + TAF + emtricitabine*		
elvitegravir + cobicistat + TAF (or tenofovir disoproxil fumarate [TDF]) + emtricitabine		
raltegravir + TAF (or TDF) + emtricitabine		

# Treatment Guidelines

- Department of Health and Human Services, 2019
  - Recommended Antiretroviral Regimen Options for Treatment-Naïve Patients

Treatment Options for Most Treatment-Naïve Adults and Adolescents (DHSS)	
INSTI-Based Regimen	Co-formulated Availability
bictegravir + tenofovir alafenamide (TAF) + emtricitabine (AI)	ABC/3TC FTC/TAF
dolutegravir + abacavir + lamivudine <sup>a</sup> – only for patients who are HLA-B* 5701 negative (AI)	3TC/TDF TDF/FTC
dolutegravir + tenofovir <sup>b</sup> + emtricitabine <sup>a</sup> (AI)	BIC/TAF/FTC DTG/ABC/3TC EVG/c/TDF/FTC EVG/c/TAF/FTC
dolutegravir + lamivudine (AI) – except for individuals with HIV RNA > 500,000 copies/mL, HBV co-infection, or in whom ART is to be started before result availability of HIV genotypic resistance testing for reverse transcriptase or HBV testing	
raltegravir + TDF + emtricitabine <sup>a</sup> (BI)	

# Treatment Guidelines

- [Department of Health and Human Services, 2019](#)

## Alternative/Other Treatment Options in Treatment-Naïve Adults and Adolescents (DHSS) – Recommended for Certain Clinical Situations

INSTI-Based	NNRTI-Based	Protease Inhibitor-Based	Co-formulated Availability
elvitegravir + cobicistat + tenofovir <sup>b</sup> + emtricitabine <sup>a</sup> (BI)	doravirine + tenofovir alafenamide <sup>b</sup> + lamivudine (BIII)	atazanavir + cobicistat (or ritonavir) + tenofovir <sup>b</sup> + emtricitabine (BI)	ATV/c DRV/c
raltegravir + abacavir + lamivudine <sup>a</sup> – only for patients who are HLA-B*5701 negative and HIV RNA < 100,000 copies/mL(CII)	doravirine + tenofovir disoproxil fumarate <sup>b</sup> + lamivudine (BI)	darunavir + ritonavir + tenofovir <sup>b</sup> + emtricitabine <sup>a</sup> (AI) darunavir + cobicistat + tenofovir <sup>b</sup> + emtricitabine <sup>a</sup> (AI)	LPV/r ABC/3TC FTC/TAF
	efavirenz + lamivudine+ TDF (BI)	darunavir + cobicistat (or ritonavir) + abacavir + lamivudine <sup>a</sup> (BII) — only for patients who are HLA-B*5701 negative	3TC/TDF TDF/FTC
	efavirenz + emtricitabine + TDF (BI)		DOR/TDF/3TC DRV/c/FTC/TAF
	efavirenz + emtricitabine + TAF (BII)	darunavir + ritonavir + lamivudine once daily (CI), if ABC, TAF, and TDF cannot be used	EFV/3TC/TDF FTC/RPV/TAF RPV/FTC/TDF TDF/FTC/EFV
rilpivirine + tenofovir <sup>b</sup> + emtricitabine <sup>a</sup> – only for patients with HIV RNA < 100,000 copies/mL and CD4 > 200 cells/mm <sup>3</sup> (BI)		darunavir + ritonavir + raltegravir twice daily (CI) if HIV RNA < 100,000 copies/mL, CD4 > 200 cells/mm <sup>3</sup> , and if ABC, TAF, and TDF cannot be used dolutegravir + lamivudine (AI), except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available	

# HIV Agents

- **cobicistat (Tybost)**

- **October 2019: FDA modified indication to specify use with darunavir (800 mg once daily) in patients  $\geq$  40 kg**

- **Indication**

- To increase systemic exposure of atazanavir or darunavir (once daily dosing regimen) in combination with other antiretroviral agents in the treatment of HIV-1 infection in adults and in pediatric patients:

- Weighing at least 35 kg coadministered with atazanavir or
- **Weighing at least 40 kg coadministered with darunavir**

- **Warnings and Precautions**

- Assess creatinine clearance (CrCl) before initiating treatment
- When Tybost is used in combination with a TDF-containing regimen, cases of acute renal failure and Fanconi syndrome have been reported
- Tybost in combination with more than one antiretroviral that requires pharmacokinetic enhancement (i.e., two protease inhibitors or elvitegravir in combination with a protease inhibitor) is not recommended
- Use with HIV-1 protease inhibitors other than atazanavir or darunavir administered once daily is not recommended

- **Dosage**

- Treatment-naïve or treatment-experienced
  - 150 mg Tybost orally once daily with atazanavir 300 mg orally once daily
- Treatment-naïve or treatment-experienced with no darunavir resistance-associated substitutions
  - 150 mg Tybost orally once daily with darunavir 800 mg orally once daily
- Recommended dosage in pediatric patients: Tybost 150 mg orally once daily

- **Availability**

- Tablets: 150 mg

# HIV Agents

- **doravirine (Pifeltro)**

- **October 2019: FDA approved expanded indication to include patients who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known substitutions associated with resistance to doravirine. Previously only approved in patients with no prior ARV treatment history**

- **Indication**

- In combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients:

- With no prior antiretroviral treatment history, OR
- **To replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to doravirine**

- **Warnings and Precautions**

- Monitor for Immune Reconstitution Syndrome
- Contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers as significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of treatment

- **Dosage**

- One tablet taken orally once daily with or without food in adult patients

- **Availability**

- Tablets: 100 mg

# HIV Agents

- **doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo)**
  - **October 2019: FDA approved expanded indication to include patients who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known substitutions associated with resistance to doravirine. Previously only approved in patients with no prior ARV treatment history**
  - **Indication**
    - A three-drug combination of doravirine (a nonnucleoside reverse transcriptase inhibitor [NNRTI]), lamivudine, and tenofovir disoproxil fumarate (both nucleoside analogue reverse transcriptase inhibitors) and is indicated as a complete regimen for the treatment of HIV-1 infection in adult patients:
      - With no antiretroviral treatment history, OR
      - **To replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of Delstrigo**
  - **Warnings and Precautions**
    - BBW: Posttreatment acute exacerbations of Hepatitis B
    - Monitor for Immune Reconstitution Syndrome
    - Contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers as significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of treatment
  - **Dosage**
    - One tablet taken orally once daily with or without food in adult patients
  - **Availability**
    - Tablets: 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate

# HIV Agents

- **emtricitabine/tenofovir alafenamide (TAF) (Descovy)**

- **December 2019: FDA approved new indication in at-risk adults and adolescents  $\geq 35$  kg for pre-exposure prophylaxis (PrEP) to reduce risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex**

- **Indication**

- HIV-1 Treatment:

- In combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg
- In combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg and less than 35 kg

- HIV-1 PrEP:

- **Indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex. Individuals must have a negative HIV-1 test immediately prior to initiating Descovy for HIV-1 PrEP**

- **Warnings and Precautions**

- **BBW: Severe acute exacerbations of hepatitis B (HBV) have been reported in HBV-infected individuals who have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF) and may occur with discontinuation of Descovy**

- **Dosage**

- Recommended dosage:

- Treatment of HIV-1 Infection: One tablet taken once daily with or without food in patients with body weight at least 25 kg
- **HIV-1 PrEP: One tablet taken once daily with or without food in individuals with body weight at least 35 kg**

- **Availability**

- Tablets: 200 mg of FTC and 25 mg of TAF

# HIV Agents

- **cobicistat /darunavir/ emtricitabine/ tenofovir alafenamide fumarate (Symtuza)**
  - **March 2020: FDA approved expanded indication to now include use as a complete regimen for the treatment of HIV-1 infection in pediatric patients weighing  $\geq 40$  kg who have no prior antiretroviral treatment history or who are virologically suppressed (HIV-1 RNA  $< 50$  copies/mL) on a stable antiretroviral regimen for  $\geq 6$  months and have no known substitutions associated with resistance to darunavir or tenofovir. Previously indicated for adult patients who met this criteria**
  - **Indication**
    - Indicated as a complete regimen for the treatment of HIV-1 infection in adults and **pediatric patients weighing at least 40 kg:**
      - Who have no prior antiretroviral treatment history or
      - Who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir
  - **Warnings and Precautions**
    - **BBW:** Severe acute exacerbations of hepatitis B (HBV) have been reported in HBV-infected individuals who have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF) and may occur with discontinuation of Symtuza
    - Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) including some fatalities can occur with Symtuza. Monitor liver function before and during therapy, especially in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases
  - **Dosage**
    - One tablet taken once daily with food in adults and pediatric patients, weighing at least 40 kg
  - **Availability**
    - Tablets: 800 mg of darunavir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (equivalent to 11.2 mg of tenofovir alafenamide fumarate)

# HIV Agents

- **dolutegravir (Tivicay; Tivicay PD)**

- **June 2020: FDA approved new formulation of Tivicay, Tivicay PD, and is approved for the treatment of HIV-1 in treatment-naïve and treatment-experienced, INSTI-naïve pts aged at least 4 weeks and weighing at least 3 kg**
- **June 2020: FDA also expanded Tivicay indication to include treatment-naïve and treatment-experienced, INSTI-naïve pts weighing 14 kg to < 30 kg (Tivicay PD is still preferred in those < 20 kg per labeling). Previously, Tivicay was only indicated in pediatric patients of this population weighing at least 30 kg**

- **Indication**

- **Tivicay and Tivicay PD are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults (treatment-naïve or -experienced) and in pediatric patients (treatment-naïve or -experienced but INSTI- naïve) aged at least 4 weeks and weighing at least 3 kg**
- Tivicay is indicated in combination with rilpivirine as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure or known substitutions associated with resistance to either antiretroviral agent

- **Warnings and Precautions**

- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. An alternative treatment to dolutegravir should be considered at the time of conception through the first trimester of pregnancy due to the risk of neural tube defects. Counsel adolescents and adults of childbearing potential to use effective contraception

- **Dosage**

- Dosing stratified by weight and history of treatment experience/naïve

- **Availability**

- Tivicay tablets: 10 mg, 25 mg, and 50 mg
- Tivicay PD tablets for oral suspension: 5 mg

# HIV Agents

- **emtricitabine/tenofovir disoproxil fumarate (Truvada)**
  - **June 2020: PI updates to the language for the HIV-1 pre-exposure prophylaxis (PrEP) indication**
    - Includes removing the factors that help to identify at risk individuals as well as information on delay in starting PrEP for patients with clinical symptoms and recent exposure
    - Also revised wording regarding PrEP being used in combination with safer sex practices
    - Still remains indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection
    - Indication also still requires individuals to have a negative HIV-1 test immediately prior to initiating for HIV-1 PrEP
  - **Indication**
    - HIV-1 Treatment:
      - In combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 17 kg
    - HIV-1 PrEP:
      - Indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection. Individuals must have a negative HIV-1 test immediately prior to initiating TRUVADA for HIV-1 PrEP
  - **Dosage**
    - Treatment of HIV-1 Infection: One tablet taken once daily with or without food in patients with body weight at least 17 kg
    - HIV-1 PrEP: One tablet taken once daily with or without food in individuals with body weight at least 35 kg
  - **Availability**
    - Tablets: 200 mg/300 mg, 167 mg/250 mg, 133 mg/200 mg, and 100 mg/150 mg of emtricitabine and tenofovir disoproxil fumarate, respectively

# HIV Agents

- **darunavir/cobicistat (Prezcobix)**

- **July 2020: FDA approved expanded indication for use for the treatment of HIV-1 infection in treatment-naïve and treatment-experienced with no darunavir resistance-associated substitutions expanded to include pediatric pts weighing  $\geq 40$  kg; previously, it was approved for use only in adults**

- **Indication**

- Indicated for the treatment of HIV-1 infection in treatment naïve and treatment-experienced adults and **pediatric patients** weighing at least 40 kg with no darunavir resistance-associated substitutions (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V)

- **Warnings and Precautions**

- Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) including some fatalities can occur with Prezcobix. Monitor liver function before and during therapy, especially in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases
- Not recommended in combination with other antiretroviral drugs that require pharmacokinetic boosting
- When used in combination with a tenofovir disoproxil fumarate (tenofovir DF) containing regimen, cases of acute renal failure and Fanconi syndrome have been reported

- **Dosage**

- **One tablet taken once daily with food in adults and pediatric patients weighing at least 40 kg**

- **Availability**

- Tablets: 800 mg of darunavir and 150 mg of cobicistat

# HIV Agents

- **atazanavir/cobicistat (Evotaz)**

- **July 2020: FDA approved expanded indication for use for the treatment of HIV-1 infection, in combination with other agents, expanded to include pediatric pts weighing  $\geq 35$  kg; previously, it was approved for use only in adults**

- **Indication**

- **Indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg**
- Limitation of Use: Use of Evotaz in treatment-experienced patients should be guided by the number of baseline primary protease inhibitor resistance substitutions

- **Warnings and Precautions**

- **Contraindicated in patients with previously demonstrated hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of this product**
- Cardiac conduction abnormalities: PR interval prolongation may occur in some patients. Consider ECG monitoring in patients with preexisting conduction system disease or when administered with other drugs that may prolong the PR interval
- Severe skin reactions: Discontinue if severe rash develops
- Renal impairment: Not recommended for use in treatment experienced patients with end-stage renal disease managed with hemodialysis
- Hepatic impairment: Not recommended in patients with any degree of hepatic impairment

- **Dosage**

- **One tablet once daily, taken orally with food in adults and pediatric patients weighing at least 35 kg**

- **Availability**

- **Tablets: 300 mg of atazanavir and 150 mg of cobicistat**

# HIV Agents

- **fostemsavir (Rukobia)**

- **July 2020: FDA approved Rukobia, an HIV-1 gp120-directed attachment inhibitor, in combination with other ARVs for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current ARV regimen due to resistance, intolerance, or safety considerations**

- **Indication**

- **In combination with other antiretroviral(s), is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations**

- **Warnings and Precautions**

- **Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapies**
- **QTc prolongation: Use Rukobia with caution in patients with a history of QTc prolongation or with relevant pre-existing cardiac disease or who are taking drugs with a known risk of Torsade de Pointes**
- **Elevations in hepatic transaminases in patients with hepatitis B or C virus co-infection: Elevations in hepatic transaminases were observed in a greater proportion of subjects with HBV and/or HCV co-infection compared with those with HIV mono-infection**

- **Dosage**

- **One tablet taken orally once daily with or without food**

- **Availability**

- **Extended-release tablets: 600 mg**

# HIV Agents

- **dolutegravir/lamivudine (Dovato)**

- **August 2020: FDA approved expanded indication to include use as a complete regimen to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA < 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure (previously only indicated as complete regimen in treatment-naive adults)**
- **Indication**
  - **Indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of Dovato**
- **Warnings and Precautions**
  - **BBW: All patients with HIV-1 should be tested for the presence of HBV prior to or when initiating Dovato. Emergence of lamivudine-resistant HBV variants associated with lamivudine-containing antiretroviral regimens has been reported**
  - **Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. An alternative treatment to Dovato should be considered at the time of conception through the first trimester of pregnancy due to the risk of neural tube defects. Counsel individuals of childbearing potential to use effective contraception**
  - **Pregnancy: An alternative treatment to Dovato should be considered at the time of conception through the first trimester due to the risk of neural tube defects**
- **Dosage**
  - One tablet taken orally once daily with or without food
- **Availability**
  - Tablets: 50 mg of dolutegravir and 300 mg of lamivudine

# HIV Agents

- **New Generic**

- efavirenz/lamivudine/tenofovir disoproxil fumarate – May 2020:
  - FDA-approved AB-rated generic version of Symfi Lo by Laurus Labs

- **Discontinuation**

- **didanosine (Videx)- February 2020:**

- Videx (didanosine) 125 mg, 200 mg, 250 mg and 400 mg capsules, by BMS, have been discontinued
  - Discontinuation dates are as follows: 125 mg capsule (3/31/2020), 200 mg capsule (2/14/2020), 250 mg capsule (3/31/2020), 400 mg capsule (11/20/2019)
- BMS is also discontinuing the Videx 2 g and 4 g pediatric solution; discontinuation dates are March 31, 2020 and May 21, 2019, respectively
  - No other formulations of the pediatric formulation are currently available
- Generic versions of these capsules remain available
- These discontinuations are based on a marketing decision

- **indinavir (Crixivan)- April 2020:**

- FDA has reported Merck's Crixivan capsules (400 mg) will be discontinued on or near August 2020

- **nevirapine (Viramune)- June 2020:**

- Boehringer Ingelheim has discontinued Viramune 200 mg tablets
- Generic nevirapine IR and ER tablets and oral suspension are available



# Antivirals: Influenza Agents



# Disease State Description - Antiviral, Influenza

- Common illness affecting most people at least once in their lifetime
  - Uncomplicated illness typically resolves after 3 to 7 days
  - Often self-limiting
  - Persons at higher risk for influenza complications: < 2 years or ≥ 65 years old, immunocompromised patients, pregnant/postpartum patients, < 19 years old + long-term ASA therapy, American Indians/Alaska Natives, extremely obese patients, nursing homes/other chronic care facility patients, and patients with specific, chronic disease states
- Influenza vaccination is the primary method for preventing influenza
  - Inactivated influenza vaccines are available in quadrivalent and trivalent formulations, while recombinant influenza vaccine and LAIV4 are available in quadrivalent formulations
  - There is also a high-dose inactivated influenza vaccine and adjuvanted inactivated influenza vaccine available in trivalent formulations
  - For the 2018–2019 season, the ACIP voted to recommend that providers may administer any licensed, age-appropriate influenza vaccine, including LAIV4 when appropriate; this was a change from the previous 2 seasons (2016–2017 and 2017–2018) during which time the ACIP recommended that LAIV4 not be used
  - Virus strains included in the 2019–2020 US trivalent influenza vaccines contain hemagglutinin (HA) derived from an A/Brisbane/02/2018 (H1N1)pdm09–like virus, an A/Kansas/14/2017 (H3N2)–like virus, and a B/Colorado/06/2017–like virus (Victoria lineage)
  - Quadrivalent influenza vaccines contain HA derived from the 3 viruses contained in the trivalent vaccine plus a B/Phuket/3073/2013–like virus (Yamagata lineage)

*Centers for Disease Control and Prevention, 2019*

# Treatment Guidelines - Antiviral, Influenza

- Centers for Disease Control and Prevention, 2019

- There are 3 FDA-approved neuraminidase inhibitor antiviral drugs recommended by CDC for the 2019-2020 season:
  - oseltamivir (Tamiflu)
  - zanamivir (Relenza)
  - peramivir (Rapivab)
- The fourth recommended FDA-approved product is the cap-dependent endonuclease inhibitor baloxavir marboxil (Xofluza)
  - Adamantanes (amantadine and rimantadine) are not recommended for use in the U.S. due to resistance to these drugs by many influenza A influenza B viruses
- Studies indicate that early antiviral treatment can reduce the risk of complications from influenza, such as pneumonia, respiratory failure, and death
- Antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who has severe, complicated, or progressive illness; is hospitalized; or is at high risk for influenza complications
- According to the CDC, oseltamivir (oral or enterically-administered) is the recommended antiviral for patients with severe, complicated, or progressive illness or who are hospitalized
- Insufficient data for Relenza, Rapivab, or Xofluza in patients with severe influenza

- Infectious Diseases Society of America, 2018

- Key recommendations include
  - Early antiviral treatment (oseltamivir or inhaled zanamivir for 5 days or single-dose IV peramivir) to reduce symptom duration and severity in select patients
  - Rapid molecular assays to improve detection
  - Chemoprophylaxis in select situations (oseltamivir or inhaled zanamivir)
- No recommendations made regarding baloxavir marboxil, as it was approved after the finalization of the guidelines

# Treatment Guidelines - Antiviral, Influenza

2019-2020 Season	Medications	Resistance/Activity
Medications recommended	oseltamivir (Tamiflu; oral) zanamivir (Relenza; inhalation) peramivir (Rapivab; IV) baloxavir marboxil (Xofluza; oral)	Low level of resistance Activity against influenza A and B
Medications not recommended	amantadine and rimantadine	High level of resistance No activity against influenza B

- Clinical benefit greatest when antiviral treatment is administered within 48 hours of illness onset
- Treatment:
  - Outpatient with acute uncomplicated influenza: 2 doses per day of oral oseltamivir or inhaled zanamivir for 5 days, or 1 dose of IV peramivir for 1 day
  - Outpatient with severe or complicated influenza: oseltamivir is recommended; inhaled zanamivir is not recommended because of the lack of data for use
  - Oral oseltamivir is preferred for treatment of pregnant women
- Prophylaxis: recommended duration is 7 days
  - Antiviral medications are approximately 70% to 90% effective in preventing influenza
  - Can be considered for prophylaxis in certain situations and within 48 hours of exposure; widespread and routine use is not recommended

# Anti-infective - Antiviral, Influenza

- **baloxavir marboxil (Xofluza)**

- **October 2019: FDA approved expanded indication Xofluza**

- **Indication**

- **Treatment of acute, uncomplicated influenza in patients  $\geq 12$  years of age who have been symptomatic for  $\leq 48$  hours and who are otherwise healthy or at high risk of developing influenza-related complications**

- **Warnings and Precautions**

- A risk of serious bacterial infections, may coexist with, or occur as a complication of influenza. Baloxavir marboxil and oseltamivir have not been shown to prevent these complications, including bacterial infection. There is no evidence of efficacy of baloxavir marboxil, oseltamivir, zanamivir in any illness due to pathogens other than influenza viruses
- Co-administration of baloxavir marboxil (Xofluza) with polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc) should be avoided

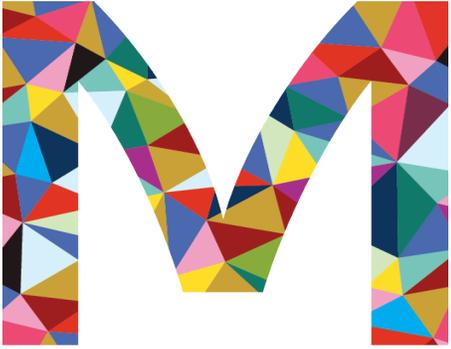
- **Dosage**

- Adults:

- In patients weighing 40 kg to  $< 80$  kg, a single dose of 40 mg is recommended
- In patients weighing  $\geq 80$  kg, 80 mg is recommended

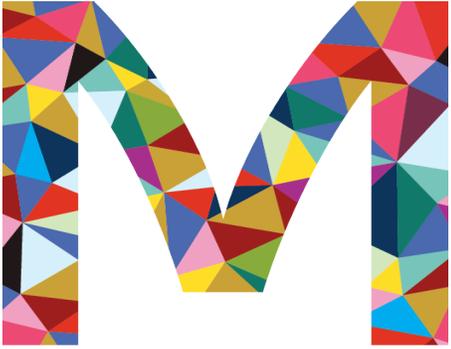
- **Availability**

- Tablets: 20 and 40 mg



# Cardiovascular Agents: Sinus Node Inhibitors





# Endocrine and Metabolic Agents: Pituitary Suppressants

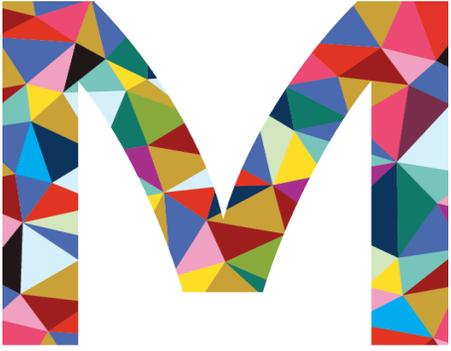


# Disease State Description – Pituitary Suppressants

- Uterine leiomyomata (fibroids)
  - Benign tumors that develop in the smooth muscle of the uterus
  - They are often described according to their location in the uterus: Subserosal (under the uterine serosa), Intramural (within the myometrium), Submucosal (just below the endometrium)
  - The true incidence and prevalence of uterine leiomyomata in the general female population are unknown because the condition is frequently asymptomatic and therefore not identified
  - The exact cause of these tumors is unknown; however, estrogen and progesterone have been implicated in the promotion of uterine fibroid growth
- American College of Obstetricians and Gynecologists (ACOG), 2016
  - Most women affected by uterine leiomyomata are asymptomatic and require no treatment unless rapid growth is observed or there are other reasons to suspect pelvic malignancy
  - Myomas can cause symptoms including menstrual irregularities (intermenstrual bleeding or menorrhagia), progressive pelvic pressure, pelvic pain, back pain, frequent urination or difficulty urinating, constipation, and distortion of the uterine or abdominal wall
    - Myomas may affect fertility and may prolapse or degenerate causing acute onset pelvic pain
  - Treatment goals focus on the management of symptoms
    - Treatment selection is based, in part, on the woman's preference and desire for uterine preservation and future fertility
    - Surgical treatment includes myomectomy (removing the myomas with reconstruction and preservation of the uterus), hysterectomy, and uterine artery embolization (UAE)
    - Medical therapies include oral contraceptives and progestin-releasing intrauterine devices (IUDs) to help reduce menorrhagia, non-steroidal anti-inflammatory drugs NSAIDs for pain management, mifepristone, and GnRH agonists to shrink the fibroids

# Endocrine – Pituitary Suppressants

- **elagolix/estradiol/norethindrone acetate; elagolix (OriaHnn)**
  - **May 2020: FDA approved combination of elagolix, a GnRH antagonist, with the estradiol/norethindrone, a combination of estrogen and progestin**
  - **Indication**
    - **Indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women**
  - **Warnings and Precautions**
    - **OriaHnn is contraindicated in women with high risk of arterial, venous thrombotic, or thromboembolic disorders, current or history of breast cancer or other hormonally-sensitive malignancies, known liver impairment or disease and undiagnosed abnormal uterine bleeding**
    - **Contraindicated with any degree of hepatic impairment**
  - **Dosage**
    - **1 elagolix/ estradiol/ norethindrone acetate capsule in the morning and 1 elagolix capsule in the evening, for up to 24 months**
    - **Doses should be taken at approximately the same time each day and can be taken without regard to food**
  - **Availability**
    - **Oral capsules co-packaged; carton containing 4 weekly blister packs each with 7 morning capsules and 7 evening capsules**
    - **Morning capsules: elagolix 300 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg**
    - **Evening capsules: elagolix 300 mg**



# Gastrointestinal Agents: Irritable Bowel Syndrome (IBS) Agents/GI Motility



# Disease State Description - Irritable Bowel Syndrome (IBS) Agents/GI Motility

- Constipation

- A syndrome that is defined by bowel symptoms specific to the difficult passage of stool, infrequent passage of stool, abnormal hardness of stool, or a feeling of incomplete evacuation after a bowel movement
- Though constipation can occur secondary to another disease (e.g., Parkinson's disease, spinal cord injury), idiopathic constipation occurs independent of any other underlying disorder
- Chronic idiopathic constipation (CIC) is diagnosed if there are < 3 spontaneous bowel movements (SBMs) per week with symptoms occurring for  $\geq 6$  months and at least 2 of the previously mentioned bowel symptoms

*American Gastroenterological Association, 2013*

# Disease State Description - Irritable Bowel Syndrome (IBS) Agents/GI Motility

- Irritable bowel syndrome (IBS)
  - A functional bowel disorder which can be chronic, relapsing, and often life-long
  - Occurs in up to 15% of the population and is up to 2.5 times more common in women than men
  - Characterized by symptoms of abdominal pain or discomfort associated with abnormal stool frequency, abnormal stool consistency, abnormal stool passage, and/or bloating or abdominal distension, which may or may not be relieved by defecation, at least 3 days per month in the past 3 months
    - Can also present with non-colonic features (e.g., functional urinary and gynecologic problems, gallbladder and stomach symptoms, back pain, migraine, and depression) which can lead to inappropriate patient referrals
  - Patients present with a combination of symptoms that are typically constipation predominant (IBS-C), diarrhea predominant (IBS-D), and/or alternating between both, or mixed (IBS-M)
  - Causes have not been fully identified, but could potentially include gut hypersensitivity, disturbed colonic motility, post-infective bowel dysfunction, or a defective anti-nociceptive system
  - There may also be contributing factors (e.g., stress, food intolerance, abnormal intestinal flora) which can hinder the effectiveness of treatment if left unresolved

*American Gastroenterological Association, 2013*

# Treatment Guidelines

- Opioid-induced constipation (OIC) is a common adverse effect of opioid therapy
  - American Pain Society (APS) and American Academy of Pain Medicine (AAPM), 2009
    - Recommend that patients receiving chronic opioid therapy with non-cancer pain that have common adverse effects, including constipation, should be anticipated and addressed appropriately
  - American Society of Interventional Pain Physicians (ASIPP), 2012
    - Recommend for patients receiving chronic non-cancer pain medications to be initiated on a prophylactic bowel regimen (e.g., increased fluid and fiber intake, stool softeners, laxatives) before the development of constipation and definitely after its development
  - American Gastroenterological Association, 2019
    - Recommends use of traditional laxatives as first-line agents
    - However, in patients with laxative refractory OIC, it is recommended that peripherally acting mu-opioid receptor antagonists (PAMORAs), such as naldemedine and naloxegol, are utilized over no treatment
    - Methylnaltrexone (Relistor) is suggested over no treatment, but this was given a conditional recommendation due to low quality of evidence
    - Additionally, the guidelines makes no recommendations for intestinal secretagogues (e.g., lubiprostone [Amitiza]) or 5-HT agonists (e.g. prucalopride [Motegrity]) due to limited consistent evidence to support their use

# Irritable Bowel Syndrome (IBS) Agents/GI Motility

- **tenapanor (Ibsrela)**

- In September 2019, FDA approved Ibsrela for treatment of irritable bowel syndrome with constipation (IBS-C) in adults

- **Indications:**

- Treatment of irritable bowel syndrome with constipation (IBS-C) in adults

- **Limitations:**

- **Diarrhea:** Patients may experience severe diarrhea. If severe diarrhea occurs, suspend dosing and rehydrate patient

- **BBW:**

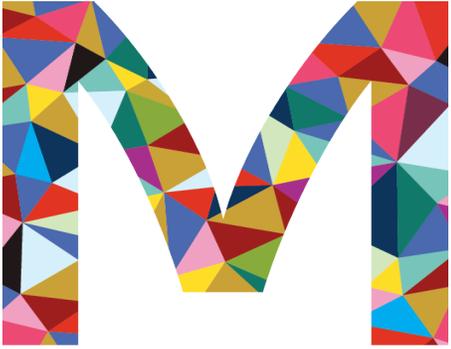
- Contraindicated in patients less than 6 years of age; in young juvenile rats, tenapanor caused death presumed to be due to dehydration
- Avoid use in patients 6 years to less than 12 years of age
- The safety and effectiveness have not been established in pediatric patients less than 18 years of age

- **Dosing:**

- 50 mg orally twice daily

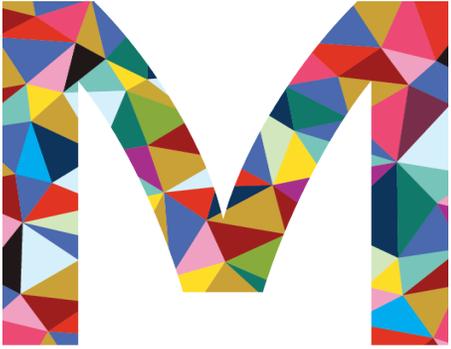
- **Formulations:**

- Tablets: 50 mg



# Gastrointestinal Agents: Phosphate Binder Agents





# Genitourinary Agents: Overactive Bladder Agents



# Disease State Description/Guidelines - Overactive Bladder Agents

- Overactive bladder (OAB) is a chronic and debilitating syndrome that is characterized by urinary urgency with or without urge incontinence, usually in combination with urinary frequency (8 or more voiding episodes per 24 hours) and nocturia (awakening 1 or more times per night to void)
  - Prevalent in ~16% of men and 17% of women
  - ~20% in those older than 60 years of age

## American Urological Association (AUA), 2019 Revisions

- 1st line therapy:
  - Recommends behavioral therapy (e.g., bladder training, bladder control strategies, pelvic floor muscle training, and fluid management)
  - Pharmacological therapy may be combined with behavioral therapy as first-line treatment as well
- 2nd line therapy:
  - Oral antimuscarinics or beta-3 adrenergic receptor agonists should be offered as second-line therapy
  - There may be consideration of combination anti-muscarinic and beta-3 adrenergic receptor agonist in patients refractory to monotherapy with either mechanism alone
  - Surgery is reserved for patients with severe refractory OAB symptoms or who are not candidates for oral therapy

# Overactive Bladder Agents

- **mirabegron ER**

- In January 2020, FDA approved first generic for Myrbetriq by Sawai Pharmaceutical

- Indications:

- Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency

- Treatment of overactive bladder with symptoms or urge urinary incontinence, urgency, and urinary frequency in combination with solifenacin

- Precautions/Contraindications:

- While not contraindicated, it should be used cautiously in patients with uncontrolled narrow-angle glaucoma or gastric and/or urinary retention

- Dosage:

- 25 to 50 mg daily (may be used with or without solifenacin 5 mg once daily)

- 25 mg daily (for moderate hepatic impairment and severe renal impairment)

- Formulations:

- 25 mg, 50 mg tablets

- **tolterodine extended-release (Detrol LA)**

- Discontinuation (October 2019)

- Pfizer will discontinue manufacture of Detrol LA 2 mg and 4 mg blister packs

- Bottles of 30, 90, and 500 count remain

# Overactive Bladder Agents

- **solifenacin succinate (Vesicare LS)**

- In May 2020, FDA approved Vesicare LS

- Indications:

- Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients ages  $\geq 2$  years

- Precautions/Contraindications:

- QT Prolongation: Should be used with caution in patients with a known history of QT prolongation or patients taking medications known to prolong the QT interval

- Angioedema and Anaphylactic Reactions: Promptly discontinue VESicare LS and provide appropriate therapy

- GI Disorders: VESicare LS is not recommended for use in patients with decreased gastrointestinal motility

- Dosage:

- Recommended once daily dose of VESicare LS is based on patient weight

- Patients should take VESicare LS orally followed by liquid (e.g., water or milk)

- Formulations:

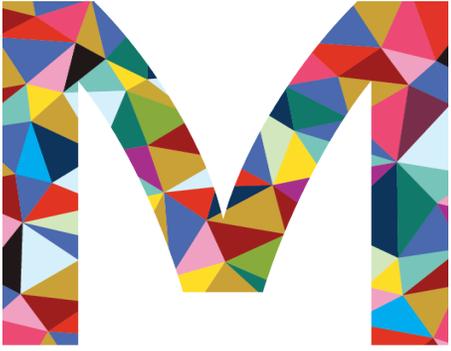
- Oral suspension: 5 mg/5 mL (1 mg/mL)

- **darifenacin (Enablex)**

- Discontinuation (June 2020)

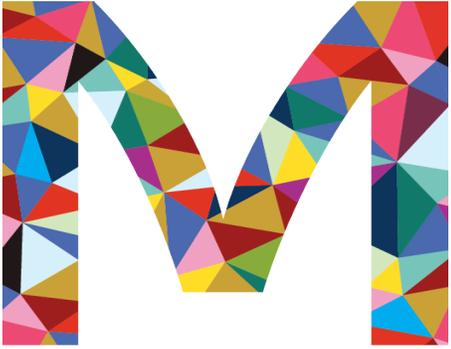
- Allergan has made a business decision to permanently discontinue all strengths of Enablex

- Generic versions are available



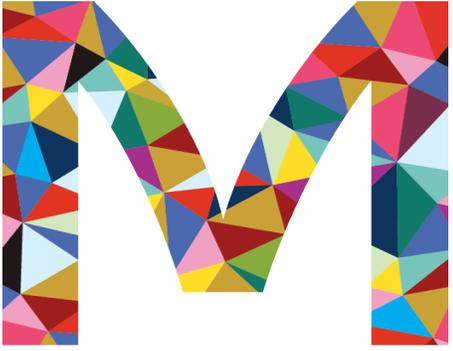
# Hematological Agents: Hereditary Angioedema Agents





# Miscellaneous Therapeutic Classes: Potassium Removing Agents





# Multiple Sclerosis Agents



# Disease State Description - Multiple Sclerosis Agents

- Multiple sclerosis (MS) is a complex human autoimmune-type inflammatory disease of the central nervous system (CNS)
  - More than 2.3 million people worldwide have MS; 1 million people in the U.S.
  - Multiple sclerosis occurs most commonly in whites, with rare cases in African-Americans and Asian-Americans
- Although the etiology is predominantly unknown, MS is characterized pathologically by demyelination and subsequent axonal degeneration
  - The nerve degeneration associated with MS can result in a wide variety of symptoms, including sensory disturbances (numbness, paresthesias, burning, and pain) in the limbs, optic nerve dysfunction, ataxia, fatigue, and bladder, bowel, and sexual dysfunction
  - Severe cases may result in partial or complete paralysis
  - While cognitive impairment occurs in approximately 50% of people with MS, only 10% experience serious intellectual deterioration
- MS can be categorized as either relapsing-remitting MS (observed in 85% to 90% of patients) or primary progressive MS (observed in 10% of patients)
  - Relapses or “attacks” typically present subacutely, with symptoms developing over hours to several days, persisting for several days or weeks, and then gradually dissipating

*National Medical Society, 2017*

# Disease State Description - Multiple Sclerosis Agents

- The clinical course of MS falls into 1 of the following categories, with the potential to progress from less severe to more serious types:
  - **Relapsing-remitting MS (RRMS):** Clearly defined, self-limited attacks of neurologic dysfunction, followed by periods of remission without disease progression. Most patients experience a recovery of function that is often, but not always, complete
  - **Primary progressive MS (PPMS):** Nearly continuous worsening of disease not interrupted by distinct relapses; some of these individuals have occasional plateaus and temporary minor improvements
  - **Secondary progressive MS (SPMS):** Relapsing-remitting disease course at onset, followed by progression with or without occasional relapses, minor remissions, and plateaus; most patients eventually convert to progressive MS
  - **Progressive-relapsing MS (PRMS):** Progressive disease from onset, with clear, acute relapses that may or may not resolve with full recovery; unlike RRMS, the periods between relapses are characterized by continuing disease progression
  - **Clinically isolated syndromes (CIS):** the first episode of neurologic symptoms due to inflammation or demyelination lasting at least 24 hours. Patients with MRI-detected brain lesions consistent with MS are at high risk of developing MS

*National Medical Society, 2017*

# Guidelines - Multiple Sclerosis Agents

- American Academy of Neurology (AAN), 2019
  - Issued guidelines regarding vaccinations in patients with MS
  - Recommend clinicians discuss immunization options with patients to develop an optimal strategy for each patient, taking into account all vaccine standards and local recommendations, patient risks and benefits, contraindications, and patient preferences
  - Notably, they recommend that prescribers should assess and address vaccination status at least 4 to 6 weeks prior to initiating immune-suppressing MS therapy, as advised by each agent’s prescribing information (Level B), and further state that clinicians should address vaccination status as soon as possible following diagnosis, regardless of the initial therapeutic plan, to prevent future treatment delays (Level C)
  - They also recommend that all patients receive an annual influenza vaccine, unless contraindicated (Level B)
  - Recommend against the use of live attenuated vaccines in patients receiving immune-suppressing MS therapy or in those who have recently discontinued one of these agents; however, the use of these vaccines may be recommended if the risk of infection is high and alternatives are unavailable (Level C)
  - Prescribers should also screen for select infections, including hepatitis, tuberculosis, and varicella zoster, as described in product labeling of individual products or regardless of this recommendation in endemic or high-risk areas (Level A), treating discovered latent infections (Level B), prior to initiating therapy. Vaccination should be delayed in patients experiencing a relapse until clinical resolution or no longer active (Level B)

# Multiple Sclerosis Agents

- **fingolimod**

- **December 2019: FDA approved fingolimod 0.5 mg capsules (by Biocon, Sun, and HEC) as first-time generics of Gilenya**
- **Launch is not expected due to litigation**
- **Biocon and Sun have agreed to not launch their generic capsules until Patent Office or court decisions**
- **HEC's launch is currently blocked due to injunction**

# Multiple Sclerosis Agents

- **ozanimod (Zeposia)**
  - **March 2020: FDA approved Zeposia, a sphingosine-1-phosphate (S1P) receptor modulator, for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults**
  - **Indication**
    - **Relapsing forms of MS, to include clinically isolated syndrome (CIS), relapsing-remitting disease, and active secondary progressive disease, in adults**
  - **Limitation**
    - **Infections: May increase the risk of infections. Obtain a complete blood count (CBC) before initiation of treatment. Monitor for infection during treatment and for 3 months after discontinuation. Do not start in patients with active infections**
    - **Liver Injury: Discontinue if significant liver injury is confirmed. Obtain liver function tests before initiating treatment**
    - **Fetal Risk: Women of childbearing potential should use effective contraception during treatment and for 3 months after stopping treatment**
    - **Increased Blood Pressure (BP): Monitor BP during treatment**
  - **Dosage**
    - **Assessments are required prior to initiating**
    - **Titration is required for treatment initiation**
    - **The recommended maintenance dosage is 0.92 mg orally once daily**
    - **If a dose is missed within the first 2 weeks of treatment, reinitiate with the titration regimen**
  - **Availability**
    - **Capsules: 0.23 mg, 0.46 mg, 0.92 mg**

# Multiple Sclerosis Agents

- **monomethyl fumarate (Bafiertam)**

- **April 2020: FDA approved Bafiertam for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults**
- **Indication**
  - Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adult
- **Limitation**
  - Contraindicated if co-administered with dimethyl fumarate or diroximel fumarate
  - Anaphylaxis and Angioedema: Discontinue and do not restart treatment if these occur
  - Progressive Multifocal Leukoencephalopathy (PML): Withhold treatment at the first sign or symptom suggestive of PML
  - Herpes zoster and other serious opportunistic infections: Consider withholding treatment in cases of serious infection until the infection has resolved
  - Lymphopenia: Obtain a CBC including lymphocyte count before initiating treatment, after 6 months, and every 6 to 12 months thereafter. Consider interruption of treatment if lymphocyte counts  $<0.35 \times 10^9/L$  persist for more than six months
- **Dosage**
  - Blood tests are required prior to initiation
  - Starting dose: 95 mg twice a day, orally, for 7 days
  - Maintenance dose after 7 days: 190 mg (administered as two 95 mg capsules) twice a day, orally
- **Availability**
  - Delayed-release capsules: 95 mg

# Multiple Sclerosis Agents

- **dimethyl fumarate**

- **August 2020: First generic approved for Biogen's Tecfidera from Mylan**

- **Indication**

- **Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults**

- **Limitation**

- **Anaphylaxis and Angioedema: Discontinue and do not restart treatment if these occur**

- **Progressive Multifocal Leukoencephalopathy (PML): Withhold treatment at the first sign or symptom suggestive of PML**

- **Herpes zoster and other serious opportunistic infections: Consider withholding treatment in cases of serious infection until the infection has resolved**

- **Lymphopenia: Obtain a CBC including lymphocyte count before initiating treatment, after 6 months, and every 6 to 12 months thereafter. Consider interruption of treatment if lymphocyte counts  $<0.35 \times 10^9/L$  persist for more than six months**

- **Dosage**

- **Starting dose: 120 mg twice a day, orally, for 7 days**

- **Maintenance dose after 7 days: 240 mg twice a day, orally**

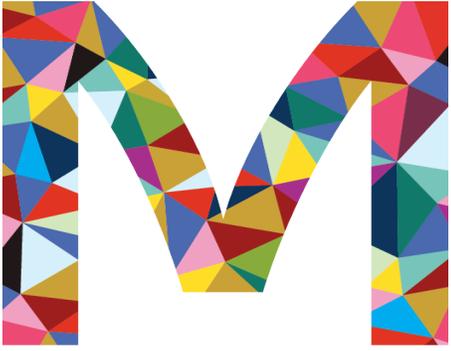
- **Availability**

- **Delayed-release capsules: 120 and 240 mg**

# Multiple Sclerosis Agents

- **ofatumumab (Kesimpta)**

- **August 2020:** FDA has approved a new indication for ofatumumab and a new brand name to correspond with the new use, Kesimpta
- **Indication**
  - Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
- **Limitation**
  - **Infections:** Delay treatment administration in patients with an active infection until the infection is resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment
  - **Injection-Related Reactions:** Management for injection-related reactions depends on the type and severity of the reaction.
  - **Reduction in Immunoglobulins:** Monitor the level of immunoglobulins at the beginning, during, and after discontinuation of treatment until B-cell repletion. Consider discontinuing if a patient develops a serious opportunistic infection or recurrent infections if immunoglobulin levels indicate immune compromise
  - **Fetal Risk:** May cause fetal harm based on animal data. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception during treatment and for 6 months after stopping treatment
- **Dosage**
  - Administer by subcutaneous injection only
  - Initial Dosing: 20 mg administered at Week 0, 1, and 2
  - Subsequent Dosing: 20 mg administered monthly starting at Week 4
- **Availability**
  - Injection: 20 mg/0.4 mL solution in a single-dose prefilled Sensoready® Pen
  - Injection: 20 mg/0.4 mL solution in a single-dose prefilled syringe



# Oncology Agents: LHRH Analogs - Injectable



# Disease State Description - LHRH Analogs - Injectable

- **Central Precocious Puberty (CPP)**

- Precocious puberty refers to the appearance of hormonal and physical characteristics of pubertal development at an earlier age than is considered normal, before age 8 years in girls and before age 9 years in boys
- Central Precocious Puberty (CPP) or true precocious puberty, which is gonadotropin-dependent, is the premature activation of the hypothalamic-pituitary gonadal (HPG) axis
- CPP occurs in 1 out of 5,000 to 10,000 children. It is much more common in girls than in boys
- About 80% to 90% of CPP cases are idiopathic in females compared to over 50% in males
- Other causes are due to changes in the brain, genetic problems, or certain tumor-releasing hormones

- [American Academy of Pediatrics \(AAP\), 2015](#)

- Published a clinical report regarding evaluation of children with signs of early puberty
- It recommends GnRH analogs injections or histrelin implant
- The goals do not include preservation of linear growth potential but simply involve suppression of menses, as for some girls with significant developmental disabilities, treatment with medroxyprogesterone depot, administered intramuscularly every 3 months may be considered
- Therapy is typically continued until pubertal suppression is no longer providing benefit to the child

- [Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology, 2009](#)

- Concludes that all available GnRH agonists are effective despite their different routes of administration, dosing, and duration of action
- Products included in the group's statement are nafarelin and buserelin nasal sprays and subcutaneous leuprolide, deslorelin, histrelin, and triptorelin; buserelin and deslorelin are not approved in the U.S.
  - Favors the depot products due to improved compliance
  - The 3-month formulation of leuprolide is comparable with the once monthly formulation
  - They conclude that the choice of agent depends on patient and physician preference and on local marketing approval

# Guidelines - Multiple Sclerosis Agents

- [American Academy of Neurology \(AAN\), 2019](#)
  - Issued guidelines regarding vaccinations in patients with MS
  - Recommend clinicians discuss immunization options with patients to develop an optimal strategy for each patient, taking into account all vaccine standards and local recommendations, patient risks and benefits, contraindications, and patient preferences
  - Notably, they recommend that prescribers should assess and address vaccination status at least 4 to 6 weeks prior to initiating immune-suppressing MS therapy, as advised by each agent’s prescribing information (Level B), and further state that clinicians should address vaccination status as soon as possible following diagnosis, regardless of the initial therapeutic plan, to prevent future treatment delays (Level C)
  - They also recommend that all patients receive an annual influenza vaccine, unless contraindicated (Level B)
  - Recommend against the use of live attenuated vaccines in patients receiving immune-suppressing MS therapy or in those who have recently discontinued one of these agents; however, the use of these vaccines may be recommended if the risk of infection is high and alternatives are unavailable (Level C)
  - Prescribers should also screen for select infections, including hepatitis, tuberculosis, and varicella zoster, as described in product labeling of individual products or regardless of this recommendation in endemic or high-risk areas (Level A), treating discovered latent infections (Level B), prior to initiating therapy. Vaccination should be delayed in patients experiencing a relapse until clinical resolution or no longer active (Level B)

# LHRH Analogs - Injectable

- **LHRH Analogs- Injectables**
  - Zoladex
  - Vantas
  - Eligard
  - Trelstar
  - Leuprolide Acetate
  - Lupron
  - **Fensolvi**

# LHRH Analogs - Injectable

- **leuprolide acetate (Fensolvi)**

- **May 2020: FDA approval of Fensolvi, a gonadotropin releasing hormone (GnRH) agonist indicated for the treatment of pediatric patients  $\geq 2$  years of age with central precocious puberty**

- **Indication**

- **Treatment of pediatric patients 2 years of age and older with central precocious puberty**

- **Limitation**

- **Initial Rise of Gonadotropins and Sex Steroid Levels: During the early phase of therapy, gonadotropins and sex steroids rise above baseline because of the initial stimulatory effect of the drug. Therefore, an increase in clinical signs and symptoms of puberty including vaginal bleeding may be observed during the first weeks of therapy or after subsequent doses. Instruct patients and caregivers to notify the physician if these symptoms continue beyond the second month after administration**

- **Psychiatric events: Have been reported in patients taking GnRH agonists. Events include emotional lability, such as crying, irritability, impatience, anger, and aggression. Monitor for development or worsening of psychiatric symptoms**

- **Convulsions: Have been observed in patients with or without a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and in patients on concomitant medications that have been associated with convulsions**

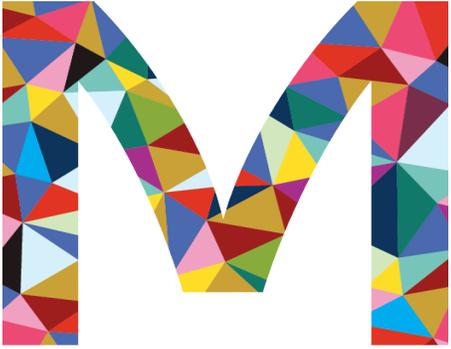
- **Dosage**

- **The dose of Fensolvi is 45 mg administered by subcutaneous injection once every six months**

- **Measure height every 3 to 6 months and monitor bone age periodically**

- **Availability**

- **For injectable suspension: 45 mg of leuprolide acetate supplied in a kit**



# Substance Use Disorder: Agents for Opioid Withdrawal



# Disease State Description - Agents for Opioid Withdrawal

- Prescription and illicit opioid abuse and misuse has reached national interest and was declared a National Public Health Emergency by the Department of Health and Human Services (DHHS) Acting Secretary in 2017
- The 2018 National Survey on Drug Use and Health (NSDUH) reported there was an estimated 31.9 million Americans aged 12 years and older who were current (past month) illicit drug users
  - There were approximately 10.3 million people aged 12 or older in the United States (US) who misused opioids in the past year
  - Approximately 20.3 million people aged 12 or older in 2018 were considered to have a substance use disorder (SUD) in the past year, including 14.8 million people with an alcohol use disorder, 8.1 million people with an illicit drug use disorder, and 2 million had an opioid use disorder
- In 2020, the US Preventive Services Task Force issued a final recommendation statement on screening for unhealthy drug use. For adults, they recommended screening implemented when services for accurate diagnosis, effective treatment, and appropriate care can be offered or referred (Grade B)

# Guidelines - Agents for Opioid Withdrawal

- American Society of Addiction Medicine (ASAM), 2020

- State that the choice of medication (e.g., buprenorphine, methadone, naltrexone) should be a shared decision between the clinician and patient and should consider patient preferences, treatment history, concomitant medical conditions, and treatment setting
- Additionally, all FDA-approved medications should be available options to all patients with individual needs taken into consideration for deciding between buprenorphine, methadone, and naltrexone, in conjunction with psychosocial treatment services, although they do provide some additional context for treatment selection
  - There is no recommended time limit for the pharmacological treatment of opioid use disorder
  - Methadone is recommended for patients who may benefit from additional supervision in an opioid treatment program (OTP), buprenorphine may be dispensed in OTP or in office-based opioid treatment (OBOT), while naltrexone may be prescribed in any setting
    - Oral naltrexone requires special attention to medication adherence and may require observed administration for some patients
  - The combined use of benzodiazepines and sedative-hypnotics increases the risk of serious adverse effects when administered with methadone and buprenorphine; however, the harm of untreated opioid use disorder may outweigh the risk
  - Buprenorphine and methadone are the standard treatment options for managing the acute withdrawal from opioids
    - When buprenorphine is selected for managing opioid withdrawal, buprenorphine should not be initiated until there are objective signs of opioid withdrawal and at a dose to suppress the withdrawal symptoms
    - ASAM notes that methadone and buprenorphine are more effective in decreasing symptoms and aiding in the completion in withdrawal
  - Additionally, the group states that alpha-2 adrenergic agonists, such as clonidine (not approved for this use) and lofexidine are safe and effective to manage opioid withdrawal
  - The focused update also includes recommendations for special populations (e.g., pregnant women patients suffering from pain, adolescents, patients with co-occurring psychiatric conditions, patients in the criminal justice system) because this may impact drug selection, psychosocial services offered, and overall care planning
  - ASAM recommends that naloxone, for the reversal of opioid overdose, and training for patients and significant others should be provided to patients being treated for or with a history of opioid use disorder

# Agents for Opioid Withdrawal

- FDA, 2019

- FDA announced changes to the Transmucosal Immediate-Release Fentanyl (TIRF) REMS program
- Changes include requiring prescribers to document a patient's opioid tolerance concurrently with each prescription of a TIRF medicine for outpatient use
- Requiring inpatient pharmacies to develop internal policy and procedures to verify opioid tolerance in hospitalized patients requiring TIRF medicines
- TIRF meds for outpatient use must have evidence or other documentation of safe use conditions, including concurrent documentation of opioid tolerance; and requiring the development of a new patient registry to monitor for serious adverse events including overdose (both fatal and non-fatal)

- CDC, 2019

- CDC clarified that their guidelines on opioid prescribing are not intended to deny opioid therapy for pain management for any patients with chronic pain, particularly in pts with sickle cell disease, undergoing cancer treatment, and cancer survivors with chronic pain
- It aims to ensure that clinicians and patients consider all safe and effective treatment options

# Agents for Opioid Withdrawal

- FDA, 2020

- The FDA has released a drug safety communication and a MedWatch for opioid pain relievers and opioid use disorder (OUD) agents
  - Requiring manufacturers for all opioid pain relievers and OUD treatments (e.g., buprenorphine, methadone and naltrexone) add recommendations on naloxone to the product labeling for Healthcare Practitioners to consider and discuss prescribing naloxone
  - Recommending Healthcare Practitioners discuss and consider naloxone use with all patients at the time of prescribing
  - Recommends Healthcare Practitioners consider prescribing naloxone when a patient has household members (e.g., children, close contacts) who may be at risk for accidental ingestion or opioid overdose
    - In addition, for patients that are not receiving a prescription for an opioid analgesic or OUD treatment, consideration should be given to prescribing naloxone for them if they are at a higher risk of opioid overdose (e.g., current/prior diagnosis of OUD or prior opioid overdose)
- When these meds are prescribed or renewed, the FDA is recommending the potential need for a naloxone prescription to be evaluated

# Agents for Opioid Withdrawal

- **Opioid Antagonists**
  - Lucemyra
  - Evzio
  - Naloxone
  - Naltrexone
  - **Narcan**
  - **Vivitrol**
  
- **Opioid Antagonists – Subcutaneous– NO UPDATES**
  - Sublocade
  - Probuphine Implant
  
- **Opioid Antagonists – Transmucosal**
  - **Bunavail**
  - **Suboxone**
  - Buprenorphine Monotherapy/HCl
  - Zubsolv
  - Suboxone generic

# Agents for Opioid Withdrawal

- **naltrexone (Vivitrol)**

- September 2019:

- Package insert updated to emphasize that Vivitrol must be prepared and administered by a Healthcare Practitioner

- October 2019 (FDA Recall):

- Alkermes issued a voluntary recall of 2 lots of Vivitrol 380 mg injection kit due to an incorrect needle size being include in the package; it includes a 1" needled rather than the intended 1-1/2" needle

- **naloxone nasal spray (Narcan)**

- August 2020 (Manufacturer Communication):

- The manufacturer, Emergent, has announced the FDA approval of an extension to the shelf life of their naloxone nasal spray (Narcan); previously 24 months, the shelf life has been extended to 36 months

- **buprenorphine/naloxone (Bunavail)**

- August 2020 (Discontinuation):

- The FDA lists Bunavail's marketing status as discontinued

# Agents for Opioid Withdrawal

- **buprenorphine/naloxone sublingual film (Suboxone)**

- **November 2019: Indication was expanded to include induction therapy**

- **Indication**

- **Treatment of opioid dependence (induction and maintenance); should be used as part of a complete treatment plan to include counseling and psychosocial support**

- **Limitation**

- Addiction, Abuse, and Misuse: Buprenorphine can be abused in a similar manner to other opioids. Clinical monitoring appropriate to the patient's level of stability is essential. Monitor patients for conditions indicative of diversion or progression of opioid dependence and addictive behaviors. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits
- Respiratory Depression: Life-threatening respiratory depression and death have occurred in association with buprenorphine use. Warn patients of the potential danger of self-administration of benzodiazepine or other CNS depressants while under treatment

- **Dosage**

- **Induction of opioid dependence treatment:** Day 1: initial dose of 2/0.5 mg or 4/1 mg; may titrate upwards in 2 mg to 4 mg increments of buprenorphine, at 2-hour intervals to maximum of 8/2 mg; Day 2: up to 16/4 mg as a single dose
- **Maintenance treatment of opioid dependence treatment:**
  - Titrate dosage in increments of 2–4 mg/day of buprenorphine to a dose that holds the patient in treatment and suppresses opioid withdrawal symptoms
  - Doses above 24 mg/day have not shown any added benefit
  - Following induction to opioid dependence treatment, a target dose of 16/4 mg buprenorphine/naloxone sublingually once daily is suggested; however, doses ranging from 4 to 24 mg/day of the buprenorphine component may be required; patients may require treatment indefinitely and should continue for as long as the patient continues to benefit

- **Availability**

- 2/0.5 mg, 4/1 mg, 8/2 mg, 12/3 mg sublingual films