Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Washington Drug Utilization Review (DUR) Board Meeting

October 20th, 2021

Umang Patel, Pharm.D.

Agenda Topics

- Overview of Disease State
- Indications
- Dosage & Formulations
- Guideline Updates

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Analgesics, Narcotics – Long-Acting

ANALGESICS : OPIOID AGONISTS - LONG ACTING

Disease State Description - Opioid, Long-Acting

- While definitions vary, chronic pain is generally defined as pain lasting > 3 months or past the time required for normal tissue healing
  - It has various etiologies, including injury, inflammation, and underlying medical conditions
- Approximately 11.2% of adults report daily pain, which is greatly misunderstood
  - Historically, data have suggested that pain may be undertreated, but newer estimates imply that opioid treatment for pain may be overutilized
  - An estimated 20% of patients presenting to outpatient providers with noncancer pain or pain-related diagnoses, whether acute or chronic, receive an opioid prescription
- Likewise, per capita opioid prescriptions increased by 7.3% from 2007 to 2012, with prescribers writing 66.5 opioid prescriptions for every 100 Americans in 2016
  - Unfortunately, approximately 165,000 people have died from overdoses related to opioid pain medications in the United States (U.S.) from 1999 to 2014
  - Likewise, drug related deaths have tripled from 1999 to 2015, and during 2015 alone 33,091 persons in the United States died from opioid related overdoses
  - Opioid related overdose was higher among males (13.7%) in comparison to females (7.1%)
  - Despite this, persistent pain that is uncontrolled may have clinical, psychological, and social consequences; thus, it is critical to weigh the risks and benefits of opioid use and reevaluate patients routinely for appropriate dose, duration, and treatment choice, including both pharmacologic and non-pharmacologic modalities

CDC, 2017

Guidelines - Opioid, Long-Acting

- **American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP), 2020**
  - Published a new clinical practice guideline on the managing acute pain associated from non–low back, musculoskeletal injuries in adults who are outpatient
  - Recommendations are provided for nonpharmacologic and pharmacologic treatment modalities
  - Clinicians are recommended to treat patients with topical NSAIDs with or without menthol gel as first-line therapy to decrease or relieve symptoms and to improve physical functioning and the patient's treatment satisfaction
  - It is suggested that clinicians treat patients with oral NSAIDs (to reduce/relieve symptoms and to improve physical function) or with oral acetaminophen to reduce pain
  - Additionally, it is suggested that clinicians treat patients with specific acupressure for reduction of pain and improvement of physical functioning or with transcutaneous electrical nerve stimulation to reduce pain
  - Lastly, it is suggested against clinicians treating patients with opioids, including tramadol

Analgesics - Opioid, Long-Acting

- **FDA Communications**
  - **January 2021**
    - **The FDA released an update on the steps being taken to address the opioid crisis, particularly in regards to the REMS programs**
    - **Other efforts include reducing unnecessary exposure to Rx opioids and preventing new addiction; support for treating opioid use disorder, assisting in the development of new pain treatments, and addressing contributors to the illegal importation/sale of opioids**
    - **Regarding the REMS program, the FDA is strengthening the program for transmucosal immediate-release fentanyl (TIRF) products to ensure the benefits continue to outweigh the risks by finalizing modifications to the REMS program**
    - **Efforts are also underway to assess the opioid analgesics REMS**
  - **September 2021**
    - **FDA announced public workshop that will reconsider mandatory prescriber education for opioids**
    - **Goal is to improve education to minimize burden on healthcare delivery system**

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Antiemetic/Antivertigo Agents

ANTIEMETICS / ANTIVERTIGO AGENTS : 5-HT3 RECEPTOR ANTAGONISTS
ANTIEMETICS / ANTIVERTIGO AGENTS : SUBSTANCE P/NEUROKININ 1 (NK1) RECEPTOR ANTAGONISTS
ANTIEMETICS / ANTIVERTIGO AGENTS : SUBSTANCE P/NEUROKININ 1 RECEPTOR ANTAGONIST COMBINATIONS

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Angiotensin Modulators

ANTIHYPERTENSIVES : DIRECT RENIN INHIBITOR COMBINATIONS
ANTIHYPERTENSIVES : DIRECT RENIN INHIBITORS
ANTIHYPERTENSIVES : NEPRILYSIN INHIB (ARNI)-ANGIOTENSIN II RECEPT ANTAG COMBINATIONS

Disease State Description - Angiotensin Modulators

- **Hypertension**
  - Approximately 108 million (45%) adults in the United States have high blood pressure along with 1 of 3 American adults having prehypertension
  - The highest prevalence is among African American men and women
    - Approximately 54% of African American men and women have high blood pressure compared to about 46% of white men and women and 39% of non-Hispanic Asians and 36% of Hispanics
  - It is estimated that hypertension is controlled in only 24% of patients with the condition

Center for Disease Control, 2020

Treatment Guidelines - Angiotensin Modulators

- The American Heart Association (AHA), 2020
  - Issued a Scientific Statement regarding the accurate measurement of blood pressure (BP).
  - Ambulatory BP monitoring is considered the standard for out-of-office BP assessment
  - Automated oscillometric devices have been validated to provide accurate BP measurements while reducing human errors, even without an observer being present
  - For high-risk adults with stage 1 hypertension who have preexisting CVD or an estimated 10-year ASCVD risk of at least 10%, the guideline recommends initiating drug treatment for those with an average BP of 130/80 mm Hg or higher (class I recommendation, high-quality evidence)
  - For lower-risk adults without preexisting CVD and an estimated 10-year ASCVD risk less than 10%, the BP threshold for drug treatment is 140/90 mm Hg or higher (class I recommendation, low-quality evidence)
  - For high-risk adults with stage 1 hypertension who have preexisting CVD or an estimated 10-year ASCVD risk of at least 10%, the guideline recommends initiating drug treatment for those with an average BP of 130/80 mm Hg or higher (class I recommendation, high-quality evidence)
  - For lower-risk adults without preexisting CVD and an estimated 10-year ASCVD risk less than 10%, the BP threshold for drug treatment is 140/90 mm Hg or higher (class I recommendation, low-quality evidence)

Treatment Guidelines - Angiotensin Modulators

- The Kidney Disease: Improving Global Outcomes (KDIGO), 2020
  - The organization published its first guideline on managing diabetes in patients with chronic kidney disease (CKD)
  - They recommend that patients with diabetes, hypertension, and albuminuria should start treatment with an ACE inhibitor or ARB along with regular glycemic control, targeting A1c in their specific target range
- The Kidney Disease: Improving Global Outcomes (KDIGO), 2021
  - Recommend the use of ARBs or other renin-angiotensin-system inhibitors for patients with CKD, diabetes, hypertension, and moderately to severely increased albuminuria, but they recommend avoiding the combination of an ACE inhibitor, ARB, or direct renin inhibitor in patients with CKD, regardless of diabetes diagnosis

- US Preventative Task Force (USPSTF), 2020
  - As update to it 2013 recommendations on screening for high blood pressure in pediatric patients, the USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for high blood pressure in children and adolescents aged 3 to 18 years (Grade 1)
  - This is in contrast to the American Academy of Pediatrics who recommend annual screening of all patients for hypertension and screening at each visit beginning at age 3 years for those at high-risk
- US Preventative Task Force (USPSTF), 2021
  - USPSTF published a Final Recommendation Statement for screening for hypertension in adults
  - The panel recommend office blood pressure measurement (OBPM)
  - The USPSTF recommends obtaining blood pressure measurements outside of the clinical setting for diagnostic confirmation before starting treatment
  - They concluded with high certainty that screening for hypertension in adults has substantial net benefit

Angiotensin Modulators

- **sacubitril/valsartan (Entresto)**
  - **February 2021: FDA approved expanded indication to read to reduce the risk of CV death and hospitalization for HF in adults with chronic HF, and benefits are clearly evident in patients with LVEF below normal. Previously, this indication read to reduce the risk of CV death and hospitalization for HF in patients with chronic HF, specifying in NYHA Class II-IV and reduced EF.**
  - **Indication**
    - **To reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal**
    - For the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. ENTRESTO reduces NT-proBNP and is expected to improve cardiovascular outcomes
  - **Warnings and Precautions**
    - BBW: Pregnancy Category X
  - **Dosage**
    - Stratified by indication and weight (See TCR and/or PI)
  - **Availability**
    - Film-coated tablets: 24/26 mg; 49/51 mg; 97/103 mg

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Hepatitis C Agents

ANTIVIRALS : HEPATITIS C AGENTS

Disease State Description – Hepatitis C Agents

- Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States (US)
  - In approximately 15% to 25% of patients who become infected with hepatitis C, the virus is eliminated during the acute phase of the infection by T cell-mediated antiviral mechanisms; however, in the other 75% to 85% of patients, the HCV persists for decades
  - An estimated 23,000 to 46,000 children in the US have HCV
  - Approximately 2.7 million people in the US are chronically infected, although it is estimated that nearly 75% of these people may be unaware of their infection due to the insidious progression of the disease
  - HCV accounts for 40% of chronic liver disease in the US. In patients with chronic HCV infection followed for 20 years, disease progression to cirrhosis occurs in about 20% to 25%
  - Of those who develop cirrhosis, approximately 30% will develop end-stage liver disease over the next 10 years and 1% to 2% per year will develop hepatocellular carcinoma
  - HCV infection is the most common reason for liver transplantation and results in an estimated 8,000 to 10,000 deaths per year in the US
- The most important risk for HCV infection is injection-drug use, which accounts for at least 60% of acute HCV infections in the US
  - Other modes of transmission include mother-to-infant, receiving a blood or organ donation prior to 1992, occupational exposures, chronic hemodialysis, and contaminated devices shared for non-injection drug use, such as intranasal illicit drug use
  - Sexual transmission also occurs but generally seems to be inefficient except among human immunodeficiency virus (HIV)-infected men who have unprotected sex with men
  - Other risk factors include incarceration and receiving a tattoo in an unregulated setting
    - It is estimated that 29% of incarcerated persons in the North America are anti-HCV positive

Centers for Disease Control and Prevention, 2018

Disease State Description – Hepatitis C Agents

- Hepatitis C viral genotype is an important factor in selecting the optimal treatment planning, dictating drug selection, dose, and duration of treatment

- There are 6 HCV genotypes and more than 50 subtypes, and the distribution of HCV genotypes varies across the world
  - Genotype 1 is the most common worldwide and accounts for about 70% to 75% of US infections
    - Among African Americans, the frequency of genotype 1 is even higher at an estimated 90%
    - In the US, genotype 1a and 1b represent about 75% and 25% of genotype 1 cases, respectively
  - Genotypes 2 and 3 account for the majority of the other approximate 25% to 30% HCV infections in the US
  - Genotype 4 predominates in Egypt
  - Genotype 5 is localized to South Africa
  - Genotype 6 to Hong Kong and Southeast Asia

American Association of for the Study of Liver Diseases, 2017

Guidelines – Hepatitis C Agents

- The US Preventative Services Task Force, 2020
  - In 2020, the United States Preventive Services Task Force (USPSTF) expanded the population for a 1-time screening to asymptomatic adults 18 to 79 years of age
  - Similarly, joint guidelines from the American Association for Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) recommend a 1-time, routine, opt-out HCV testing for anyone 18 years and older

- Centers for Disease Control and Prevention (CDC), 2020
  - Recommends that in areas where the HCV infection rate is ≥ 0.1%, all adults be screened at least once for hepatitis C virus (HCV) infection, and that all pregnant women be screened during each pregnancy

Updated Information

- **sofosbuvir/velpatasvir (Epclusa)**
  - **June 2021: FDA approved use of Epclusa for treatment of HCV genotypes 1-6 in patients ≥ 3 years old without cirrhosis or with compensated cirrhosis or with decompensated cirrhosis used in combination with ribavirin; previously only for those ≥ 6 years old**
  - **Indications:**
    - **Treatment of adults and pediatric patients 3 years of age and older with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection**
      - **Without cirrhosis or with compensated cirrhosis**
      - **With decompensated cirrhosis for use in combination with ribavirin**
  - **Precautions/Contraindications:**
    - BBW: Risk of Hepatitis B Virus Reactivation- Test all patients for evidence of current or prior HBV infection before initiation of HCV treatment
    - Bradycardia with amiodarone coadministration: Serious symptomatic bradycardia may occur in patients taking amiodarone with a sofosbuvir-containing regimen, particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease
  - **Dosage:**
    - Dosing and treatment length is stratified by genotype and liver function (Found in PI or TCR)
  - **Formulations:**
    - Tablets: 400 mg of sofosbuvir and 100 mg of velpatasvir; 200 mg of sofosbuvir and 50 mg of velpatasvir
    - Oral Pellets: 200 mg of sofosbuvir and 50 mg of velpatasvir; 150 mg of sofosbuvir and 37.5 mg of velpatasvir

Updated Information

- **glecaprevir/pibrentasvir (Mavyret)**
  - **June 2021: FDA approved use of Mavyret in patients as young as 3 years old who have HCV genotype 1-6 without cirrhosis or with compensated cirrhosis or with HCV genotype 1 who had prior treatment with an HCV NS5A inhibitor or NS3/4A protease inhibitor, but not both; previously only indicated in patients ≥ 12 years old**
  - **Indications:**
    - **Treatment of adult and pediatric patients 3 years and older with chronic HCV genotype (GT) 1, 2, 3, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A)**
    - **Treatment of adult and pediatric patients 3 years and older with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both**
  - **Precautions/Contraindications:**
    - BBW: Risk of Hepatitis B Virus Reactivation- Test all patients for evidence of current or prior HBV infection before initiation of HCV treatment
  - **Dosage:**
    - Dosing and treatment length is stratified by age, genotype and liver function (Found in PI or TCR)
  - **Formulations:**
    - Tablets: 100 mg glecaprevir and 40 mg pibrentasvir
    - Oral Pellets: 50 mg glecaprevir and 20 mg pibrentasvir

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

HIV/AIDs

ANTIVIRALS : HIV

ANTIVIRALS : HIV COMBINATIONS

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 (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/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 – HIV Agents

- 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 – HIV Agents

- 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/µL)	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 – HIV Agents

- International Antiviral Society, 2020
  - State that HIV testing is recommended at least once for anyone who has ever been sexually active and more often for individuals at ongoing risk for infection
  - The panel continues to conclude that, after confirmed diagnosis of HIV infection, antiretroviral therapy should be started as soon as possible, including immediately after diagnosis, regardless of CD4 cell count
  - Samples for HIV-1 RNA level, CD4 cell count, HIV genotype for NRTI, NNRTI, and PI, laboratory tests to exclude active viral hepatitis, and chemistries should be drawn before beginning ART, but treatment may be started before results are available
  - Results of testing for HLA-B*5701 allele should be available if an abacavir-containing regimen is anticipated
  - Regimens should be selected or changed based on resistance test results, with consideration of dosing frequency, pill burden, adverse effect profiles, co-morbidities, and drug interactions
  - Patients receiving antiretroviral treatment should be monitored regularly and treatment failure should be detected and managed early, with the goal of therapy, even in previously treated patients, being HIV-1 RNA suppression below commercially available assay quantification limits
  - Furthermore, the USA Panel of the IAS indicates that an INSTI plus 2 NRTIs are generally recommended for initial therapy, with unique patient circumstances (e.g., concomitant diseases and conditions, potential for pregnancy, cost) guiding the treatment choice
  - NNRTIs and abacavir should not be used for rapid ART start
  - The group states that TDF is not recommended for individuals with or at risk for kidney or bone disease (osteopenia or osteoporosis); however, if it is not available or if there is a substantial cost difference, TDF (with emtricitabine or lamivudine) is effective and generally well tolerated
  - CD4 cell count, HIV RNA level, genotype, and other laboratory tests for general health and co-infections are recommended at specified points before and during ART
  - If a regimen switch is indicated, treatment history, tolerability, adherence, and drug resistance history should first be assessed: 2 or 3 active drugs are recommended for a new regimen.

Treatment Guidelines – HIV Agents

- 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 3TC/TDF TDF/FTC BIC/TAF/FTC DTG/ABC/3TC EVG/c/TDF/FTC EVG/c/TAF/FTC
dolutegravir + abacavir + lamivudine[a] – only for patients who are HLA-B* 5701 negative (AI)	
dolutegravir + tenofovir[b] + emtricitabine[a] (AI)	
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[a] (BI)	

Treatment Guidelines – HIV Agents

- 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[b] + emtricitabine[a] (BI)	doravirine + tenofovir alafenamide[b] + lamivudine (BIII)	atazanavir + cobicistat (or ritonavir) + tenofovir[b] + emtricitabine (BI)	ATV/c DRV/c LPV/r ABC/3TC FTC/TAF 3TC/TDF TDF/FTC DOR/TDF/3TC DRV/c/FTC/TAF EFV/3TC/TDF FTC/RPV/TAF RPV/FTC/TDF TDF/FTC/EFV
raltegravir + abacavir + lamivudinea– only for patients who are HLA-B* 5701 negative and HIV RNA < 100,000 copies/mL(CII)	doravirine + tenofovir disoproxil fumarate[b] + lamivudine (BI)	darunavir + ritonavir + tenofovir[b] + emtricitabine[a] (AI)	
		darunavir + cobicistat + tenofovir[b] + emtricitabine[a] (AI)	
	efavirenz + lamivudine+ TDF (BI)	darunavir + cobicistat (or ritonavir) + abacavir + lamivudine[a] (BII) — only for patients who are HLA-B*5701 negative	
	efavirenz + emtricitabine + TDF (BI)		
	efavirenz + emtricitabine + TAF (BII)	darunavir + ritonavir + lamivudine once daily (CI), if ABC, TAF, and TDF cannot be used	
	rilpivirine + tenofovir[b] + emtricitabine[a] – only for patients with HIV RNA < 100,000 copies/mL and CD4 > 200 cells/mm^3 (BI)	darunavir + ritonavir + raltegravir twice daily (CI) if HIV RNA < 100,000 copies/mL, CD4 > 200 cells/mm^3, 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

- maraviroc (Selzentry)
  - **October 2020: FDA approved expanded indication to include treatment of HIV-1-infection in pediatric patients weighing at least 2 kg; previously, it was approved for use only in patients 2 years of age and older weighing at least 10 kg**
  - **Indication**
    - **A CCR5 co-receptor antagonist indicated in combination with other antiretroviral agents for the treatment of only CCR5-tropic HIV-1 infection in adults and pediatric patients weighing at least 2 kg**
    - **Limitations of Use: Not recommended in patients with dual/mixed- or CXCR4-tropic HIV-1**
  - **Warnings and Precautions**
    - BBW: Hepatotoxicity has been reported which may be preceded by severe rash or other features of a systemic allergic reaction (e.g., fever, eosinophilia, or elevated IgE)
    - Lactation: Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission
  - **Dosage**
    - Tablets and oral solution are taken twice daily by mouth and may be taken with or without food
    - Must be given in combination with other antiretroviral medications
  - **Availability**
    - Tablets: 25 mg, 75 mg, 150 mg and 300 mg
    - Oral Solution: 20 mg per mL

HIV Agents

- rilpivirine (Edurant)
  - **January 2021: FDA approved use in combination with oral cabotegravir (Vocabria), for short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine**
  - **Indication**
    - A human immunodeficiency virus type 1 (HIV-1) specific, non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve patients 12 years of age and older and weighing at least 35 kg with HIV-1 RNA less than or equal to 100,000 copies/mL
    - **In combination with Vocabria (cabotegravir), for short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine**
  - **Warnings and Precautions**
    - Pregnancy: Total rilpivirine exposures were generally lower during pregnancy compared to the postpartum period
    - Lactation: Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission
    - Patients may develop redistribution/accumulation of body fat (5.5) or immune reconstitution syndrome
  - **Dosage**
    - One tablet taken once daily with a meal
  - **Availability**
    - 25 mg tablets

HIV Agents

- cabotegravir (Vocabria)
  - **January 2021: FDA has approved oral cabotegravir (Vocabria), an HIV-1 integrase strand transfer inhibitor (INSTI), in combination with rilpivirine (Edurant), for short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable ARV regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine, for use as: 1) an oral lead-in to evaluate tolerability of cabotegravir prior to initiation of cabotegravir/rilpivirine extended-release injection (Cabenuva) and as 2) an oral therapy for patients who will miss planned injection dosing of cabotegravir/rilpivirine (Cabenuva)**
  - **Indication**
    - **A human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with EDURANT (rilpivirine) for short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine, for use as:**
      - **Oral lead-in to assess the tolerability of cabotegravir prior to administration of Cabenuva (cabotegravir; rilpivirine) extended-release injectable suspensions**
      - **Oral therapy for patients who will miss planned injection dosing with Cabenuva**
  - **Warnings and Precautions**
    - **<u>Lactation</u>: Breastfeeding is not recommended due to the potential for HIV1 transmission**
  - **Dosage**
    - **One tablet of Vocabria 30 mg taken orally once daily for approximately 1 month in combination with one tablet of Edurant (rilpivirine) 25 mg taken orally once daily with a meal**
  - **Availability**
    - **Tablets: 30 mg**

HIV Agents

- cabotegravir and rilpivirine (Cabenuva)
  - **January 2021: The FDA has approved cabotegravir and rilpivirine (Cabenuva) as a complete regimen for the treatment of HIV-1 infection in adults to replace a current antiretroviral (ARV) regimen in those who are virologically suppressed on a stable ARV regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine**
  - **Indication**
    - **A 2-drug co-packaged product of cabotegravir, a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI), and rilpivirine, an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated 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 with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine**
  - **Warnings and Precautions**
    - **Pregnancy: After oral use of rilpivirine, exposures were generally lower during pregnancy compared with the postpartum period**
  - **Dosage**
    - **Initiate injections (600 mg of cabotegravir and 900 mg of rilpivirine) on the last day of oral lead-in and continue with injections (400 mg of cabotegravir and 600 mg of rilpivirine) every month thereafter**
  - **Availability**
    - **Cabotegravir extended-release injectable suspension and rilpivirine extendedrelease injectable suspension, co-packaged as follows:**
      - **Cabenuva 400-mg/600-mg Kit: single-dose vial of 400 mg/2 mL (200 mg/mL) cabotegravir; single-dose vial of 600 mg/2 mL (300 mg/mL) rilpivirine**
      - **Cabenuva 600-mg/900-mg Kit: single-dose vial of 600 mg/3 mL (200 mg/mL) cabotegravir; single-dose vial of 900 mg/3 mL (300 mg/mL) rilpivirine**

HIV Agents

- abacavir, dolutegravir, and lamivudine (Triumeq)
  - **March 2021: FDA approved expanded use in HIV-1 infected patients with renal impairment and creatinine clearance of ≥ 30 to 49 mL/min. As this is a fixed-dose tablet, use is not recommended in patients with CrCl < 30 mL/min. Previously, Triumeq was not recommended in patients with a CrCl < 50 mL/min**
  - **Indication**
    - A combination of dolutegravir (integrase strand transfer inhibitor [INSTI]), abacavir, and lamivudine (both nucleoside analogue reverse transcriptase inhibitors) is indicated for the treatment of HIV-1 infection in adults and in pediatric patients weighing at least 40 kg
  - **Warnings and Precautions**
    - BBW: Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, a component of Triumeq. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment
    - BBW: Hypersensitivity Reactions
    - Pregnancy Testing: Pregnancy testing is recommended before initiation of TRIUMEQ in adolescents and adults of childbearing potential
  - **Dosage**
    - Adults and pediatric patients weighing at least 40 kg: One tablet daily. May be taken with or without food
    - If dosing with certain UGT1A or CYP3A inducers, then the recommended dolutegravir dosage regimen is 50 mg twice daily. An additional 50-mg dose of dolutegravir, separated by 12 hours from Triumeq, should be taken
    - **Because Triumeq is a fixed-dose tablet and cannot be dose adjusted, it is not recommended in patients with creatinine clearance less than 30 mL per minute or patients with hepatic impairment**
  - **Availability**
    - Tablets: 600 mg of abacavir, 50 mg of dolutegravir, and 300 mg of lamivudine

HIV Agents

- dolutegravir/lamivudine (Dovato)
  - **March 2021: PI updated to include expanded use in HIV-1 infected patients with renal impairment and creatinine clearance (CrCl) of ≥ 30 to 49 mL/min. As this is a fixed-dose tablet, use is not recommended in patients with CrCl < 30 mL/min. Previously, Dovato was not recommended in patients with a CrCl < 50 mL/min**
  - **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

- bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy)
  - **October 2021: FDA approved for the use in patients weighing at least 14 kg; previously it was only indicated in patients weighing at least 25 kg. The indication now reads that it is approved as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 14 kg who have no ARV treatment history or to replace the current ARV regimen in those 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 its individual components**
  - **Indication**
    - A three-drug combination of bictegravir (BIC), a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI), and emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV-1 nucleoside analog reverse transcriptase inhibitors (NRTIs), and is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 14 kg who have 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 Biktarvy
  - **Dosage**
    - Recommended dosage in adults and pediatric patients weighing at least 25 kg: One tablet containing 50 mg BIC, 200 mg FTC, and 25 mg TAF taken once daily with or without food
    - Recommended dosage in pediatric patients weighing at least 14 kg to less than 25 kg: One tablet containing 30 mg BIC, 120 mg FTC, and 15 mg TAF taken once daily with or without food
  - **Availability**
    - Tablets: 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF; 30 mg of BIC, 120 mg of FTC, and 15 mg of TAF

HIV Agents

- **Discontinuations**
  - **efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla)- February 2021:**
    - FDA announced that Gilead will be discontinuing manufacture of Atripla as of July 2021
    - Supply is expected to be available until December 2021
    - There are no generics equivalents for this product
  - **atazanavir (Reyataz)- May 2021:**
    - FDA announced that BMS will discontinue manufacture of Reyataz (atazanavir) 150 mg
    - Product will be available until December 31, 2021; generic versions remain available
  - **tipranavir (Aptivus)- July 2021:**
    - The FDA has announced the discontinuation of the 100 mg/mL presentation of tipranavir oral solution (Aptivus solution)
  - **nevirapine (Viramune)- October 2021:**
    - The FDA has announced Boehringer Ingelheim will be discontinuing Viramine (nevirapine) oral suspension, 50 mg/5mL (NDC 0597-0047-24)

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Androgenic Agents, Injectables/Oral

ENDOCRINE AND METABOLIC AGENTS : ANDROGENS – TESTOSTERONE

Bone Resorption Suppression and Related Agents

ENDOCRINE AND METABOLIC AGENTS : BONE DENSITY REGULATORS - SCLEROSTIN INHIBITORS

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Antimigraine Agents

MIGRAINE AGENTS : CALCITONIN GENE-RELATED PEPTIDE (CGRP) RECEPTOR ANTAGONISTS

MIGRAINE AGENTS : SELECTIVE SEROTONIN AGONISTS 5-HT(1)

Disease State Description - Antimigraine Agents

- **Migraine Headache**
  - Accounts for 10% to 20% of all headaches in adults and affects over 39 million men, women, and children in the United States (U.S.)
  - Headache is one of the most common complaints by patients when presenting to a physician
    - 64% of physician-diagnosed patients who experience migraines and 41% of undiagnosed migraine sufferers reported severe impairment or the need for bed rest due to their migraine symptoms
    - In addition, 18% of women, 6% of men, and 10% of children experience migraine, an epidemiologic profile that has remained stable over many years
  - Approximately 85% of patients with migraine headaches suffer less than 3 to 4 attacks per month
    - The median frequency of migraine attacks among migraine sufferers is 1.5 per month
  - Migraine headache must be differentiated from tension-type headache
    - Key criteria for the diagnosis of migraine headache includes an episodic headache lasting from 4 to 72 hours with at least 2 of the following symptoms: unilateral pain, throbbing, aggravated by routine physical activity, pain of moderate to severe intensity
    - During the headache at least 1 of the following are present: nausea and/or vomiting, or photophobia and phonophobia

Migraine Research Foundation, 2021

- **Cluster Headache (CH)**
  - A severe, primary headache disorder characterized by extreme pain on one side of the head and autonomic symptoms (e.g., nasal congestion, lacrimation)
  - CH periods can persist for weeks to months with daily or more frequent attacks of 15 to 180 minutes in duration
  - The estimated lifetime prevalence of CH is more than one in 1,000. CH can be either episodic or chronic in nature with episodic CH being the predominant form
  - Individuals with episodic CH experience periods of attack followed by periods of remission, whereas individuals with chronic CH have minimal to no periods of remission between headache attacks

American Headache Society, 2016

Antimigraine Agents

- **rimegepant (Nurtec ODT)**
  - **June 2021: FDA has approved a new indication for rimegepant for the preventive treatment of episodic migraine in adults. Rimegepant was already indicated for the acute treatment of migraine with or without aura in adults**
  - **Indication**
    - Acute treatment of migraine with or without aura in adults
    - **Preventive treatment of episodic migraine in adults**
  - **Warnings**
    - Exposures were significantly higher in subjects with severe hepatic impairment. Avoid use in patients with severe hepatic impairment (Child-Pugh C)
  - **Dosage**
    - Recommended dosage for acute treatment of migraine: 75 mg taken orally, as needed.; the safety of using more than 18 doses in a 30-day period has not been established
    - **Recommended dosage for preventive treatment of episodic migraine: 75 mg taken orally every other day; the maximum dose in a 24-hour period is 75 mg**
  - **Availability**
    - Orally disintegrating tablets: 75 mg

Antimigraine Agents

- **atogepant (Qulipta)**
  - October 2021: FDA approved Qulipta, a calcitonin gene-related peptide receptor (CGRP) antagonist indicated for the preventive treatment of episodic migraine in adults
  - Indication
    - The preventative treatment of episodic migraine in adults
  - Warnings
    - Pregnancy: Based on animal data, may cause fetal harm
    - Avoid use in patients with severe hepatic impairment
  - Dosage
    - Recommended dosage is 10 mg, 30 mg, or 60 mg taken orally once daily with or without food
    - Severe Renal Impairment or End-Stage Renal Disease: 10 mg once daily
  - Availability
    - Tablets: 10 mg, 30 mg, and 60 mg

- **New Generic**
  - Zolmitriptan- October 2021
    - FDA has approved the first generic to AstraZeneca's Zomig (zolmitriptan) nasal spray from Padagis Israel

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Pulmonary Arterial Hypertension Agents

PULMONARY HYPERTENSION AGENTS : ENDOTHELIN RECEPTOR ANTAGONISTS
PULMONARY HYPERTENSION AGENTS : PROSTACYCLIN RECEPTOR AGONISTS
PULMONARY HYPERTENSION AGENTS : PROSTAGLANDIN VASODILATORS
PULMONARY HYPERTENSION AGENTS : SGC STIMULATOR
PULMONARY HYPERTENSION AGENTS- PHOSPHODIESTERASE INHIBITORS (PDEI)

Disease State Description - Pulmonary Arterial Hypertension

- The prevalence varies substantially depending on the type, etiology, and underlying condition; estimated to be ~15 per million people
- Pulmonary hypertension (PH) is characterized by an increase in pulmonary arterial pressure and secondary right ventricular failure. This is defined as a resting mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg
- Symptoms include dyspnea, dizziness, syncope, fatigue, edema (peripheral), angina, palpitations, and other symptoms, all of which are exacerbated by exertion
- PH does not have a cure and, if left untreated, PH is a life-threatening disease with poor prognosis
- Management of PH should be limited to specialized centers where clinicians are experienced in the evaluation and treatment of patients with PH
- Although the number of approved therapies for PAH has grown in the past years, the prognosis is still poor, with approximately 50% mortality within the first 5 years after diagnosis

World Health Organization, 2013

Disease State Description - Pulmonary Arterial Hypertension

- There are many causes of PAH including idiopathic or underlying disease and hereditary causes
  - Cellular changes in the walls of pulmonary arteries, and it appears that mutations in the bone morphogenetic protein receptor type 2 (BMPR2) gene plays a key role in the pathogenesis of heritable PAH
  - Other etiologies in PAH include drugs and toxins, collagen vascular resistance, human immunodeficiency virus (HIV), portal hypertension, chronic thromboembolism, and congenital heart disease
- The World Health Organization (WHO) classifies PH patients into 5 groups based on etiology
  - Group I now refers to pulmonary arterial hypertension (PAH)
  - Group II refers to PH due to left heart disease
  - Group III refers to PH due to lung disease
  - Group IV refers to PH due to blood clots in the lungs
  - Group V refers to refers to PH due to blood and other rare disorders
- In 2013, clinical classifications were updated to provide the same PH classifications for adult and pediatric patients. In addition, the individual categorization of the persistent PH of neonates (PPHN) was included

American College of Cardiology, 2013

Pulmonary Arterial Hypertension Agents

- **treprostinil (Tyvaso)**
  - **April 2021: FDA approved Tyvaso for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability; effectiveness was established predominately in pts with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%)**
  - **Indication**
    - **Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%)**
    - **Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%)**
  - **Warnings**
    - **Tyvaso may cause symptomatic hypotension**
    - **Tyvaso inhibits platelet aggregation and increases the risk of bleeding**
  - **Dosage**
    - **Administer undiluted, as supplied. A single breath of Tyvaso delivers approximately 6 mcg of Treprostinil**
    - **Administer in 4 separate treatment sessions each day approximately 4 hours apart, during waking hours**
    - **Initial dosage: 3 breaths (18 mcg) per treatment session. If 3 breaths are not tolerated, reduce to 1 or 2 breaths**
    - **Titrate to target maintenance doses of 9 to 12 breaths per treatment session, 4 times daily**
  - **Availability**
    - **Sterile solution for oral inhalation: 2.9 mL ampule containing 1.74 mg treprostinil (0.6 mg per mL)**

Pulmonary Arterial Hypertension Agents

- **selexipag (Uptravi)**
  - **August 2021: FDA approved 1,800 mcg as a lyophilized powder SDV for reconstitution and dilution for IV administration twice daily over 80 minutes in patients with PAH who are temporarily unable to take oral therapy**
  - **Indication**
    - Treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH
  - **Warnings**
    - Nursing mothers: Discontinue treatment or breastfeeding
    - Severe hepatic impairment: Avoid use
  - **Dosage**
    - Tablets starting dose: 200 mcg twice daily
    - Increase the dose by 200 mcg twice daily at weekly intervals to the highest tolerated dose up to 1600 mcg twice daily
    - Maintenance dose is determined by tolerability
    - Moderate hepatic impairment: Starting dose 200 mcg once daily, increase the dose by 200 mcg once daily at weekly intervals to the highest tolerated dose up to 1600 mcg
    - **Injection dose is determined by the patient's current dose of tablets. Administer injection by intravenous infusion, twice daily**
  - **Availability**
    - Tablets: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg, 1600 mcg
    - **For Injection: 1800 mcg of selexipag as a lyophilized powder in a single-dose vial for reconstitution and dilution**

Updated Information

- **Recall**
  - **Sildenafil – December 2020**
    - Avkare issued voluntary recall for 1 lot of Sildenafil 100 mg tablets (Lot 36884; exp 03/2022) and 1 lot of Trazodone 100 mg tablets (Lot 36783; exp 06/2022) to the consumer level due to a product mix-up resulting in the agents inadvertently packaged together during bottling at a third-party facility
    - To date, no adverse events related to the recall have been reported

- **REMS Update**
  - **ambrisentan (Letairis) - December 2020**
    - Updates to the approved ambrisentan REMS, including modifications to the Prescriber and Pharmacy Guide
    - On the REMS website, updates were made to the inpatient pharmacy requirements for enrolled patients who are continuing therapy in the inpatient setting and are already being cared for by a certified prescriber to correspond with the current inpatient pharmacy requirements in the approved REMS
    - Also, a provision now included for prescribers to grant greater than a 30-day supply for females of reproductive potential due to travel or personal extenuating circumstances
    - Certified outpatient pharmacy listings and links to Spanish materials on the REMS website were also added as well as a new office contact portal
  - **macitentan (Opsumit) – May 2021**
    - A shared system REMS for macitentan was approved
  - **ambrisentan (Letairis) – June 2021**
    - Ambrisentan Share System REMS updated to align the inpatient and outpatient pharmacy requirements and removal of the term “for approval” from the Outpatient Pharmacy requirement regarding the authorization to dispense a greater than 30-day supply

Appendices

Opioid, Long-Acting – Guidelines

- 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

Opioid, Long-Acting – Guidelines

- **Department of Health and Human Services, 2019**
  - In October 2019, the HHS published a new guideline for clinicians on dosage reduction or discontinuation of long-term opioid analgesics
  - This guidance discusses the risks of opioid taper and advises that opioids should not be quickly tapered or discontinued abruptly due to the potential for opioid withdrawal which can result in acute withdrawal symptoms, pain exacerbation, psychological distress, and suicidal ideation in patients who are physiologically dependent
  - Except for life-threatening circumstances (e.g., impending overdose), it is not recommended to abruptly reduce an opioid dose or discontinue an opioid
  - Guidance details situations when it may be appropriate to taper to a reduced dosage (e.g., pain improvement, patient request, no clinically meaningful improvement in pain or function with opioids, increasing doses without improvements in pain, signs of opioid misuse, side effects impacting function or quality of life, risks for an impending overdose/serious event, concurrent medications or comorbidities increasing the risk for adverse events, extended treatment period without clear benefits versus harms)
  - Other key recommendations include: referring patients with serious mental illness, high suicide risk, or suicidal ideation to a behavioral health provider prior to taper; assessing patients for opioid use disorder if they show signs of opioid misuse and offering medication-assisted treatment if appropriate; advising patients of risks for overdose if they abruptly return to their higher dose; tapering by 5% to 20% every 4 weeks is common, but longer tapering schedules may be required; and considering transition to buprenorphine for patients on high doses and unable to taper

Guidelines - Antimigraine Agents

- American Headache Society (AHS), 2019
  - Published its position statement on integrating new migraine treatments into clinical practice
  - There were no changes in recommended usage or place in therapy for agents in this class from previous guidelines
  - Included recommendations regarding use non-triptan, injectable agents, including Botox and monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) (Ajovy, Emgality or the CGRP receptor Aimovig) for migraine prevention in patients who experience episodic (CGRP agents only) or chronic (both classes) migraine

- American Academy of Neurology (AAN) & American Headache Society (AHS), 2019
  - In their 2012 practice guidelines (reaffirmed 2015), pharmacologic treatment for episodic migraine prevention in adults, the AAN and the AHS advise that antiepileptic drugs (divalproex sodium, sodium valproate, topiramate) and beta-blockers (metoprolol, propranolol, timolol) are established as effective in migraine prevention, with the exception of frovatriptan which is established for short-term menstrually associated migraine (MAM) prevention
  - Naratriptan, zolmitriptan, antidepressants (amitriptyline, venlafaxine), and beta-blockers (atenolol, nadolol) are probably effective in migraine prevention; but no triptan is approved for the prevention of migraines
  - **In 2019, AAN and AHS updated the guidelines for acute treatment of migraine in children and adolescents**
  - **They endorse the use of sumatriptan/naproxen and almotriptan oral tablets, rizatriptan ODT, and nasal zolmitriptan in adolescents to reduce headache pain**
  - **Triptans have more supportive evidence in adolescents than in children, where NSAIDs and acetaminophen are recommended options**

Treatment Guidelines, European Society of Cardiology (ESC) and the European Respiratory Society (ERS), February 2016

- **At the time of diagnosis of PAH**, the **suggested initial approach is the adoption of general measures** (exercise training, psychosocial support, rehabilitation) **and the initiation of supportive therapy** (oral anticoagulation, diuretics, digoxin, and long-term oxygen therapy, if needed
- **Patients who are at low or intermediate risk for 1-year mortality can be treated with either initial monotherapy or initial oral combination therapy**
- **If initial monotherapy** is chosen, **no evidence-based first-line monotherapy can be proposed** because there are no head-to-head comparisons
- If **initial combination therapy** is chosen, **ambrisentan plus tadalafil has been given a higher grade recommendation** because the combination has proven to be superior to initial ambrisentan or tadalafil monotherapy in delaying clinical failure

Treatment Guidelines, European Society of Cardiology (ESC) and the European Respiratory Society (ERS), February 2016

Therapy	Recommendation	Strength of Recommendation
Initial monotherapy	WHO-FC II: ambrisentan (Letairis), bosentan (Tracleer), macitentan (Opsumit), sildenafil (Revatio), tadalafil (Adcirca), riociguat (Adempas), and selexipag (Uptravi) WHO-FC III: ambrisentan, bosentan, macitentan, sildenafil, tadalafil, riociguat, selexipag, IV epoprostenol (Flolan®/Veletri®), inhaled iloprost (Ventavis), SC or inhaled treprostinil (Remodulin®, Tyvaso) and oral or IV treprostinil (Orenitram, Remodulin) WHO-FC IV: IV epoprostenol (Level I, Grade A), ambrisentan, bosentan, macitentan, sildenafil, tadalafil, riociguat, inhaled iloprost, SC, IV or inhaled treprostinil	Level I, Grade A or B for all Level I, Grade A or B Level IIa or IIb, Grade B or C for treprostinil Level IIb, Grade C
Initial combination therapy	WHO-FC II: • Ambrisentan + tadalafil • Other endothelin receptor antagonist (ERA) + phosphodiesterase type 5 inhibitor (PDE-5i) WHO-FC III: • Ambrisentan + tadalafil • Other ERA + PDE-5i, bosentan + sildenafil + IV epoprostenol, bosentan + IV epoprostenol, other ERA or PDE-5i + SC treprostinil, other ERA or PDE-5i + other IV prostacyclin analogues WHO-FC IV: • Ambrisentan + tadalafil • Other ERA + PDE-5i, bosentan + sildenafil + IV epoprostenol, bosentan + IV epoprostenol, other ERA or PDE-5i + SC treprostinil, other ERA or PDE-5i + other IV prostacyclin analogues	Grade I, Level B Grades IIa, Grade C Grade I, Level B Grades IIa, or IIb Grade C Grades IIa, or IIb Grade C

American College of Chest Physicians (CHEST), 2014 (Updated 2018)

- At the time of diagnosis of PAH
  - The suggested **initial approach** is
    - **Treatment of contributing causes of PAH** (e.g., sleep apnea, systemic hypertension)
    - The **adoption of general measures** (supervised exercise activity, influenza and pneumonia vaccinations, and avoidance of pregnancy, high altitudes, and non-essential surgery)
    - The **initiation of supportive therapy** (oxygen therapy if needed to maintain oxygen saturations > 91%)
    - Palliative care

- Unless there is a contraindication, acute vasoreactivity testing should be performed at a facility with experience in performing and interpreting the test (UCBS)
  - **A trial of high dose oral calcium channel blockers (CCB), such as amlodipine, diltiazem, or nifedipine, is recommended in patients with a positive acute vasoreactive test**
  - Furthermore, **CCBs should not be used empirically to treat PAH** in the absence of demonstrated acute vasoreactivity (UCBS)
  - Patients should be followed closely for response and side effects of therapy. Alternative or additional PAH therapy should be initiated if improvement to WHO FC I or II are not seen after the trial of a CCB

American College of Chest Physicians (CHEST), 2014 (Updated 2018)

- In treatment-naive patients who are not candidates for, or who have failed CCB therapy, treatment is based on WHO functional class (UCBS)
  - In treatment-naïve patients with WHO FC I
    - Continued monitoring for disease progression is advised (UCBS)
  - **In treatment-naïve patients with WHO FC II**
    - **Initial combination therapy with ambrisentan and tadalafil to improve 6-minute walk distance (6MWD) is suggested (weak recommendation, moderate quality evidence)**
    - **In patients who are unwilling to take or cannot tolerate combination therapy, then monotherapy with ambrisentan, sildenafil (strong recommendations, low quality evidence for both), bosentan, macitentan, tadalafil, or riociguat (UCBS for all 4 products) is recommended**
  - **In treatment-naïve patients with WHO FC III without rapid disease progression or poor prognosis**
    - **Initial combination therapy with ambrisentan and tadalafil to improve 6MWD is suggested (weak recommendation, moderate quality evidence)**
    - **In patients who are unwilling to take or cannot tolerate combination therapy, then monotherapy with ambrisentan, bosentan, sildenafil (strong recommendations, low or moderate quality to improve 6MWD for all 3 products), macitentan, tadalafil, or riociguat (UCBS for all 3 products) is recommended**
  - For treatment-naïve patients with WHO FC IV
    - Initial therapy with a parenteral prostanoid agent is recommended (UCBS)
    - In patients who cannot comply with parenteral administration, inhaled prostanoid in combination with an oral endothelin receptor antagonist or an oral PDE-5 inhibitor are alternatives (UCBS)