AHCCCS
Arizona Health Care Cost Containment System

AHCCCS Pharmacy and Therapeutics Committee

29 April 2019

Welcome and Introductions

- Sara Salek, MD, Chief Medical Officer, AHCCCS

  - Meeting Minutes July 17, 2018
  - Review
  - Vote

Welcome and Introductions

- Sara Salek, MD, Chief Medical Officer, AHCCCS
  - P&T Operational Policy Update

Welcome and Introductions

- Sara Salek, MD, Chief Medical Officer, AHCCCS
  - Conflict of Interest Statement

Magellan Class Reviews

Classes for Review: Non-Supplemental Rebate Class Review

- Antidepressants, Other
- Antidepressants, SSRIs
- Bronchodilators, Beta Agonists
- Bone Resorption Suppression and Related Agents
- Colony Stimulating Factors
- Enzyme Replacement for Gaucher Disease
- Erythropoiesis Stimulating Proteins
- Hypoglycemics, Alpha-Glucosidase Inhibitors

Magellan Class Reviews

Classes for Review: Non-Supplemental Rebate Class Review

- Hypoglycemics – Metformins
- Hypoglycemics – SGLT2s
- Immune Globulins
- Oncology, Oral - Hematologic
- Ophthalmic – Anti-Inflammatories / Immunomodulators
- Otic Antibiotics
- PAH Agents, Oral and Inhaled
- Thrombopoiesis Stimulating Proteins

Magellan Drug Class Reviews

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Antidepressants, Other

Antidepressants, Other

PRODUCT LIST AND FDA-APPROVED INDICATIONS

Drug	Manufacturer	Major Depressive Disorder (MDD)	Generalized Anxiety Disorder (GAD)	Social Anxiety Disorder (SAD)	Panic Disorder	Other Indications
bupropion HBr (Aplenzin®)	Valeant	X	--	--	--	--
bupropion HCl ER (Forfivo XL®)	generic•, Almatica	X	--	--	--	--
bupropion HCl ER (Wellbutrin® XL)	generic, Valeant	X	--	--	--	prevention of major depressive episodes associated with seasonal affective disorder
bupropion HCl IR	generic	X	--	--	--	--
bupropion HCl SR (Wellbutrin® SR)	generic, GlaxoSmithKline	X	--	--	--	--
desvenlafaxine ER base	Alembic/Sun	X	--	--	--	--
desvenlafaxine ER base (Khedezla™)	generic•, Pernix	X	--	--	--	--

Antidepressants, Other

desvenlafaxine succinate ER (Pristiq®)	generic, Wyeth/Pfizer	X	--	--	--	--
duloxetine (Cymbalta®)	generic, Eli Lilly	X	X	--	--	diabetic peripheral neuropathic pain; fibromyalgia; chronic musculoskeletal pain
isocarboxazid (Marplan®)	Medilink/Validus	X 2nd line therapy	--	--	--	--
levomilnacipran (Fetzima®)	Allergan/Forest	X	--	--	--	--
mirtazapine tablet and ODT (Remeron®; Remeron SolTab)	generic, Organon	X	--	--	--	--
nefazodone	Teva	X	--	--	--	--
phenelzine (Nardil®)	generic, Pfizer	X 2nd line therapy	--	--	--	--
selegiline (Emsam®)	Mylan Specialty	X	--	--	--	--

Antidepressants, Other

tranylcypromine (Parnate®)	generic, Concordia	X 2nd line therapy	--	--	--	--
trazodone	generic	X	--	--	--	--
venlafaxine	generic	X	--	--	--	--
venlafaxine ER capsule (Effexor XR®)	generic, Wyeth/Pfizer	X	X	X	X	--
venlafaxine ER tablet (Venlafaxine ER)	generic, Trigen	X	--	X	--	--
vilazodone HCl (Viibryd®)	Allergan	X	--	--	--	--
vortioxetine (Trintellix®†)	Takeda	X	--	--	--	--

IR = immediate release; ER = extended release; SR = sustained release

* Authorized generic available

† In 2016, the FDA approved a brand name change for Trintellix, previously Brintellix, due to errors related to name confusion with Brilinta® (ticagrelor).[i]

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Antidepressants, Other

- In 2017, depression was reported in 7.1% of the U.S. population
- Adverse event and safety profiles of TCAs and MAOIs have greatly reduced their use as first-line agents
- The 2010 American Psychiatric Association (APA) treatment guidelines for patients with MDD recommend an SSRI, SNRI, mirtazapine, and bupropion as appropriate for initial treatment of most patients
- According to the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines on unipolar depression from 2013 and 2015, no single class of antidepressants has proven to be more effective or have a more rapid onset than another; however, limited data suggest that select TCAs and venlafaxine may be slightly more effective in severely depressed hospitalized patients

Antidepressants, Other

- When response is inadequate with trial of a first-line therapy, strategies for treatment include maximizing the dose, switching to another class or another drug within the class, or combination therapy
- Per the 2016 American College of Physicians (ACP) guidelines, treatment with either CBT or second-generation antidepressants for MDD is recommended
- Non-SSRI antidepressants are most often used as first-line therapy in children in the presence of comorbidities
- In 2018, the North American Menopause Society and National Network on Depression Centers published consensus guidelines for the treatment of perimenopausal depression

Antidepressants, Other

- These note that SSRIs and SNRIs, particularly desvenlafaxine, have been shown to improve menopause-associated symptoms; however, none of the agents in this class are approved for symptoms of menopause
- The 2008 WFSBP guidelines recommend SSRIs, SNRIs, and pregabalin as first-line therapies for the treatment of anxiety, obsessive-compulsive, and post-traumatic stress disorders
- The 2009 APA treatment guidelines recommend SSRIs, SNRIs, TCAs, and benzodiazepines as first-line pharmacotherapy for panic disorder
- For Seasonal Affective Disorder, the International Consensus Group on Depression and Anxiety (ICGDA) expert panel guidelines recommend SSRIs as first-line therapy

Antidepressants, Other

- All of the antidepressants have a boxed warning regarding suicidality in children, adolescents, and young adults
- Effectiveness is generally comparable among classes and within classes of antidepressants
- Pharmacotherapy should be selected based on adverse event profiles, co-morbidities, drug interactions, pharmacokinetics, patient preference, cost, and historical patient response

Antidepressants, SSRIs

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Antidepressants, SSRIs

PRODUCT LIST AND FDA-APPROVED INDICATIONS

Drug	Mfr	MDD	GAD	SAD	Panic Disorder	PTSD	OCD	PMDD	Bulimia Nervosa	VMS
citalopram (Celexa®)	generic, Allergan	X	--	--	--	--	--	--	--	--
escitalopram (Lexapro®)	generic, Allergan	X (≥ 12 years)	X	--	--	--	--	--	--	--
fluoxetine	generic, Alvogen	X (≥ 8 years)	--	--	X	--	X (≥ 7 years)	--	X	--
fluoxetine (Prozac®)	generic, Dista	X (≥ 8 years)	--	--	X	--	X (≥ 7 years)	--	X	--
fluoxetine (Sarafem®)	Actavis/Allergan	--	--	--	--	--	--	X	--	--
fluoxetine ER (Prozac Weekly™)	generic	X	--	--	--	--	--	--	--	--
fluvoxamine	generic	--	--	--	--	--	X (≥ 8 years)	--	--	--
fluvoxamine ER	generic	--	--	--	--	--	X	--	--	--

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Antidepressants, SSRIs

paroxetine HCl (Paxil®)	generic, Apotex	X	X	X	X	X	X	--	--	--
paroxetine HCl controlled release (Paxil® CR)	generic, Apotex	X	--	X	X	--	--	X	--	--
paroxetine mesylate (Brisdelleä)	generic, Sebela	--	--	--	--	--	--	--	--	X
paroxetine mesylate (Pexeva®)	Sebela	X	X	--	X	--	X	--	--	--
sertraline (Zoloft®)	generic, Pfizer	X	--	X	X	X	X (≥ 8 years)	X	--	--

MDD = major depressive disorder; GAD = generalized anxiety disorder; SAD = social anxiety disorder; PTSD = post-traumatic stress disorder; OCD = obsessive-compulsive disorder; PMDD = premenstrual dysphoric disorder; VMS = moderate-to-severe vasomotor symptoms associated with menopause

Indications are for use in adults only unless additional ages specified.

*Fluoxetine is also indicated in combination with olanzapine for the treatment of acute depressive episodes associated with bipolar I disorder in adults and pediatric patients ≥ 10 years of age and treatment resistant depression in adults. Fluoxetine monotherapy is not approved for either of the aforementioned indications. Details on the use of fluoxetine in combination may be found in another therapeutic class review of the co-formulated agent fluoxetine/ olanzapine (Symbyax®).

Antidepressants, SSRIs

- SSRIs are generally considered first-line therapy for their FDA-approved indications due to improved tolerability, lower lethality in overdose, safety in cardiovascular disease, and lesser incidence of weight gain
- SSRIs have comparable efficacy and adverse event profiles for their FDA-approved indications
- SSRIs are preferred as a first medication trial for OCD

Antidepressants, SSRIs

- SSRIs are the recommended first-line medications for the treatment of PTSD
- Fluoxetine is the only SSRI medication approved by the FDA for the treatment of bulimia and has been shown to reduce the episodes of binge-eating and purging behavior, and their chance of relapse
- SSRIs are used most often for the treatment of children with MDD because studies of SSRIs were the first to show antidepressant efficacy in children; SSRIs are also first-line agents for the treatment of anxiety disorders in children.

Bronchodilators, Beta Agonists

Bronchodilators, Beta Agonists

Long-Acting Agents

- aformoterol tartrate - (Brovana Solution)
- formoterol fumarate - (Perforomist Solution)
- indacaterol maleate - (Arcapta Neohaler)
- olodaterol HCl - (Striverdi Respimat)
- salmeterol xinafoate - (Serevent Diskus)

Nebulized Agents

- albuterol sulfate - (AccuNeb; albuterol neb soln 0.63mg & 1.25mg, 2.5mg/0.5ml, 2.5mg/3ml & 5mg/ml)
- levalbuterol HCl – (levalbuterol neb soln; levalbuterol neb soln conc; Xopenex Neb Soln)

Bronchodilators, Beta Agonists

Oral Agents

- albuterol sulfate - (albuterol ER, syrup & tablet)
- metaproterenol sulfate - (metaproterenol syrup & tablet)
- terbutaline sulfate - (terbutaline)

Short-Acting Agents

- albuterol sulfate - (ProAir HFA; ProAir Respiclick; Proventil HFA; Ventolin HFA)
- levalbuterol tartrate - (Xopenex HFA)

Bronchodilators, Beta Agonists

- Prevalence and incidence of asthma in the U.S. continues to rise, affecting approximately 8.3% of the US population
- Beta$_2$-agonist bronchodilators are used for the treatment and prevention of bronchospasm associated with asthma, prophylaxis of exercise-induced bronchospasm (EIB), and in the treatment of Chronic Obstructive Lung Disease (COPD)
- Mainstay of asthma therapy is the use of inhaled corticosteroids (ICS) alone or in combination with long-acting beta$_2$-agonists (LABAs) as controller medications
- These agents lead to improvements in symptoms, reducing the need for short-acting beta$_2$-agonists (SABAs) for quick relief by relaxing airway smooth muscle

Bronchodilators, Beta Agonists

- The 2018 GINA guidelines offer a control-based management plan which adjusts treatment through a continuous cycle of assessment and review of the patient's response to therapy as it relates to symptom control, future risk of exacerbations, and side effects
- The 2019 GOLD guidelines place a great focus on the assessment of inhaler technique and adherence to improve therapeutic outcomes
- COPD pharmacotherapy of bronchodilators is intended to decrease symptoms, reduce the frequency and severity of exacerbations, improve health status and exercise tolerance
- Bronchodilator medications are central to management of COPD. They improve emptying of the lungs, reduce dynamic hyperinflation at rest and during exercise, and improve exercise performance
- Bronchodilators are given either on an as-needed basis for relief of persistent or worsening symptoms, or on a regular basis to prevent/reduce symptoms

Bronchodilators, Beta Agonists

- Regular bronchodilation does not modify the decline of lung function in mild COPD or the prognosis of the disease
- While short-acting beta agonists (SABAs) can be used on an as-needed basis in mild COPD, regular treatment with a long-acting beta agonist (LABA) is required as the disease progresses
- Delivery system selection as well as the patients' ability to properly use the device are important factors in the clinical success of bronchodilator therapy
- Metered dose inhalers (MDIs) are pressurized spray inhalers, available in suspension and solution
- Spacer chambers may be used with most MDIs to make them easier to use and help deliver a greater amount of medicine to the airway

Bronchodilators, Beta Agonists

- Dry-powder inhalers (DPIs) are breath-actuated devices that release the medicine in the form of a dry powder upon inhalation
- Nebulizers, may be the only viable alternative delivery system for certain children and those unable to use inhalers due to the inability to synchronize breaths and device actuation
- Some of the newer delivery devices, (like Respimat devices), are not breath-activated, but still require coordination of actuation and inhalation
- Oral dosage forms of albuterol are less utilized than the inhaled forms due to systemic beta-adrenergic stimulation, especially in patients sensitive to these effects, such as those with cardiovascular disease
- Levalbuterol is the R-enantiomer form of albuterol. It has similar efficacy to albuterol and there are no significant differences in adverse effects

Bronchodilators, Beta Agonists

- Salmeterol has a later onset of action than the rest of the LABAs
- There are no comparative data to suggest that arformoterol or formotero are superior in efficacy or safety to the other agents.
- Consideration should be made to the boxed warning which appears in the labeling for all single-component LABAs and may discourage the use of these agents. In December 2017, however, the FDA removed the boxed warning from the inhaled corticosteroids (ICS)/LABA combination inhalers.

Bronchodilators, Beta Agonists

2018 GINA Guidelines Stepwise Approach	
Adults and Children 6 Years and Older	
Step 1	As-needed reliever medication • Recommended: SABA • Alternative Controller: consider addition of low dose ICS (controller option)
Step 2	One controller AND an as-needed reliever medication (SABA is preferred) • Preferred controller: low-dose ICS • Alternative controllers: leukotriene modifier or low dose theophylline (if over 12 years)
Step 3	One or 2 controllers and an as-needed reliever medication • Preferred for adolescents and adults: low-dose ICS AND a LABA as maintenance plus as-needed and reliever therapy† SABA OR ICS/formoterol maintenance • Preferred for children 6 to 11 years of age: medium dose ICS + as-needed SABA • Alternative controllers: medium dose ICS, OR low-dose ICS + leukotriene modifier, OR low-dose ICS + low-dose sustained-release theophylline* • Sublingual immunotherapy (SLIT) may be considered in adults with allergic rhinitis or house dust mite sensitivity and exacerbations despite ICS use

Bronchodilators, Beta Agonists

2018 GINA Guidelines Step Approach	
Adults and Pediatrics 6 Years and Older	
Step 4	Two or more controllers AND an as-needed reliever medication • Preferred for adolescents and adults: medium/high-dose ICS + LABA plus as-needed SABA OR low-dose ICS/ formoterol maintenance and reliever therapy • Preferred for children 6 to 11 years of age: referral to expert for assessment and advice • Alternative controllers: For adults and adolescents: high dose ICS/LABA, OR medium-dose ICS + LABA and/or leukotriene modifier or sustained release theophylline, OR add tiotropium • Sublingual immunotherapy (SLIT) may be considered in adults with allergic rhinitis or house dust mite sensitivity and exacerbations despite ICS use
Step 5	Higher level of care and/or add-on treatment • In addition to Step 4 treatment, refer for add-on treatment: Tiotropium; monoclonal antibody treatment (omalizumab [anti-IgE therapy]; benralizumab, mepolizumab or reslizumab [anti-IL-5 therapy]); low dose oral corticosteroids; or sputum guided therapy

Bronchodilators, Beta Agonists

2019 GOLD Guidelines	
Assessment of Airflow Limitation	
Gold 1	Mild, FEV1 ≥ 80% predicted
Gold 2	Moderate, FEV1 50% to 79% predicted
Gold 3	Severe, FEV1 30% to 49% predicted
Gold 4	Very severe, FEV1 < 30% predicted

Bronchodilators, Beta Agonists

2019 GOLD Guidelines	
Assessment of Exacerbation Risk and Symptoms	
Patient Group A	Low Risk, Less Symptoms: 0 to 1 exacerbations per year (not leading to hospitalization); and CAT score < 10 or mMRC grade 0 to 1
Patient Group B	Low Risk, More Symptoms: 0 to 1 exacerbations per year (not leading to hospitalization); and CAT score ≥ 10 or mMRC grade ≥ 2
Patient Group C	High Risk, Less Symptoms: ≥ 2 exacerbations per year or ≥ 1 exacerbation leading to hospitalization; and CAT score < 10 or mMRC grade 0 to 1
Patient Group D	High Risk, More Symptoms: ≥ 2 exacerbations per year or ≥ 1 exacerbation leading to hospitalization; and CAT score ≥ 10 or mMRC grade ≥ 2

mMRC - Modified British Medical Research Council questionnaire used only to assesses breathlessness

Bone Resorption Suppression and Related Agents

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Bone Resorption Suppression and Related Agents

PRODUCT LIST AND FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Bisphosphonates		
alendronate (Binosto®)	Mission	Treatment and prevention of osteoporosis in postmenopausal women Treatment to increase bone mass in men with osteoporosis
alendronate* (Fosamax®)	generic, Merck	Treatment and prevention of osteoporosis in postmenopausal women Treatment to increase bone mass in men with osteoporosis Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent of 7.5 mg or greater of prednisone and who have low bone mineral density Treatment of Paget's disease of bone in men and women
alendronate/ vitamin D (Fosamax Plus D™)	Merck	Treatment of osteoporosis in postmenopausal women Treatment to increase bone mass in men with osteoporosis
etidronate	generic	Treatment of Paget's disease of bone Prevention and treatment of heterotopic ossification following total hip replacement or spinal cord injury
ibandronate (Boniva®)	generic, Roche	Treatment and prevention of osteoporosis in postmenopausal women
risedronate† (Actonel®)	generic, Actavis/Allergan	Treatment and prevention of osteoporosis in postmenopausal women Treatment to increase bone mass in men with osteoporosis Prevention and treatment of glucocorticoid-induced osteoporosis in men and women who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent of 7.5 mg or greater of prednisone for chronic diseases Treatment of Paget's disease of bone in men and women
risedronate delayed-release (Atelvia™)	generic, Actavis/Allergan	Treatment of osteoporosis in postmenopausal women

Bone Resorption Suppression and Related Agents

Calcitonins		
calcitonin-salmon*,†	generic	Treatment of postmenopausal osteoporosis in females greater than 5 years postmenopause when alternative treatments are not suitable. Fracture reduction efficacy has not been demonstrated.

* Manufacturing of Miacalcin (calcitonin-salmon) nasal spray was discontinued in February 2017.

† Manufacturing of Fortical (calcitonin-salmon) nasal spray was discontinued in September 2016.

Bone Resorption Suppression and Related Agents

Others		
abaloparatide (Tymlos™)	Radius Health	Treatment of osteoporosis in postmenopausal women who are at high risk for fractures
denosumab (Prolia™)	Amgen‡	Treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture, or in patients who have failed or are intolerant to other available osteoporosis therapy Treatment of osteoporosis associated with newly initiated or sustained systemic glucocorticoid therapy in men and women at high risk for fracture. Treatment of bone loss in men with prostate cancer on androgen deprivation therapy Treatment of bone loss in women undergoing breast cancer therapy with adjuvant aromatase therapy Treatment to increase bone mass in men diagnosed with osteoporosis and a high fracture risk who have failed or are intolerant to other potential therapies
raloxifene (Evista®)	generic, Eli Lilly	Treatment and prevention of osteoporosis in postmenopausal women Reduction in risk of invasive breast cancer in postmenopausal women who either have osteoporosis or are at high risk for invasive breast cancer
teriparatide (Forteo™)	Eli Lilly	Treatment of osteoporosis in postmenopausal women who are at high risk for fractures Increase of bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fractures Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture

†Amgen is also the manufacturer of denosumab (Xgeva™), indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors, treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity, and treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy. It is administered as a 120 mg subcutaneous (SC) injection every 4 weeks. Xgeva will not be addressed in this therapeutic class review.

Bone Resorption Suppression and Related Agents

- Approximately 10 million Americans have a diagnosis of osteoporosis, and an additional 43 million have low bone mass, placing them at increased risk for this disease
- The North American Menopause Society (NAMS), in its 2010 position statement, recommends bisphosphonates as first-line drugs to treat postmenopausal women with osteoporosis
- The 2014 National Osteoporosis Foundation (NOF) Clinician's Guide to Prevention and Treatment of Osteoporosis states that the treatment agent of choice should be based on available clinical information in addition to intervention thresholds
- The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis recommend alendronate, risedronate, zoledronic acid, and denosumab as initial therapy for most patients at high risk of fracture

Bone Resorption Suppression and Related Agents

- Per the AACE/ACE, teriparatide, denosumab, or zoledronic acid should be considered for patients unable to use oral therapy and as initial therapy for patients at especially high fracture risk

- According to the ACP's published update in 2017 for the treatment of low bone density and osteoporosis to prevent fractures in men and women, pharmacologic treatment to reduce the risk for hip and vertebral fractures in women with known osteoporosis and treatment should occur for 5 years

- ACP recommends against using menopausal estrogen or estrogen with progesterone or raloxifene for osteoporosis treatment in women

Bone Resorption Suppression and Related Agents

- Regarding therapy in men, the ACP recommends that clinicians offer treatment with bisphosphonates to reduce the risk of vertebral fractures in those with clinical osteoporosis

- According to the American College of Rheumatology's (ACR) 2017 updated guidance on managing glucocorticoid-induced osteoporosis in adults and children, treatment should include optimal calcium and vitamin D intake and lifestyle changes consistent with good bone health

- ACR's recommendations on antiresorptive treatment are based on individual patient characteristics, including fracture risk, age, and special populations

- In patients with moderate to high risk of fracture, oral bisphosphonates are generally recommended as first-line therapy, per the ACR; subsequent treatments may include IV bisphosphonates, teriparatide, denosumab, and raloxifene

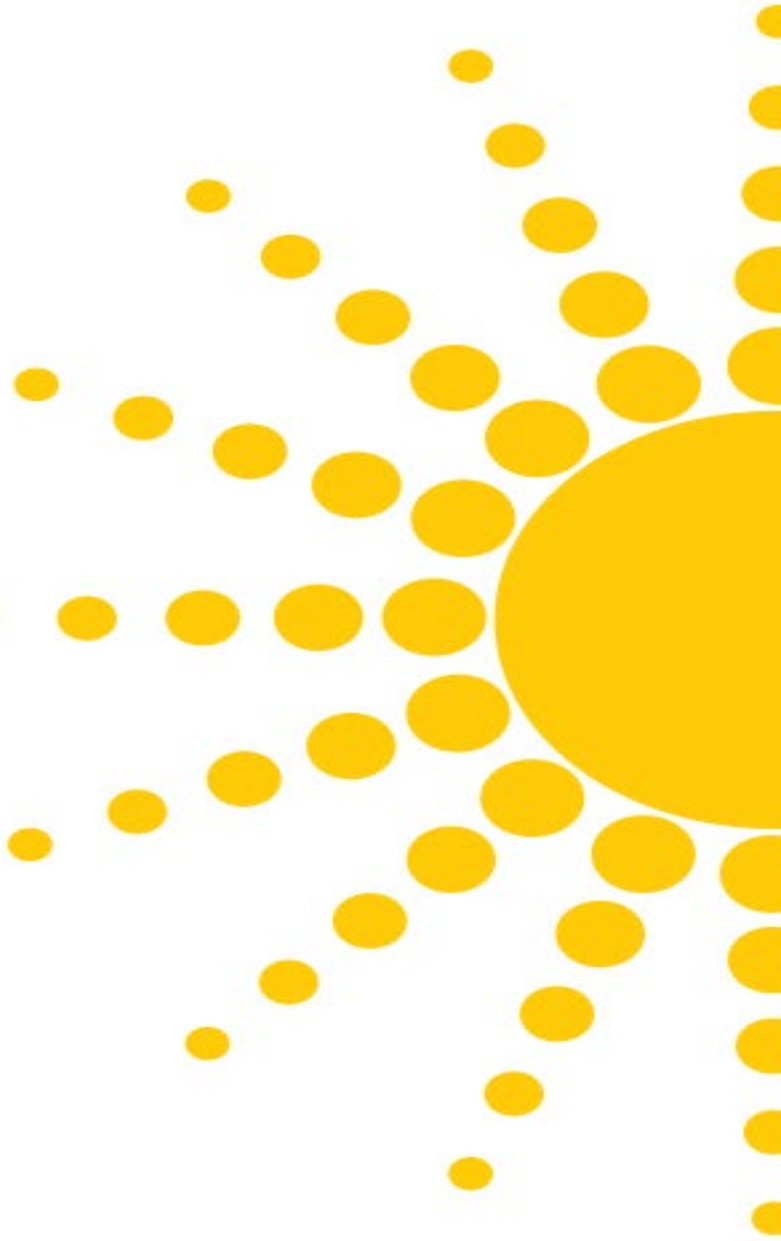
Bone Resorption Suppression and Related Agents

- Clinical trials have shown a decreased risk of fractures with alendronate, calcitonin-salmon, ibandronate, raloxifene, risedronate, denosumab and teriparatide in women with osteoporosis

- Teriparatide showed the greatest increase in BMD in clinical trials, ranging from 5% to more than 10%; bisphosphonates increased BMD about 2% to 5%; calcitonin and raloxifene trials showed BMD increases of approximately of 1% to 2%

- When compared to once-weekly regimens, once-monthly dosing regimens do not appear to give rise to greater treatment adherence and persistence

Colony Stimulating Factors



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Colony Stimulating Factors

PRODUCT LIST AND FDA-APPROVED INDICATIONS

Drug	Manufacturer	Cancer patients receiving myelosuppressive chemotherapy *(To reduce incidence of infection (febrile neutropenia)*	Acute Myeloid Leukemia (AML) patients receiving chemotherapy *(Following induction or consolidation chemotherapy to reduce time to neutrophil recovery and the duration of fever in adults)*	Bone Marrow Transplant (BMT)	Peripheral Blood Progenitor Cell Collection and Therapy	Severe Chronic Neutropenia *(To reduce the incidence and duration of neutropenia in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia)*	Hematopoietic Syndrome of Acute Radiation Syndrome *(To Increase survival in patients acutely exposed to myelosuppressive doses of radiation)*
filgrastim (Neupogen®)	Amgen	X	X	X[a]	X	X	X
filgrastim-aafi (Nivestym™)	Pfizer	X	X	X[a]	X	X	--
filgrastim-sndz (Zarxio®)	Sandoz	X	X	X[a]	X	X	--

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Colony Stimulating Factors

pegfilgrastim (Neulasta®)	Amgen	X	--	--	--	--	X
pegfilgrastim-jmdb (Fulphila™)	Mylan	X	--	--	--	--	--
pegfilgrastim-cbqv (Udenyca)	Coherus	X	--	--	--	--	--
sargramostim (Leukine®)	Sanofi	--	X	X[b]	X	--	X
tbo-filgrastim (Granix®)	Teva	X	--	--	--	--	--

* Filgrastim-aafi (Nivestym) and filgrastim-sndz (Zarxio) and are biosimilars for the originator filgrastim (Neupogen), approved through the FDA 351(k) biosimilar pathway.

† Pegfilgrastim-jmdb (Fulphila) is a biosimilar to the originator pegfilgrastim (Neulasta), approved through the FDA 351(k) biosimilar pathway.

[a] In cancer patients receiving BMT to reduce duration of neutropenia and febrile neutropenia

[b] For acceleration of myeloid reconstitution after PBPC/BMT; treatment of delayed neutrophil recovery or graft failure after BMT

Colony Stimulating Factors

- Colony stimulating factors (CSF) are hematopoietic growth factors that have been shown to decrease the likelihood of chemotherapy-induced neutropenic complications and improve relative chemotherapy dose intensity
- Prophylactic CSF use can reduce the severity, risk, and duration of febrile neutropenia and decrease rates of infection
- Neupogen, Nivestym, Zarxio, Neulasta, Fulphila, and Granix are granulocyte colony-stimulating factors (G-CSF)
- Leukine is a granulocyte-macrophage colony stimulating factor (GM-CSF)

Colony Stimulating Factors

- Per the National Comprehensive Cancer Network (NCCN) v2.2018 practice guidelines for Myeloid Growth Factors base, safety data appear similar between Neupogen and Neulasta, and the subcutaneous route is preferred for all 5 agents
- To date, there are insufficient head-to-head comparative studies on the clinical benefits of G-CSFs and GM-CSF
- Subcutaneous Neupogen, Zarxio, Granix, and Neulasta have a category 1 recommendation stating there is high-level evidence from randomized controlled clinical trials
- There is also uniform NCCN consensus that they prophylactically reduce the risk of febrile neutropenia; Leukine is no longer recommended for prophylactic use
- The NCCN guidelines do not recommend CSF use in patients taking chemotherapy and radiation concurrently

Colony Stimulating Factors

- Neupogen, Zarxio, and Leukine have a 2A recommendation for therapeutic use and can be used until post-nadir absolute neutrophil count (ANC) recovery to normal or near-normal levels
- Granix and Neulasta have only been studied for prophylactic use
- NCCN guidelines recommend that high-risk patients receive prophylactic CSF regardless of the intent of treatment (category 1)
- For intermediate-risk patients, NCCN recommends individualized consideration of CSF based on the likelihood of developing febrile neutropenia, its consequences, and the implications of interfering with chemotherapy treatments
- NCCN does not recommend the routine use of CSF in patients with low risk of developing febrile neutropenia

Colony Stimulating Factors

- The guidelines recommend Neupogen (2A recommendation), Zarxio (2B recommendation), or Granix (category 2B) for allogeneic hematopoietic cell mobilization and for granulocyte transfusion
- The NCCN guidelines state there is insufficient data for consideration with regard to Nivestym and Fulphila; therefore, no recommendations will be made on their use at this time; the use of Udenyca is not addressed in the guidelines
- The 2015 American Society of Clinical Oncology's (ASCO) updated set of guidelines for the use of white blood cell growth factors state that Neulasta, Neupogen, Zarxio, and Granix can be used for the prevention of treatment-related febrile neutropenia
- The choice of agent should be based on the clinical situation, convenience, and cost (Type: evidence-based, benefit outweigh harms; Evidence quality: high; Strength of recommendation: strong)

Colony Stimulating Factors

- The recommendations for the use of CSF for primary prophylaxis include the prevention of febrile neutropenia in patients who are at high risk; clinical trial data support the use of CSF when the risk of febrile neutropenia is ≥ 20%
- In comparison to other products, Neulasta and Fulphila administration frequency may be viewed as more favorable since it only requires a single subcutaneous injection per chemotherapy cycle, whereas administration of the rest of the CSFs requires daily subcutaneous injection
- NCCN recommends Zarxio in the same instances as Neupogen; however, they do not recommend switching between the two products during treatment
- Zarxio, approved in March 2015, is the first FDA-approved biosimilar product in the US
- In 2018, the FDA approved Nivestym, a biosimilar to Neupogen, as well as Fulphila and Udenyca which are biosimilars to Neulasta

Gaucher Disease

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Gaucher Disease

PRODUCT LIST AND FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Enzyme Replacement Therapy (ERT)		
imiglucerase (Cerezyme®)	Genzyme	Long-term enzyme replacement therapy for pediatric and adults with confirmed type 1 Gaucher disease that results in 1 or more of the following conditions: ▪ anemia ▪ thrombocytopenia ▪ bone disease ▪ hepatomegaly or splenomegaly
taliglucerase alfa (Elelyso®)	Pfizer	Long-term enzyme replacement therapy for adults and pediatric patients 4 years of age and older with confirmed type 1 Gaucher disease

Gaucher Disease

velaglucerase alfa (Vpriv®)	Shire Human Genetic Therapies	Long-term enzyme replacement therapy for pediatric (4 years of age or older) and adults with type 1 Gaucher disease
Substrate Reduction Therapy		
eliglustat (Cerdelga®)	Genzyme	Treatment of adult patients with type 1 Gaucher disease who are CYP2D6 extensive metabolizers, intermediate metabolizers, or poor metabolizers as detected by an FDA-approved test
miglustat (Zavesca®)	generic*, Actelion	Treatment of adult patients with mild to moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option (e.g., due to constraints such as allergy, hypersensitivity, or poor venous access)

* Authorized generic is available.

-Patients maintained on an effective dose of imiglucerase for Gaucher disease may be switched to velaglucerase alfa or taliglucerase alfa at the same dose.

-Eliglustat (Cerdelga) limitations of use: CYP2D6 ultra-rapid metabolizers may not achieve adequate concentrations of eliglustat to achieve a therapeutic dose; a specific dosage cannot be recommended for CYP2D6 indeterminate metabolizers.

Gaucher Disease

- An autosomal recessive condition caused by deficiency of glucocerebrosidase
- This deficiency results in abnormal accumulation of glycolipids in cell lysosomes, which can lead to skeletal disease, anemia, hemorrhage, thrombocytopenia, splenomegaly, hepatomegaly, and growth retardation
- All IV enzyme replacement therapy (ERT) agents, Cerezyme, Vpriv, and Elelyso are forms of the enzyme glucocerebrosidase, whereas oral substrate reduction therapy (SRT) agents, Cerdelga and miglustat function as competitive and reversible inhibitors of the enzyme glucosylceramide synthase
- Treatment should be individualized as response may vary

Gaucher Disease

- The International Collaborative Gaucher Group (ICGG) Gaucher Registry guidelines developed from a consensus of international experts recommend ERT for symptomatic pediatric patients and for those with severe disease
- Treatment is life-long, and therapy interruptions are not recommended
- Anaphylaxis has been reported in patients treated with Elelyso
- The use of miglustat has been limited due to toxicity

Erythropoiesis Stimulating Proteins

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Erythropoiesis Stimulating Proteins

PRUDUCT LIST AND FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-approved Indications
darbepoetin (Aranesp®)	Amgen	▪ Treatment of anemia associated with chronic kidney disease (CKD) including patients on dialysis and patients not on dialysis ▪ Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy and, upon initiation, a minimum of 2 additional months chemotherapy is planned — Darbepoetin is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure or in in whom anemia can be managed by transfusion — Darbepoetin is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy — Darbepoetin is not indicated as a substitute for red blood cell (RBC) transfusion in patients who require immediate correction of anemia — Darbepoetin use has not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being
PEG-EPO (Mircera®)	Roche/Vifor	▪ Treatment of anemia associated with chronic renal failure (CRF) in ○ adult patients on dialysis and adult patients not on dialysis ○ pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ○ erythropoiesis stimulating agent (ESA) — PEG-EPO use has not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being — PEG-EPO is not indicated for treatment of anemia in patients receiving cancer chemotherapy — PEG-EPO is not indicated as a substitute for red blood cell (RBC) transfusion in patients who require immediate correction of anemia

PEG-EPO = methoxy polyethylene glycol epoetin beta; rHuEPO = recombinant human epoetin alfa; HIV = human immunodeficiency virus

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Erythropoiesis Stimulating Proteins

rHuEPO (Epogen®)	Amgen	▪ Treatment of anemia associated with CRF including patients on dialysis and patients not on dialysis to decrease the need for red blood cell (RBC) transfusion ▪ Treatment of anemia related to therapy with zidovudine (≤ 4,200 mg per week) in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL ▪ Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy and, upon initiation, hemoglobin < 10 g/dL and there is a minimum of 2 additional months of planned chemotherapy
rHuEPO (Procrit®)	Amgen (distributed by Janssen)	▪ Indicated to reduce the need for allogenic RBC transfusion among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery – rHuEPO is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy – rHuEPO is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure or in in whom anemia can be managed by transfusion – rHuEPO is not indicated as a substitute for red blood cell (RBC) transfusion in patients who require immediate correction of anemia – rHuEPO is not indicated in patients undergoing cardiac or vascular surgery – rHuEPO is not indicated for patients who are willing to donate autologous blood pre-operatively – rHuEPO use has not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being

PEG-EPO = methoxy polyethylene glycol epoetin beta; rHuEPO = recombinant human epoetin alfa; HIV = human immunodeficiency virus

Erythropoiesis Stimulating Proteins

rHuEPO-epbx* (Retacrit®)	Pfizer (Hospira)	▪ Treatment of anemia associated with CKD including patients on dialysis and patients not on dialysis to decrease the need for red blood cell (RBC) transfusion ▪ Treatment of anemia due to zidovudine administered at ≤ 4,200 mg per week in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL ▪ Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy and, upon initiation, there is a minimum of 2 additional months of planned chemotherapy ▪ Reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery – Epoetin alfa-epbx is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy – Epoetin alfa-epbx is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure or in in whom anemia can be managed by transfusion – Epoetin alfa-epbx is not indicated as a substitute for RBC transfusion in patients who require immediate correction of anemia – Epoetin alfa-epbx is not indicated in patients undergoing cardiac or vascular surgery – Epoetin alfa-epbx is not indicated for patients who are willing to donate autologous blood pre-operatively ▪ Epoetin alfa-epbx use has not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being

PEG-EPO = methoxy polyethylene glycol epoetin beta; rHuEPO = recombinant human epoetin alfa; HIV = human immunodeficiency virus

* Epoetin alfa-epbx (Retacrit) is considered biosimilar to rHuEPO (Epogen/Procrit) for its indications. Biosimilar, a term used for biologic products, means that approval is based on data demonstrating that it is highly similar to another FDA-approved biological product (a reference product) and there are no clinically meaningful differences between the 2 products.

Erythropoiesis Stimulating Proteins

- Anemia affects over 3 million Americans as it is a result of numerous diseases, as well as adverse effects of treatments
- Erythropoietin is a glycoprotein produced in the kidneys that stimulates red blood cell production from bone marrow
- The NCCN guidelines state that erythropoiesis stimulating agents (ESAs) are associated with an increased risk of thrombosis, decreased survival, and shortened time to tumor; therefore, it is advised to use the lowest ESA dose possible to maintain hemoglobin (Hb) levels sufficient to avoid blood transfusions
- The 2010 ASCO and the American Society of Hematology (ASH) joint clinical practice guidelines for the use of ESAs in patients with cancer also recommend minimizing ESA use, particularly in patients with malignancy being treated with curative intent

Erythropoiesis Stimulating Proteins

- This joint guideline recommends against the use of ESAs for the treatment of anemia associated with malignancy in patients who are not receiving concurrent myelosuppressive chemotherapy, except for patients with lower risk of myelodysplastic syndrome to avoid transfusions

- Therapy with Epogen/Procrit, Mircera, and Aranesp for CKD should not exceed target hemoglobin of greater than 11 g/dL

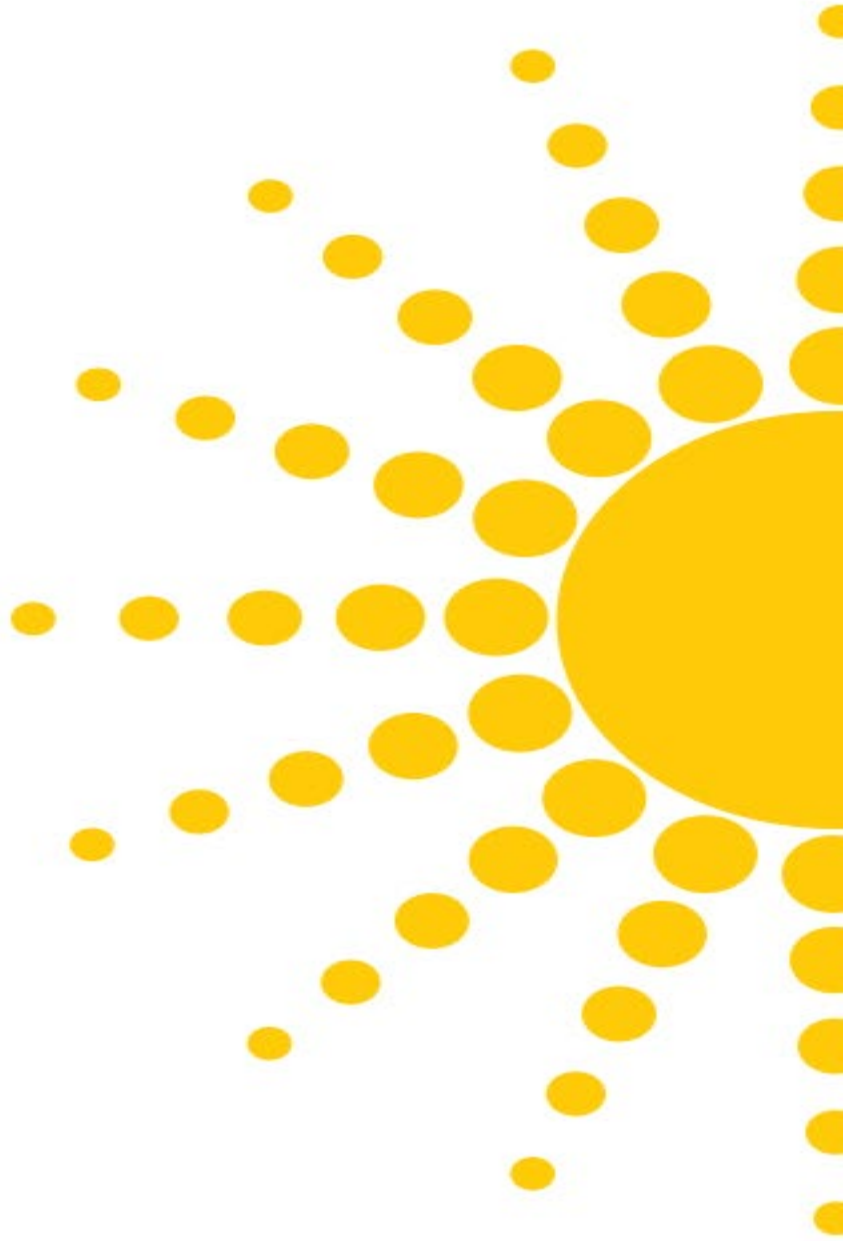
- The ASCO and ASH Update Committee maintains that all ESAs are equivalent in terms of safety and efficacy

- National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) updated 2007 guidelines state that each ESA is effective in achieving and maintaining target Hb levels

Erythropoiesis Stimulating Proteins

- Patients with endogenous serum erythropoietin levels ≤ 500 mUnits/mL, and who are receiving a dose of zidovudine ≤ 4,200 mg/week, may respond to rHuEPO therapy
- Patients with endogenous serum erythropoietin levels > 500 mUnits/mL do not appear to respond to rHuEPO therapy
- In 2011, the FDA published a safety communication regarding a more conservative dosing approach to ESAs in patients with CKD due to increased risks of cardiovascular events
- Retacrit is the first FDA-approved biosimilar to Epogen/Procrit; Retacrit is neither considered interchangeable with, nor does it carry the same indications as the reference products

Hypoglycemics, Alpha-Glucosidase Inhibitors



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Hypoglycemics, Alpha-Glucosidase Inhibitors

PRODUCT LIST AND FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication
acarbose (Precose®)	generic	Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes
miglitol (Glyset®)	Pfizer	Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes

Hypoglycemics, Alpha-Glucosidase Inhibitors

- Miglitol is more potent than acarbose on a milligram-to-milligram basis
- These agents only have a modest effect on lowering HbA1c by about 0.4 to 0.7 percent
- Relatively safe but GI side effects (e.g., bloating, flatulence, diarrhea) limit their use

Hypoglycemics, Metformins

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Hypoglycemics, Metformins

PRODUCT LIST AND FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indications
glipizide/ metformin	generic	▪ Initial therapy to improve glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise ▪ Second-line therapy in type 2 diabetics who have not achieved adequate glycemic control with a sulfonylurea or metformin alone
glyburide/ metformin (Glucovance®)	generic, BMS	▪ Initial therapy to improve glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise ▪ Second-line therapy in type 2 diabetics who have not achieved adequate glycemic control with a sulfonylurea or metformin alone ▪ In combination with a TZD in patients who do not have adequate glycemic control with Glucovance alone
metformin (Glucophage®)	generic, BMS*	▪ Improvement of glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise in patients 10 years of age and older (including in combination with a sulfonylurea or insulin)

Hypoglycemics, Metformins

metformin ER (Fortamet™ ER)	generic, Shionogi	▪ Improvement of glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise
metformin ER (Glumetza™ ER)	generic, Santarus	▪ Improvement of glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise (including in combination with a sulfonylurea or insulin)
metformin XR (Glucophage XR®)	generic, BMS*	▪ Improvement of glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise (including in combination with a sulfonylurea or insulin)
metformin **oral solution (**Riomet™)	**generic, Ranbaxy/Sun**	▪ Improvement of glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise in patients 10 years of age and older (including in combination with a sulfonylurea or insulin for ages 17 and older)

* BMS has made a business decision to discontinue Glucophage 500 mg, 850 mg, and 1,000 mg and Glucophage XR 500 mg and 750 mg. Products may remain until supply is depleted.

Hypoglycemics, Metformins

- Findings from meta-analyses support metformin as first-line therapy, citing relative safety and beneficial effects on HbA1c, weight, and cardiovascular mortality
- Per the 2019 American Diabetes Association (ADA) Standards of Medical Care in Diabetes, metformin is recommended as initial therapy for the treatment of T2DM, along with lifestyle interventions at the time of diagnosis, unless metformin is contraindicated
- The AACE/ACE 2019 diabetes management algorithm and 2015 clinical practice guidelines for developing a diabetes care plan also recommend metformin as first-line therapy

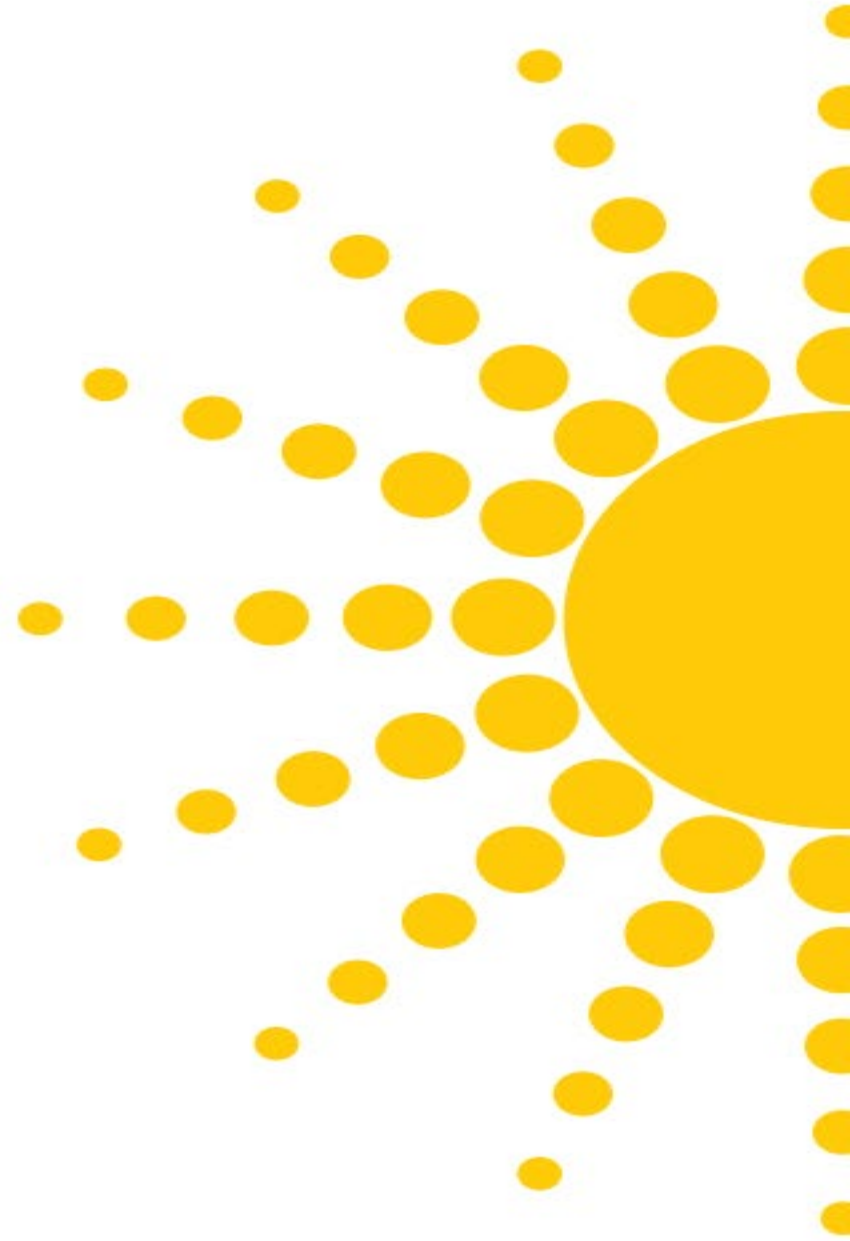
Hypoglycemics, Metformins

- The AACE/ACE guidelines list metformin as the highest recommended agent among all anti-hyperglycemic medications for monotherapy

- The ACP's revised 2017 guidelines for T2DM recommend metformin as first-line therapy

- Metformin is contraindicated in patients with:
  - renal disease or severe renal dysfunction (estimated glomerular filtration rate [eGFR] below 30 mL/minute/1.73 m2)
  - acute or chronic metabolic acidosis including diabetic ketoacidosis acute myocardial infarction
  - septicemia
  - pregnancy

Hypoglycemics, SGLT2



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Hypoglycemics, SGLT2

PRODUCT LIST AND FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indications
canagliflozin (Invokana®)	Janssen	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) To reduce the risk of major adverse cardiovascular events (MACE) in adults with T2DM and established cardiovascular disease (CVD)
canagliflozin/ metformin (Invokamet®)	Janssen	Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both canagliflozin and metformin is appropriate
canagliflozin/ metformin (Invokamet® XR)	Janssen	Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both canagliflozin and metformin is appropriate
dapagliflozin (Farxiga®)	AstraZeneca	Adjunct to diet and exercise to improve glycemic control in adults with T2DM
dapagliflozin/ metformin ER (Xigduo® XR)	AstraZeneca	Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both dapagliflozin and metformin is appropriate

Hypoglycemics, SGLT2

empagliflozin (Jardiance®)	Boehringer Ingelheim	Adjunct to diet and exercise to improve glycemic control in adults with T2DM To reduce the risk of cardiovascular death in adults with T2DM and established CVD
empagliflozin/ metformin (Synjardy®)	Boehringer Ingelheim	Adjunct to diet and exercise to improve glycemic control in adults with T2DM when both empagliflozin and metformin is appropriate
empagliflozin/ metformin ER (Synjardy® XR)	Boehringer Ingelheim	Adjunct to diet and exercise to improve glycemic control in adults with T2DM when both empagliflozin and metformin is appropriate
ertugliflozin (Steglatro™)	Merck	Adjunct to diet and exercise to improve glycemic control in adults T2DM
ertugliflozin/ metformin (Segluromet™)	Merck	Adjunct to diet and exercise to improve glycemic control in adults with T2DM who are not adequately controlled on a regimen containing ertugliflozin or metformin, or in patients who are already treated with both ertugliflozin and metformin

Agents in this review are not indicated for the treatment of type 1 diabetes or diabetic ketoacidosis.

* Effectiveness of empagliflozin/metformin (Synjardy) and empagliflozin/metformin ER (Synjardy XR) on reducing the risk of CV death in adults with T2DM and CVD has not been established.

Hypoglycemics, SGLT2

- It is estimated that over 30.3 million people in the US have diabetes; type 2 diabetes (T2DM) accounts for about 90% to 95% of all diagnosed cases of diabetes in adults
- Studies evaluating the impact of SGLT2 inhibitors on macrovascular complications, (e.g., cardiovascular outcomes) include the EMPA-REG OUTCOME and CANVAS/CANVAS-R
- The EMPA-REG OUTCOME trial reported approximately a one-third relative risk reduction for cardiovascular death, hospitalization due to heart failure, and all-cause death with use of Jardiance as compared to placebo
- CANVAS and CANVAS-R trials demonstrated a 14% risk reduction (hazard ratio [HR], 0.86 [95% CI, 0.75 to 0.97]) in first occurrence of major adverse cardiovascular event (MACE) in patients with T2DM treated with Invokana

Hypoglycemics, SGLT2

- Based on the DECLARE–TIMI 58 trial, dapagliflozin did not result in a lower rate of MACE compared to placebo; however, it did lead to reduced all-cause mortality and the composite of CV death, as well as a lower incidence of HF-related hospitalizations

- The SGLT2 inhibitors are efficacious agents in reducing HbA1c, postprandial glucose, and fasting plasma glucose, as well as reducing systolic blood pressure and weight

- The long-term safety of SGLT2 inhibitors remains to be established

- Per the 2019 ADA Standards of Medical Care in Diabetes, if metformin fails to produce the target HbA1c after 3 months of therapy, a thiazolidinedione (TZD), sulfonylurea (SU), dipeptidyl peptidase-4 (DPP-4) inhibitor, SGLT2 inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonist, or basal insulin should be added in patients without atherosclerotic cardiovascular disease (ASCVD) or CKD

Hypoglycemics, SGLT2

- In patients with ASCVD or CKD, the addition of an agent with known CV or renal benefit (select GLP-1 agonist or select SLGT2 inhibitor) is preferred
- The selection of medications should be patient-centric and prescribers should consider potential issues such as HbA1c target, impact on weight and hypoglycemia, side effects, the frequency and mode of administration, patient adherence, patient preference, and cost
- TZDs and SUs are generally considered less safe than GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors, or alpha-glucosidase inhibitors

Hypoglycemics, SGLT2

- The ADA prefers medications with proven CV and renal benefit in patients with CV and/or renal disease, respectively
- In patients with ASCVD, the addition of Jardiance (Class A recommendation), Victoza (Class A recommendation), or Invokana (Class C recommendation) is preferred
- In patients with HF or CKD, Jardiance or Invokana is preferred
- The AACE/ACE 2019 diabetes management algorithm and 2015 clinical practice guidelines for developing a diabetes care plan include the use of SGLT2 inhibitors as an alternative to metformin for monotherapy and as an appropriate add-on to metformin in dual therapy and triple therapy

Hypoglycemics, SGLT2

- Per the AACE/ACE guidelines, agents for monotherapy are recommended in the following order (highest to lowest recommendation): metformin, GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors, TZDs, alpha-glucosidase inhibitors, and sulfonylureas/secretagogue glinides.

- The ACP's revised 2017 guidelines for T2DM recommend metformin as first-line therapy, and a sulfonylurea, TZD, SGLT-2 inhibitor, or a DPP-4 inhibitor as preferred second-line treatments

- The 2018 World Health Organization (WHO) guidelines for treatment intensification in patients with T2DM recommend addition of a DPP-4 inhibitor, a SGLT2 inhibitor, or a TZD if insulin is unsuitable in patients with T2DM who do not achieve glycemic control with metformin and/or a sulfonylurea

- In 2015, the FDA issued a warning that use of SGLT2 inhibitors may lead to ketoacidosis

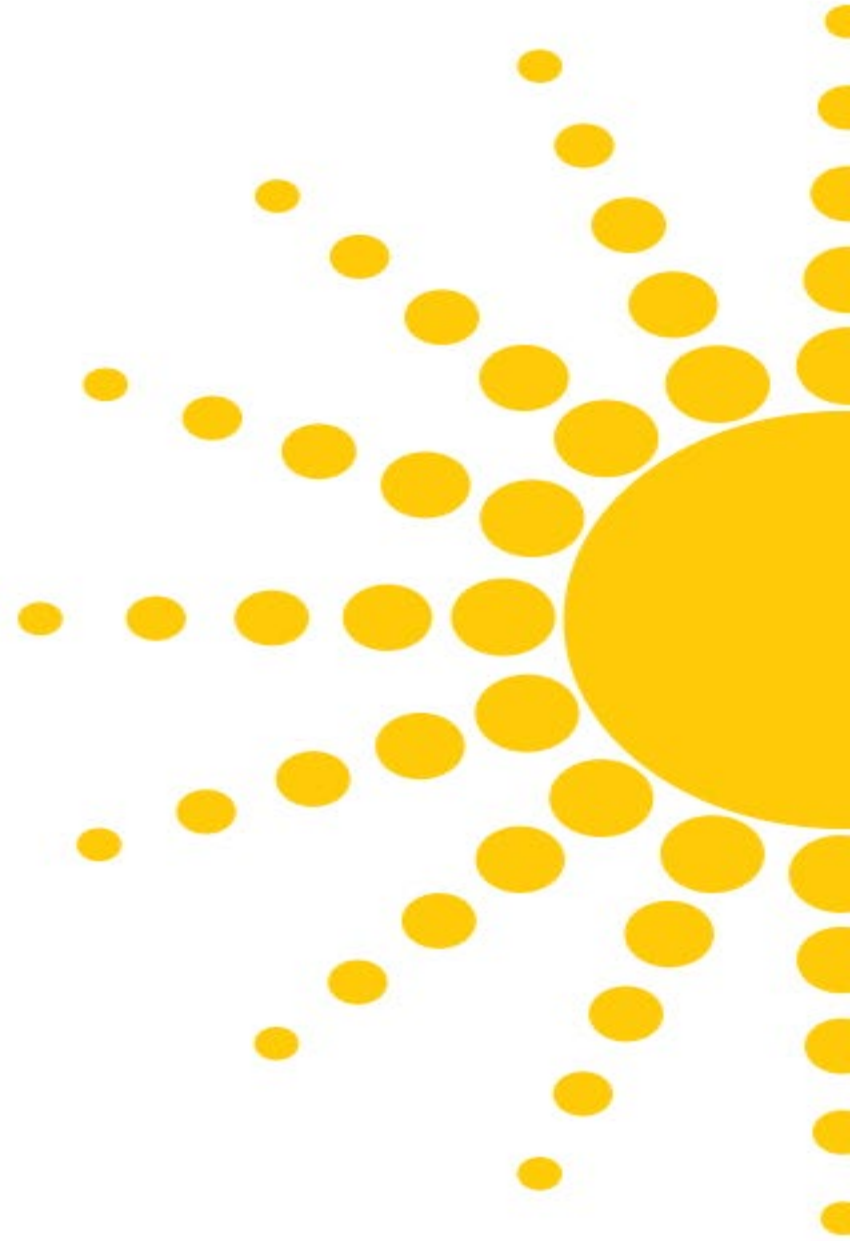
Hypoglycemics, SGLT2

- In May 2017, the FDA released a safety communication based on final safety data from the CANVAS and CANVAS-R studies, which revealed approximately a 2- fold increase in leg and foot amputations (primarily toes) in patients with T2DM who were treated with Invokana compared to placebo

- In August 2018, the FDA issued another safety communication regarding the risk of Fournier's gangrene with the use of the SGLT2 inhibitors

- The FDA recently alerted prescribers of an increased risk of bone fracture in patients treated with Invokana, Invokamet, Invokamet XR

Immune Globulins



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Immune Globulins

PRODUCT LIST AND FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indications
Intravenous		
Bivigam®	Biotest	▪ Primary humoral immunodeficiency
Carimune NF, Nanofiltered®	CSL Behring	▪ Primary humoral immunodeficiency ▪ Immune thrombocytopenic purpura
Flebogamma® DIF 5% and 10%	Grifols	▪ Primary (inherited) immunodeficiency ▪ Chronic primary immune thrombocytopenia (10% only)
Gammagard® S/D	Shire	▪ Primary humoral immunodeficiency ▪ Prevention of bacterial infections in hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell chronic lymphocytic leukemia ▪ Chronic immune thrombocytopenic purpura ▪ Prevention of coronary artery aneurysms associated with Kawasaki syndrome
Gammaplex® 5% and 10%	Bio Products Laboratory	▪ Primary humoral immunodeficiency ▪ Chronic immune thrombocytopenic purpura
Octagam® 5% and 10%	Octapharma USA	▪ Primary humoral immunodeficiency (5% only) ▪ Chronic immune thrombocytopenic purpura (10% only)
Privigen®	CSL Behring AG	▪ Primary humoral immunodeficiency ▪ Chronic immune thrombocytopenic purpura ▪ Chronic inflammatory demyelinating polyneuropathy (Limitation of use: maintenance therapy has not been studied > 6 months)

Immune Globulins

Intravenous or Subcutaneous		
Gammagard® Liquid	Shire	▪ Primary humoral immunodeficiency ▪ Multifocal motor neuropathy
Gammaked	Grifols Therapeutics (distributed by Kedrion Biopharm)†	▪ Primary humoral immunodeficiency ▪ Idiopathic thrombocytopenic purpura (IV use only) ▪ Chronic inflammatory demyelinating polyneuropathy (IV use only)
Gamunex®-C	Grifols Therapeutics	▪ Primary humoral immunodeficiency ▪ Idiopathic thrombocytopenic purpura (IV use only) ▪ Chronic inflammatory demyelinating polyneuropathy (IV use only)
Subcutaneous		
Cuvitru™	Shire	▪ Primary immune deficiency
Hizentra®	CSL Behring AG	▪ Primary immune deficiency ▪ Maintenance therapy in patients with chronic inflammatory demyelinating polyneuropathy
immune globulin 10%/recombinant human hyaluronidase Hyqvia®	Shire	▪ Primary immune deficiency‡

* In February 2018, CSL Behring announced that they have decided to discontinue the production of Carimune NF in the third quarter of 2018. Some product may remain available until supply is depleted.[1]

† Gammaked and Gamunex-C are manufactured by Grifols Therapeutics, and are identical; Kedrion Biopharma has an agreement with Grifols to market the product under a private label name (Gammaked).

‡ Safety and efficacy of chronic use of recombinant human hyaluronidase in Hyqvia have not been established in conditions other than primary immune deficiency.

Immune Globulins

The following table outlines the various phenotypic categorizations of PIDD as offered by the American Academy of Allergy, Asthma, and Immunology (AAAAI)

		IgG			
		Quantity/Quality			
		Absent/Absent	**Low/Low**	**Normal/Low**	**Low/Normal**
B cell	**Absent**	**Category I** ▪ Agamma-globulinemia ▪ SCID			
	Present		**Category II** ▪ Hyper IgM ▪ CVID	**Category III** ▪ Specific Ab Deficiency ▪ NEMO deficiency	**Category IV** ▪ Transient hypogamma-globulinemia of infancy
			▪ NEMO deficiency	▪ Subclass deficiency with specific antibody defect	▪ Primary hypogamma-globulinemia

Ab = antibody, CVID = common variable immunodeficiency, NEMO = NF-kappa B Essential Modulator, SCID = severe combined immunodeficiency

Immune Globulins

- The primary use for immune globulin therapy is the management of primary immunodeficiency disease (PIDD)
- Exogenous immune globulin product has also been FDA approved for use in multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyneuropathy (CIDP), idiopathic thrombocytopenic purpura (ITP), Kawasaki disease, and B-cell chronic lymphocytic leukemia
- Therapeutic immune globulin is prepared from pooled plasma obtained from healthy donors at plasma donation centers in the US
- These products are purified to contain 95% to 99% IgG with trace amounts of IgA and IgM
- Each product has validated their production methods to ensure low risk of transmission of viruses

Immune Globulins

- Preparation for each product differs in purification, including production methods related to fractionation, exchange chromatography, and filtration
- The AAAAI and the Clinical Immunology Society both recommend product selection to be relied heavily on patient-specific characteristics
- The subcutaneous route is as efficacious as the intravenous route for the treatment of primary immunodeficiencies
- All the products in the class have similar efficacy and safety profiles
- Due to limited supply, the use of immune globulin products should be reserved for approved indications or conditions where the benefit has been clearly established and is consistent with clinical guidelines

Oncology Oral, Hematologic Cancers

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Oncology Oral, Hematologic Cancers

PRODUCT LIST AND FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indications
acalabrutinib (Calquence®)	AstraZeneca	▪ Treatment of adults with mantle cell lymphoma (MCL) treated with at least 1 prior therapy
bosutinib (Bosulif®)	Pfizer	▪ Newly diagnosed chronic phase (CP) Ph+ CML ▪ Treatment of chronic, accelerated, or blast phase Ph+ chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy
busulfan (Myleran®)	Aspen Global/ Prasco	▪ Palliative treatment of chronic myelogenous (myeloid, myelocytic, granulocytic) leukemia
chlorambucil (Leukeran®)	Aspen Global/ Prasco	▪ Treatment of chronic lymphatic (lymphocytic) leukemia, malignant lymphomas, including lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease; chlorambucil is not curative in any of these disorders but may produce clinically useful palliation
dasatinib (Sprycel®)	Bristol-Meyers Squibb	▪ Treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib (Gleevec) ▪ Treatment of adults with Ph+ acute lymphoblastic leukemia (ALL) with resistance or intolerance to prior therapy ▪ Newly diagnosed adult patients with Ph+ CML in chronic phase ▪ Treatment of pediatric patients with Ph+ CML in chronic phase

Oncology Oral, Hematologic Cancers

enasidenib (Idhifa®)	Celgene	▪ Relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as determined with an FDA-approved test
hydroxyurea (Hydrea®)	generic, Bristol-Myers Squibb	▪ Resistant CML ▪ Locally advanced squamous cell carcinomas of the head and neck (excluding lip), in combination with concurrent chemoradiation
ibrutinib (Imbruvica®)	Pharmacyclics/ Janssen	▪ Mantle cell lymphoma (MCL) in patients who have received at least 1 prior therapy ▪ Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma ▪ Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma with 17p deletion ▪ Waldenström's macroglobulinemia ▪ Marginal zone lymphoma (MZL) requiring systemic therapy and patient has had prior anti-CD20-based therapy ▪ Chronic graft versus host disease (cGVHD) after failure of one of more lines of systemic therapy
idelalisib (Zydelig®)	Gilead	▪ Relapsed chronic CLL in combination with rituximab in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities ▪ Relapsed follicular B cell non-Hodgkin's lymphoma (FL) in patients who have received at least 2 prior systemic therapies ▪ Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least 2 prior systemic therapies

Oncology Oral, Hematologic Cancers

imatinib (Gleevec®)	generic, Novartis	▪ Newly diagnosed adult and pediatric patients with Ph+ CML in chronic phase ▪ Patients with Ph+ CML in blast crisis, accelerated phase, or chronic phase after failure of interferon-alpha therapy ▪ Adult patients with relapsed or refractory Ph+ ALL ▪ Pediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy ▪ Adult patients with myelodysplastic/myeloproliferative diseases associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements as determined with an FDA-approved test† ▪ Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation as determined with an FDA-approved test or with c-Kit mutational status unknown ▪ Adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who are FIP1L1-PDGFRα fusion kinase-negative or unknown ▪ Adult patients with unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans (DFSP) ▪ Patients with Kit (CD117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) ▪ Adjuvant treatment of adult patients following resection of Kit (CD117)-positive gastrointestinal stromal tumors (GIST)
ivosidenib (Tibsovo®)	Agios	▪ Adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as approved by an FDA-approved test
ixazomib (Ninlaro®)	Takeda/Millennium	▪ In combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in patients who have received at least 1 prior therapy

Oncology Oral, Hematologic Cancers

lenalidomide (Revlimid®)	Celgene	▪ In combination with dexamethasone for the treatment of multiple myeloma ▪ As maintenance therapy for multiple myeloma following autologous hematopoietic stem cell transplantation (auto-HSCT) ▪ Treatment of transfusion-dependent anemia due to low-or intermediate-1-risk myelodysplastic syndromes associated with a deletion of 5q cytogenetic abnormality with or without additional cytogenetic abnormalities ▪ Treatment of mantle cell lymphoma after relapse or disease progression after 2 prior therapies, 1 of which included bortezomib
melphalan (Alkeran®)	generic, Apopharma	▪ Palliative treatment of multiple myeloma ▪ Palliation of non-resectable epithelial carcinoma of the ovary
mercaptopurine (Purixan®)	generic (tablets); Nova (suspension)	▪ Acute lymphoblastic leukemia (ALL) as a component of a combination maintenance therapy regimen
midostaurin (Rydapt®)	Novartis	▪ Newly diagnosed AML that is FLT3 mutation-positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation ▪ Aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia

Oncology Oral, Hematologic Cancers

nilotinib (Tasigna®)	Novartis	▪ Accelerated phase and chronic phase Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib (Gleevec) ▪ Newly diagnosed adult and pediatric patients at least 1 year of age with Ph+ CML in chronic phase ▪ Treatment of chronic phase Ph+ CML with resistance or intolerance to prior tyrosine-kinase inhibitor (TKI) therapy in pediatric patients at least 1 year of age
panobinostat (Farydak®)	Novartis	▪ Treatment of multiple myeloma in combination with bortezomib and dexamethasone in patients who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent
pomalidomide (Pomalyst®)	Celgene	▪ For use in combination with dexamethasone for patients with multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy
ponatinib (Iclusig®)	Ariad	▪ Treatment of adult patients with T315I-positive chronic myeloid leukemia (CML) (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) ▪ Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ALL for whom no other tyrosine kinase inhibitor (TKI) is indicated
procarbazine (Matulane®)	Sigma-Tau	▪ For use in combination with other anticancer drugs for the treatment of stage 3 and stage 4 Hodgkin's disease ; used as part of the MOPP regimen (nitrogen mustard, vincristine, procarbazine, prednisone)

Oncology Oral, Hematologic Cancers

ruxolitinib (Jakafi®)	Incyte	▪ Intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF ▪ Treatment of polycythemia vera in patients who have had an inadequate response to or are intolerant of hydroxyurea
thalidomide (Thalomid®)	Celgene	▪ Treatment of newly diagnosed multiple myeloma in combination with dexamethasone ▪ Acute treatment of cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) ▪ Prevention and suppression of cutaneous manifestations of ENL recurrence as maintenance therapy
thioguanine (Tabloid®)	Aspen/Prasco	▪ For remission induction and remission consolidation of acute nonlymphocytic leukemias
tretinoin	generic	▪ For remission induction in patients with acute promyelocytic leukemia (APL), FAB classification M3 characterized by the presence of the t(15;17) translocation and/or presence of the PML/RARα gene who are refractory to, have relapsed from, or have a contraindication to anthracycline chemotherapy
venetoclax (Venclexta®)	AbbVie	▪ Treatment of CLL or SLL in patients with or without 17p deletion, as detected by an FDA-approved test, who have received at least 1 prior therapy
vorinostat (Zolinza®)	Merck, Sharp & Dohme	▪ Treatment of cutaneous manifestations of cutaneous T cell lymphoma (CTCL) in patients who have progressive, persistent, or recurrent disease on or following 2 systemic therapies

Ph+ = Philadelphia chromosome positive; CML = chronic myelogenous (myeloid) leukemia; ALL = acute lymphoblastic leukemia

Oncology Oral, Hematologic Cancers

Leukemias

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Leukemias

Chronic Myeloid Leukemia (CML)

- Accounts for 15% of all adult leukemias
- Involves a gene mutation called the Philadelphia (Ph) chromosome
- For low-risk score patients, imatinib, dasatinib, nilotinib and bosutinib are all NCCN category 1 recommendations
- For patients with an intermediate or high-risk score, dasatinib, nilotinib, and bosutinib are category 1 recommendations and are preferred over imatinib, in most situations

Leukemias

Acute Lymphocytic Leukemia (ALL)

- The most common form of childhood leukemia
- Standard therapy for the treatment is usually separated into induction, consolidation, and maintenance phases
- Daily administration of oral mercaptopurine is often included as part of a backbone treatment in the maintenance phase

Leukemias

Ph+ ALL

- The 1.2018 NCCN guidelines recommend incorporation of a TKI in the frontline regimen as an established standard of care for adolescents/young adults and adults
- Pediatric patients are also candidates for TKI therapy as imatinib has demonstrated a superior 5-year event-free survival rate
- The TKI may be combined with either chemotherapy or corticosteroids depending on the patient's age and comorbidities

Leukemias

Acute Myeloid Leukemia (AML)

- The most common form of acute leukemia among adults
- The 2.2018 NCCN guidelines include oral midostaurin in combination with cytarabine, with and without daunorubicin, as part of standard induction, consolidation, and post-remission therapies for patients with FLT3-mutated AML
- For IDH2- or IDH1- mutated AML, the NCCN guidelines recommend enasidenib (category 2A) or ivosidenib, respectively as options for treatment induction in patients who either are not candidates for or who decline intensive therapy
- If remission on enasidenib or ivosidenib is achieved in these patients, therapy should be continued on these drugs until disease progression (category 2A)
- For patients with relapsed/refractory IDH1- or IDH2-mutated AML, therapy with enasidenib or ivosidenib, respectively may be utilized (category 2A)

Leukemias

Acute Promyelocytic Leukemia (APL)

- An aggressive subtype of AML but has an estimated 80% cure rate
- As soon as a presumptive diagnosis is made, treatment with oral tretinoin must be started in order to decrease the risk of coagulopathy-related early mortality

Oncology Oral, Hematologic Cancers

Lymphomas

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Lymphomas

Hodgkin Lymphoma (HL)

- Most commonly diagnosed in patients who are between 15 and 30 years of age; currently has an estimated 80% cure rate
- The most common front-line chemotherapy regimen for adults is now ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine)
- Other commonly utilized regimens include Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone) or Escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone)

Lymphomas

Non-Hodgkin's Lymphomas (NHL)

- Chronic lymphocytic leukemia [CLL], small lymphocytic lymphoma [SLL], follicular lymphoma [FL], marginal zone lymphoma [MZL], and mantle cell lymphoma [MCL]) are classified as mature B cell lymphomas (and comprise about 85% to 90% of all NHLs), whereas cutaneous T cell lymphoma (CTCL) is not

Lymphomas

CLL/SLL

- CLL is generally a disease of the elderly, with a median age of 72 years
- In CLL, a significant portion of the abnormal lymphocytes are in the blood and in the bone marrow, while in SLL, there are a relative lack of abnormal lymphocytes in the blood and they are instead found predominantly in the lymph nodes, bone marrow and other lymphoid tissues
- Ibrutinib is a first-line therapy option for all CLL patients without del (17p) in first-line setting and in relapsed/refractory disease
- The combination therapy of chlorambucil with a CD-20 directed monoclonal antibody is a category 1 recommendation for patients unable to tolerate purine analogs or those with significant comorbidities or aged ≥ 65 years

Lymphomas

- For relapsed/refractory disease in patients without del(17p), ibrutinib monotherapy and the combination of idelalisib plus rituximab are both category 1 preferred regimens for frail patients as well as those < 65 years without significant comorbidities
- Venetoclax plus rituximab is also now considered a category 1 preferred regimen in this setting
- For CLL patients with the del (17p) cytogenetic mutation, ibrutinib is preferred for first-line treatment (category 1)
- For the treatment of relapsed/refractory disease in patients with del17p, ibrutinib or venetoclax (with or without rituximab), and idelalisib plus rituximab are all considered preferred regimens

Lymphomas

FL

- The NCCN guidelines list chlorambucil, with or without rituximab (both category 2A) as a first- or second-line or subsequent therapy option for the elderly or infirm patients
- Lenalidomide plus rituximab is a preferred regimen in the first-line setting (category 2B), and is a 2A recommendation in second-line and subsequent therapy
- Idelalisib is a second-line or subsequent therapy option (category 2A) for patients who are refractory to both alkylating agents and rituximab

Lymphomas

MCL

- NCCN guidelines indicate that lenalidomide plus rituximab (category 2A) is one of several regimens that may be utilized for induction therapy when a less aggressive regimen is indicated
- Ibrutinib plus rituximab may be utilized as a pretreatment to a modified rituximab- HyperCVAD regimen in patients > 65 years
- Preferred regimens for second-line therapy include lenalidomide with or without rituximab, ibrutinib with or without rituximab, acalabrutinib, or venetoclax (all category 2A)
- Combination ibrutinib, lenalidomide, and rituximab is a category 2B recommendation in the second-line therapy

Lymphomas

MZL

- Lenalidomide plus rituximab is a NCCN category 2B, preferred recommendation for first-line therapy
- For elderly or infirm patients, chlorambucil with or without rituximab may also be utilized in the first-line setting (category 2A)
- Both lenalidomide with or without rituximab and ibrutinib as a single agent are NCCN category 2A recommendations for second and subsequent-line therapy
- Idelalisib may be also used in the second and subsequent line treatment in patients who are refractory to both alkylators and rituximab (category 2B)

Lymphomas

Cutaneous T cell Lymphoma (CTCLs)

- A group of NHLs that primarily develop in the skin and sometimes progress to involve lymph nodes, blood, and visceral organs
- The 4.2018 NCCN guidelines recommend vorinostat for patients requiring systemic therapy

Lymphomas

Dermatofibrosarcoma protuberans

- The 1.2018 NCCN guidelines now only include imatinib for recurrence or metastatic disease; however, tumors lacking the t(17;22) translocation may not respond to imatinib

- There are currently no U.S. treatment guidelines for aggressive systemic mastocytosis, erythema nodosum leprosum, hypereosinophilic syndrome, or chronic eosinophilic leukemia

Lymphomas

Gastrointestinal Stromal Tumors (GIST)

- The 2.2018 NCCN guidelines for soft tissue sarcomas recommend imatinib for patients with GIST that is unresectable, recurrent, metastatic, or postoperatively for patients with GIST who have been completely resected but have a significant risk of recurrence (category 1)

- Imatinib may also be utilized in patients with persistent gross residual disease after surgery (category 2A)

Lymphomas

Chronic Graft versus Host Disease (cGVHD)

- Corticosteroids are most commonly the initial systemic therapy choice for most patients with moderate to severe cGVHD
- Ibrutinib is the first drug approved for cGVHD in patients who have failed at least 1 systemic treatment

Lymphomas

Multiple Myeloma (MM)

- Preferred regimens for initial therapy in transplant eligible patients are bortezomib/lenalidomide/dexamethasone (category 1) and bortezomib/cyclophosphamide/dexamethasone (category 2A)

- Other regimens that may be considered include carfilzomib/lenalidomide/dexamethasone (category2A), ixazomib/enalidomide/dexamethasone (category 2B) and bortezomib/doxorubicin/dexamethasone (category 1)

- Lenalidomide/dexamethasone may be useful in certain circumstances (category 1) as well as bortezomib plus dexamethasone with or without thalidomide (both category 1), cyclophosphamide/lenalidomide dexamethasone (category 2A), or the VTD-PACE regimen consisting of dexamethasone/thalidomide/cisplatin/doxorubicin/ cyclophosphamide/etoposide/bortezomib (category 2A)

Lymphomas

- For non-transplant eligible patients, the following combination regimens are all designated preferred, category 1 NCCN recommendations as primary therapy: bortezomib/lenalidomide/dexamethasone, lenalidomide/low-dose dexamethasone, bortezomib/cyclophosphamide/dexamethasone and daratumumab/bortezomib/melphalan/prednisone

- Other regimens that may be utilized include ixazomib/lenalidomide/dexamethasone, carfilzomib/lenalidomide/dexamethasone, or carfilzomib/cyclophosphamide/dexamethasone (all category 2A)

Lymphomas

- Single-agent lenalidomide is the preferred oral drug treatment for maintenance therapy of MM (category 1); bortezomib is listed as an additional possible option (category 2A).

- For the treatment of progressive or relapsed myeloma, preferred regimens include combination lenalidomide/dexamethasone along with bortezomib (category 2A), daratumumab, carfilzomib, elotuzumab, or ixazomib (all category 1)

- Additional preferred regimens include carfilzomib/dexamethasone and daratumumab/bortezomib/dexamethasone (both category 1)

- Panobinostat/bortezomib/dexamethasone is not listed as a preferred regimen but does have a NCCN category 1 rating

Lymphomas

Myelodysplastic Syndromes

- Patients with the chronic myelomonocytic leukemia (CMML) subtype and with a platelet derived growth factor beta (PDGFRβ) gene rearrangement may respond well to treatment with imatinib

- The del (5q) syndrome has a relatively good prognosis and is highly responsive to lenalidomide therapy

Lymphomas

Myelofibrosis (MF)

- One of the major diagnostic criteria is the presence of a pathogenetic mutation such as JAK2
- According to the 2.2018 NCCN guidelines, treatment with ruxolitinib is recommended for low- or intermediate-risk MF patients who are symptomatic, or high-risk MF patients who are not transplant candidates and have a platelet count > 50K (all category 2A)

Lymphomas

Waldenström's Macroglobulinemia/ lymphoplasmacytic lymphoma (WM/LPL)

- The 1.2018 NCCN guideline recommends treating only those patients who are symptomatic

- Ibrutinib is listed as an option for primary treatment (category 2A) and for use in patients who have received previous therapies (preferred, category 2A)

Ophthalmics, Anti-Inflammatory/Immunomodulator

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Ophthalmics, Anti-Inflammatory/Immunomodulator

PRODUCT LIST AND FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication
cyclosporine emulsion (Restasis®, Restasis Multidose™)	Allergan	Increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca
cyclosporine solution* (Cequa™)	Sun	Increase tear production in patients with keratoconjunctivitis sicca (dry eye)
lifitegrast (Xiidra™)	Shire	Treatment of signs and symptoms of dry eye disease in adults

* Cequa (cyclosporine) was approved under the United States (US) Food and Drug Administration (FDA) 505(b)(2) pathway that allows at least some data submitted for approval to be from studies not conducted by or for the applicant.

Ophthalmics, Anti-Inflammatory/Immunomodulator

- Dry eye disease (DES)/ Keratoconjunctivitis sicca (KCS) affects approximately 10% to 30% of the US population and occurs more commonly in patients over 40 years of age and in postmenopausal women

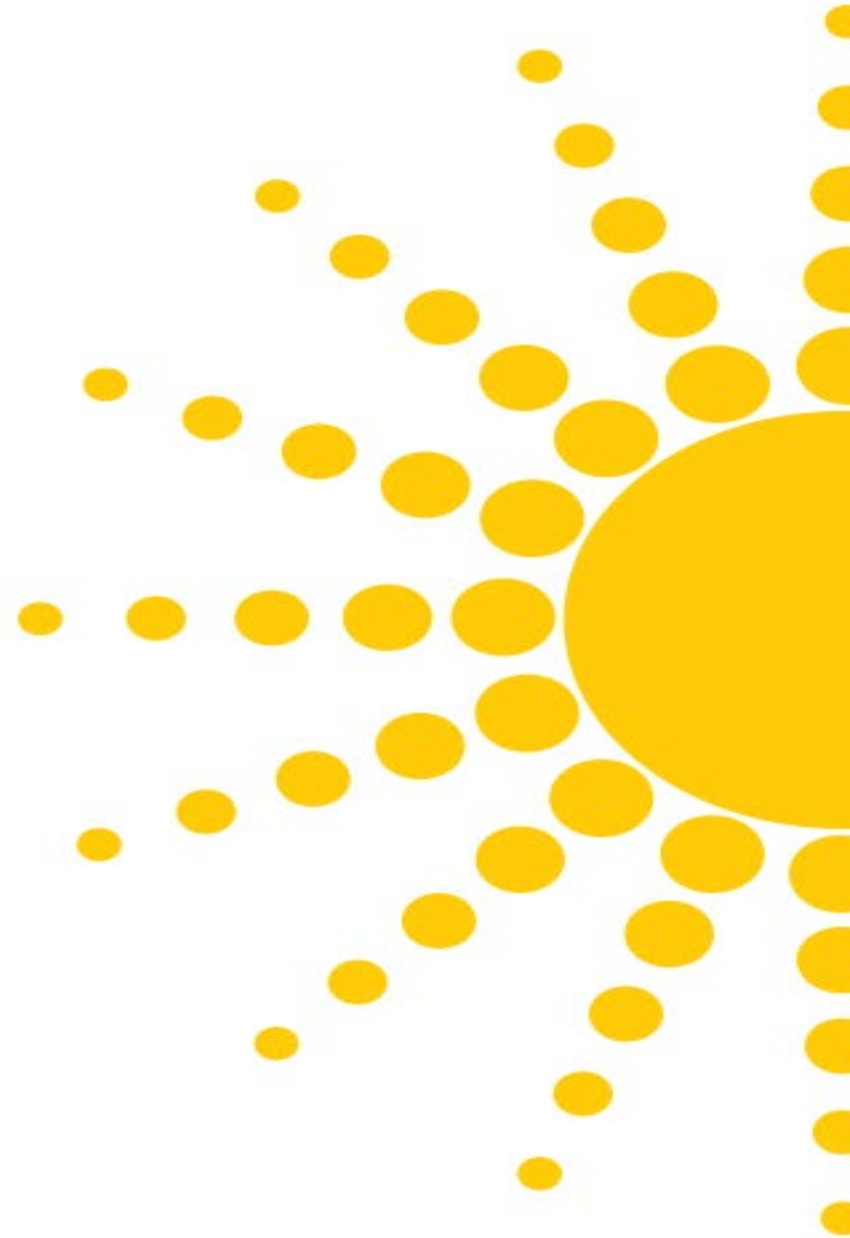
- According to the 2018 Preferred Practice Parameter on dry eye syndrome and the 2018 Cornea/External Disease Summary Benchmark from the American Academy of Ophthalmology (AAO), artificial tear substitutes are recommended for mild DES

- Recommended measures for moderate dry eyes include use of anti-inflammatory agents, such as topical cyclosporine, Xiidra, topical corticosteroids, or systemic omega-3 fatty acids supplements, along with artificial tears

Ophthalmics, Anti-Inflammatory/Immunomodulator

- For severe dry eye, in addition to the above-mentioned treatments, systemic cholinergics, systemic anti-inflammatories, mucolytic agents, autologous serum tears, contact lenses, permanent punctal occlusion, and tarsorrhaphy are recommended
- No clinical trials have been published comparing any of the 3 agents in this class, but all have demonstrated efficacy against vehicle
- Significant adverse effects are similar between the 3 agents in this class

Otic Antibiotics



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Otic Antibiotics

PRODUCT LIST AND FDA-APPROVED INDICATIONS

Drug Name	Manufacturer	Indication(s)
ciprofloxacin (Cetraxal®)	generic, Wraser	▪ Acute otitis externa due to susceptible isolates of *Pseudomonas aeruginosa* or *Staphylococcus aureus* in pediatrics (age 1 year and older) and adults
ciprofloxacin/dexamethasone (Ciprodex® Otic)	Alcon	▪ Acute otitis media in pediatric patients (age 6 months and older) with tympanostomy tubes ▪ Acute otitis externa in pediatric (age 6 months and older), adult, and elderly patients
ciprofloxacin/fluocinolone acetonide (Otovel®)	Arbor	▪ Acute otitis media in pediatric patients (age 6 months and older) with tympanostomy tubes due to *S. aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *P. aeruginosa*
ciprofloxacin/hydrocortisone (Cipro HC® Otic)	Alcon	▪ Acute otitis externa in adult and pediatric patients (1 year and older) due to *P. aeruginosa, S. aureus,* and *Proteus mirabilis*

Otic Antibiotics

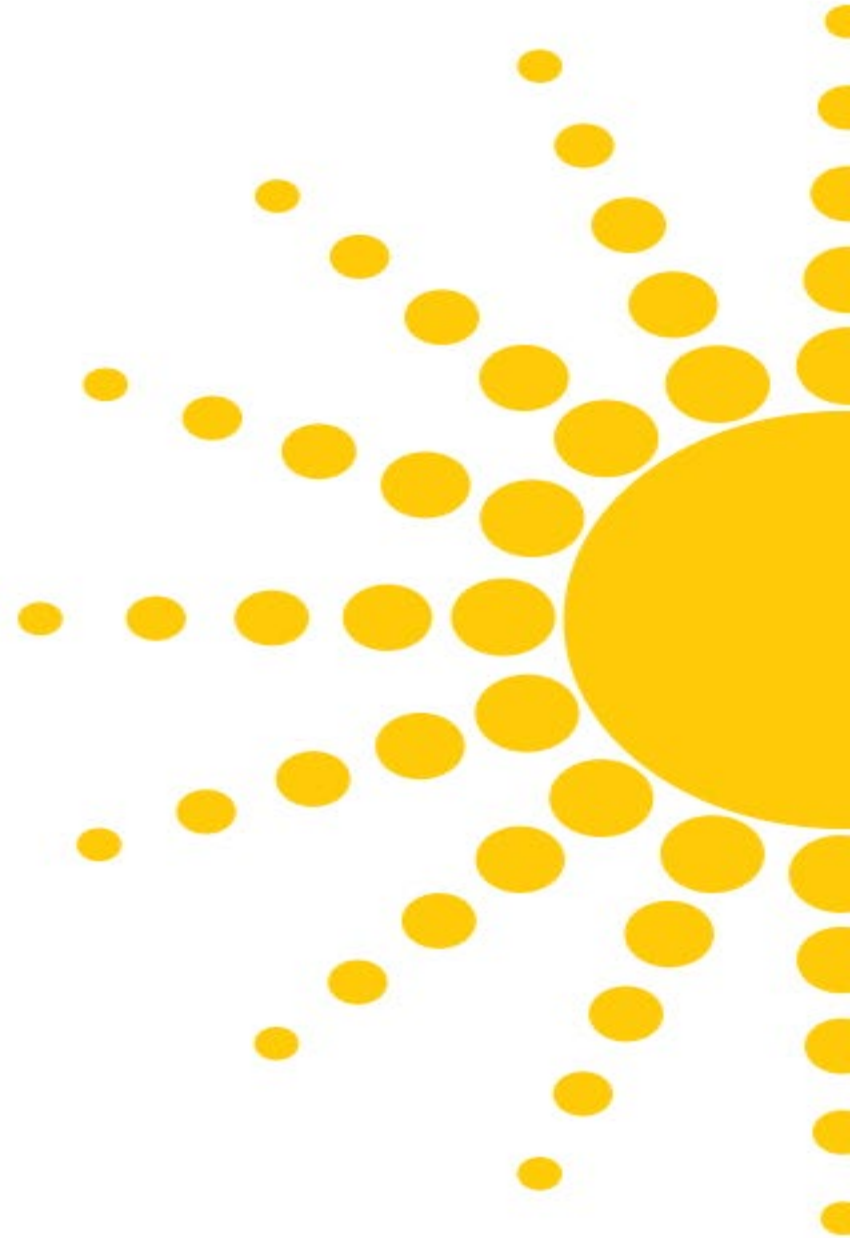
neomycin sulfate/colistin sulfate/ thonzonium bromide/ hydrocortisone (Coly-mycin® S)	Endo	▪ Treatment of superficial bacterial infections of the external auditory canal in adult and pediatric patients (1 year and older) ▪ Treatment of infections of mastoidectomy and fenestration cavities in adult and pediatric patients (1 year and older)
neomycin sulfate/polymyxin B/ hydrocortisone	generic	▪ Treatment of superficial bacterial infections of the external auditory canal in adults and pediatric patients (2 years and older)
ofloxacin	generic	▪ Otitis externa in adults and pediatric patients (6 months and older) due to *Escherichia coli, P. aeruginosa*, and *S. aureus* ▪ Chronic suppurative otitis media in patients 12 years and older with perforated tympanic membranes due to *P. mirabilis, P. aeruginosa,* and *S. aureus* ▪ Acute otitis media in pediatric patients (1 year and older) with tympanostomy tubes due to *H. influenzae, M. catarrhalis, P. aeruginosa, S. aureus,* and *S. pneumoniae*

Otiprio® (ciprofloxacin 6%) otic suspension is not included in this review but was FDA-approved in December 2015 and is administered by a health care professional. Indications are for the treatment of bilateral otitis media with effusion in patients ≥ 6 months of age undergoing tympanostomy tube placement and for the treatment of acute otitis externa due to *P. aeruginosa* or *S. aureus* in patients ≥ 6 months of age.

Otic Antibiotics

- The American Academy of Otolaryngology – Head and Neck Surgery Foundation (AAO-HNSF) 2014 guidelines for the management of acute otitis externa (AOE) in patients over 2 years of age recommend topical preparations for initial therapy of diffuse, uncomplicated AOE
- A topical aminoglycoside combined with a second antibiotic and a topical steroid is commonly prescribed to treat AOE
- While the addition of a corticosteroid may be of benefit in reducing inflammation, some consider the use of corticosteroids unnecessary
- For chronic suppurative otitis media (CSOM), aminoglycosides or fluoroquinolones can be used
- Aminoglycosides are not recommended to be used if the tympanic membrane is perforated; fluoroquinolones are not associated with ototoxicity, and ofloxacin is considered safe in cases of a perforated tympanic membrane

Pulmonary Arterial Hypertension (PAH) Agents, Oral and Inhaled



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PAH Agents, Oral and Inhaled

PRODUCT LIST AND FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Oral Agents		
ambrisentan (Letairis®)	Gilead	Treatment of pulmonary arterial hypertension (World Health Organization [WHO] Group I) to improve exercise ability and delay clinical worsening In combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability
bosentan (Tracleer®)	Actelion	Treatment of pulmonary arterial hypertension (WHO Group I) in patients with WHO Class II to IV symptoms, to improve exercise ability and decrease clinical worsening Treatment of idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR) in pediatric patients age 3 years and older which is expected to result in an improvement in exercise ability
macitentan (Opsumit®)	Actelion	Treatment of pulmonary arterial hypertension (WHO Group I) to delay disease progression which includes death, initiation of intravenous (IV) or subcutaneous (SC) prostanoids, or clinical worsening; Opsumit also reduced hospitalization for PAH
riociguat (Adempas®)	Bayer	Persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) (WHO Group IV) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class Pulmonary arterial hypertension (WHO Group I) to improve exercise capacity, improve WHO functional class and to delay clinical worsening

PAH Agents, Oral and Inhaled

selexipag (Uptravi®)	Actelion	Treatment of pulmonary arterial hypertension (WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH
sildenafil (Revatio®)	generic, Pfizer	Treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and delay clinical worsening
tadalafil (Adcirca®)	Eli Lilly, Mylan	Treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability
treprostinil (Orenitram®)	United Therapeutics	Treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise capacity
Inhalation Agents		
iloprost (Ventavis®)	Actelion	Treatment of pulmonary arterial hypertension (WHO Group I) to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration
treprostinil (Tyvaso®)	United Therapeutics	Treatment of pulmonary arterial hypertension (WHO Group I) to increase exercise ability

PAH Agents, Oral and Inhaled

- The treatment for pulmonary arterial hypertension (PAH) is complex
- 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
- The 2018 updated American College of Chest Physicians (CHEST) guidelines on therapy for PAH in adults provide treatment recommendations based on World Health Organization (WHO) functional class (FC) for patients who are not candidates for, or who have failed, high-dose oral calcium channel blocker (CCB) therapy

PAH Agents, Oral and Inhaled

- In treatment-naïve patients with WHO FC II or WHO FC III without rapid disease progression or poor prognosis, initial combination therapy with Letairis and tadalafil is suggested
- Monotherapy with Letairis, Tracleer, sildenafil, Opsumit, tadalafil, or Adempas is considered an alternative in patients who are unwilling to take or cannot tolerate combination therapy
- For treatment-naïve patients with WHO FC IV, initial therapy with a parenteral prostanoid agent is recommended
- If the patient cannot comply with parenteral administration, an inhaled prostanoid in combination with an oral endothelin receptor antagonist (ERA) or an oral phosphodiesterase type-5 (PDE-5) inhibitor is recommended

PAH Agents, Oral and Inhaled

- If symptoms still remain during treatment with an oral ERA or PDE-5 inhibitor, addition of an inhaled prostanoid is suggested
- In patients with WHO FC III and continued disease progression while on oral mono- or combination therapy, addition of a parenteral or inhaled prostanoid may be considered
- In patients with WHO FC III or IV and an inadequate response to initial therapy with mono- or combination therapy, a second or third class of PAH agents should be added
- The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) 2015 recommendations for the diagnosis and treatment of pulmonary hypertension include Uptravi as an option for monotherapy or in combination with an ERA and/or PDE-5 inhibitor in patients with WHO FC II or III
- ESC/ERS also include oral Orenitram as an option for monotherapy for WHO FC III

Thrombopoiesis Stimulating Proteins

Thrombopoiesis Stimulating Proteins

PRODUCT LIST AND FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
avatrombopag (Doptelet®)	Akarx/Dova	Treatment of thrombocytopenia in adult patients with chronic liver disease (CLD) who are scheduled to undergo a procedure
eltrombopag (Promacta®)	Novartis	Treatment of thrombocytopenia in adult and pediatric patients ≥ 1 year of age with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy ▪ Eltrombopag should only be used in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding Treatment of thrombocytopenia in patients with chronic hepatitis C (HCV) to allow the initiation and maintenance of interferon-based therapy ▪ Eltrombopag should be used only in patients with chronic HCV whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy ▪ Safety and efficacy have not been established in combination with direct acting antiviral agents approved for treatment of chronic HCV infection In combination with standard immunosuppressive therapy for first-line treatment of adult and pediatric patients ≥ 2 years of age with severe aplastic anemia Treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy Eltrombopag is *not* indicated for the treatment of myelodysplastic syndrome (MDS)

Thrombopoiesis Stimulating Proteins

fostamatinib disodium hexahydrate (Tavalisse™)	Rigel	Treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment
lusutrombopag (Mulpleta®)	Shionogi	Treatment of thrombocytopenia in adult patients with CLD who are scheduled to undergo a procedure
romiplostim (Nplate®)	Amgen	Treatment of thrombocytopenia in patients with chronic ITP who have failed to achieve an adequate response with corticosteroids, immunoglobulins, or splenectomy ▪ Romiplostim should only be used in patients with ITP whose degree of thrombocytopenia and clinical condition increases their risk for bleeding ▪ Romiplostim is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP ▪ Romiplostim should not be used in an attempt to normalize platelet counts

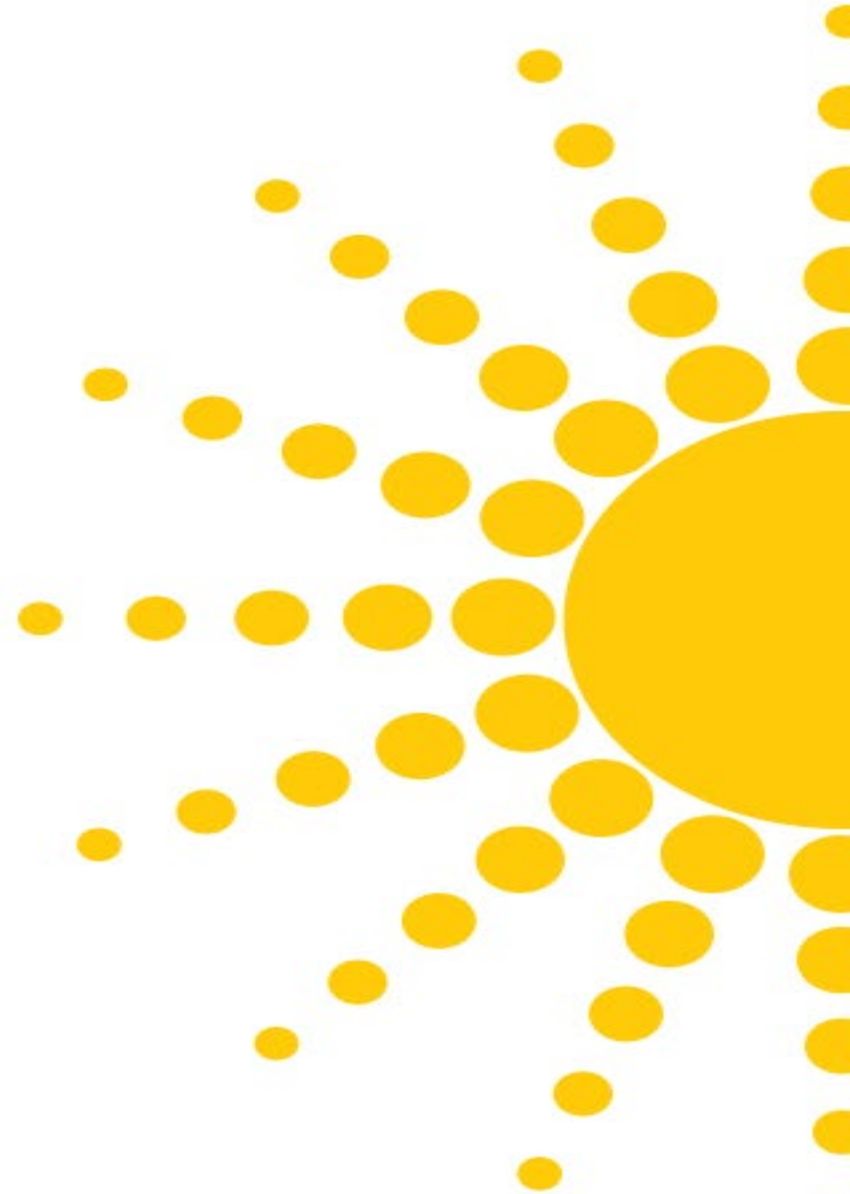
Thrombopoiesis Stimulating Proteins

- Thrombocytopenia occurs in 64% to 84% of patients chronic liver disease (CLD) with cirrhosis or fibrosis and approximately 6% of CLD patients without cirrhosis
- Per the 2010 international consensus report on primary immune thrombocytopenia (ITP) that provided a review of updated therapies for the management of ITP, corticosteroids, particularly prednisone, continue to be first-line therapy for the treatment of ITP in adults
- Second-line therapies include azathioprine, cyclophosphamide, cyclosporine, danazol, dapsone, mycophenolate mofetil, rituximab, splenectomy, thrombopoietin agonists, and vinca alkaloids
- The 2011 ASH evidence-based practice guidelines for the management of immune thrombocytopenia also recommends corticosteroids (such as prednisone)
- Either IVIG or anti-D may be used as a first-line therapy if corticosteroids are contraindicated (grade 2C)

Thrombopoiesis Stimulating Proteins

- Thrombopoietin receptor agonists may be considered for patients at risk for bleeding who have failed at least 1 other therapy and who relapse after splenectomy or have a contraindication to splenectomy (grade 1B)
- Thrombopoietin receptor agonists may also be considered in patients at risk for bleeding who have not had a splenectomy and who have failed a corticosteroid or IVIG (grade 2C)
- Pharmacotherapy for aplastic anemia includes immunosuppressive agents, hematopoietic growth factors, and fludarabine. Promacta is also indicated to treat first-line and refractory severe aplastic anemia (including in pediatric patients), but it carries a boxed warning regarding the increased risk for hepatic decompensation and death when used in combination with interferon and ribavirin
- Monotherapy with hematopoietic growth factors is not recommended for newly diagnosed patients

Executive Session



Public Therapeutic Class Votes

Butalbital/APAP/Caffeine Tablets and Capsules
FDA Daily Maximum Dosage – 6 capsules per day

P&T Meeting Dates

- **2019 Meeting Dates:**
  - May 23, 2019

- **2020 Meeting Dates:**
  - January 22, 2020
  - May 19 and 29, 2020
  - October 14, 2020