CPE Session 5

Top Ten New Drugs

Friday, 2:15 pm - 3:45 pm

ACPE: #0128-0000-16-326-L01-P/T  0.15 CEUs/1.5 Hours  Knowledge-Based Activity

Learning Objective for Pharmacists and Pharmacy Technicians:
Upon completion of this CPE activity, participants should be able to:
1. Identify top ten new drugs.
2. Describe each drug’s role in therapy.

PharmD Candidate Speakers:
Elizabeth Dudley, University of Nebraska Medical Center College of Pharmacy
Allisha Gabriel, Creighton University School of Pharmacy & Health Professions
Erin Buse, University of Nebraska Medical Center College of Pharmacy
Sarah Bailey, University of Nebraska Medical Center College of Pharmacy
Brittany League, Creighton University School of Pharmacy & Health Professions
Taylor Pick, Creighton University School of Pharmacy & Health Professions
Hailey Soukup, Creighton University School of Pharmacy & Health Professions
Jarred Vogel, University of Nebraska Medical Center College of Pharmacy
Megan Wachter, Creighton University School of Pharmacy & Health Professions
Christopher Zaleski, University of Nebraska Medical Center College of Pharmacy

Speaker Disclosure: None of the speakers have any relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This CPE activity will not include a discussion of non-FDA approved (off-label) medication use.
Briviact
(brivaracetam)
Elizabeth Dudley
Pharm.D. Candidate Class of 2017
University of Nebraska-Medical Center
College of Pharmacy

Speaker Disclosure

- Elizabeth Dudley has no relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This information will not include a discussion of non-FDA approved (off-label) medication use.

Learning Assessment
The most common adverse effects associated with Brivaracetam therapy include (select all that apply):
- Dizziness
- Fatigue
- Hypotension
- Nausea and Vomiting
- Drowsiness

Indication

- FDA Approved Indication:
  - Adjunctive therapy in the treatment of partial-onset seizures in adults and adolescents 16 years of age and older with epilepsy
- FDA approved February 19, 2016
- Currently no unapproved uses

Epilepsy

- A brain disorder causing recurrent seizures
- Seizure - an episode of relatively short duration of abnormal brain activity
  - Symptoms include uncontrolled movements or spasms, abnormal thinking and behavior and abnormal sensations
  - Violent muscle spasms, loss of consciousness
  - Occur when neurons undergo uncontrolled activation
  - Partial onset seizures begin in limited areas of the brain

Epilepsy (continued)

- Possible causes:
  - Stroke
  - Infection
  - Tumors
  - TBI
  - Abnormal brain development
- 5.1 million people in US with history of epilepsy
- 2.9 million people have active epilepsy
Mechanism of Action

- Highly selective affinity for synaptic vesicle protein 2A (SV2A) in the brain
  - Responsible for antiepileptic effect
  - 15 to 30 fold increased affinity for SV2A vs. levetiracetam
- Inhibitory activity at neuronal voltage-dependent sodium channels

Pharmacokinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>100% bioavailability</td>
</tr>
<tr>
<td>Distribution</td>
<td>0.5 L/kg</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic and extrahepatic inactive metabolites</td>
</tr>
<tr>
<td>Excretion</td>
<td>&gt;95% renally excreted</td>
</tr>
</tbody>
</table>

- Elimination half life: 9 hours
- Time to peak concentration: 1 hour (oral)

Dosing

- Initial: 50mg twice daily
  - May decrease to 25mg twice daily or increase up to 100mg twice daily based on individual patient response and tolerability
- Maximum dose: 200mg/day

Special Populations

- Pediatric
  - Only indicated for 16 years and older
- Hepatic Impairment
  - Mild to severe Child Pugh classes A, B and C
    - 25mg twice daily
    - Maximum 75mg twice daily
- Renal Impairment
  - Has not been studied in end-state renal disease requiring dialysis

Contraindications

- Hypersensitivity to brivaracetam or any components of the formulation

Precautions

- CNS depression
  - Risk greatest early in treatment
  - Caution driving or operating machinery
  - Impaired coordination, abnormal gait, fatigue, dizziness and somnolence
- Hematologic effects have been reported
  - Decreased WBC and neutrophil count
- Avoid abrupt discontinuation due to possibility of increased seizure frequency
Adverse Reactions

- The most common:
  - Drowsiness
  - Dizziness
  - Fatigue
  - Nausea and vomiting

- The most severe:
  - Thoughts about suicide
  - Attempts to commit suicide
  - Feelings of agitation
  - New or worsening depression
  - Aggression
  - Panic attacks

Drug-Drug Interactions

- Inhibition of epoxide hydroxylase
  - ↑ plasma concentration of phenytoin
  - ↑ plasma concentration of active metabolite of carbamazepine

- Inhibits CYP2C19
  - CYP2C19 inducers: phenytoin, phenobarbital, rifampin, carbamazepine, prednisone
    - ↓ plasma concentration of brivaracetam

- Rifampin
  - Increase brivaracetam dosage by up to 100% ie. double the dose

Price

<table>
<thead>
<tr>
<th>Dosage Strength</th>
<th>Wholesale Acquisition Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>25mg tab #60</td>
<td>$910.00</td>
</tr>
<tr>
<td>50mg tab #60</td>
<td>$910.00</td>
</tr>
<tr>
<td>75mg tab #60</td>
<td>$910.00</td>
</tr>
<tr>
<td>100mg tab #60</td>
<td>$910.00</td>
</tr>
</tbody>
</table>

Place in therapy

- Add on therapy in adult patients experiencing partial-onset focal seizures uncontrolled by 1 to 2 antiepileptic drugs including carbamazepine, lamotrigine and valproate
- Does not appear to add benefit in patients currently taking levetiracetam

Additional information

- Most common reason patients stopped taking the medication
  - Psychiatric disorders
- Use in combination with levetiracetam decreased effect of brivaracetam

Learning Assessment

The most common adverse effects associated with Brivaracetam therapy include (select all that apply):

a) Dizziness
b) Fatigue
c) Hypotension
d) Nausea and Vomiting
e) Drowsiness
References


• Petz G. Epilepsy. 2016.

**Entresto**  
*sacubitril/valsartan*

Allisha Gabriel  
Pharm.D. Candidate class of 2017  
Creighton University School of Pharmacy

---

**Learning Assessment**

Which two drug classes should Entresto NOT be combined with?

– ACEI  
– Beta Lactam Antibiotics  
– Angiotensin Receptor II Antagonists  
– SSRI’s

---

**Speaker Disclosure**

• Allisha Gabriel has no relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This information will not include a discussion of non-FDA approved (off-label) medication use.

---

**Indication**

• Entresto (sacubitril/valsartan) is indicated to reduce the risk of cardiovascular death and hospitalization in patients with NYHA Class II-IV chronic heart failure and reduced ejection fraction  
• There are currently no unapproved uses  
• Entresto is usually used in conjunction with other heart failure therapies; in place of an ACEI or ARB

---

**Overview of Heart Failure**

• Chronic, progressive condition in which the heart isn’t able to pump enough blood to meet the body’s need for blood and oxygen  
• Risk Factors include:  
  – Hypertension, hyperlipidemia, smoking, diabetes, obesity, poor diet, physical inactivity, excessive alcohol use

---

**Drug Formulation**

• Entresto (sacubitril/valsartan) is available in three strengths  
  – 24mg/26mg tablet  
  – 49mg/51mg tablet  
  – 97mg/103mg tablet
Mechanism of Action

- **Sacubitril**
  - Neprilysin inhibitor
  - Degrades endogenous vasoactive peptides through active metabolite LBQ657

- **Valsartan**
  - Angiotensin II receptor blocker at the AT1 receptor subtype
  - Angiotensin II is a vasoconstrictor, and stimulates production of aldosterone

How it Works

http://www.entresto.com/info/how-entresto-works.jsp

Pharmacokinetics

- **Sacubitril Valsartan**
  - Peak Concentration: 0.5 hours- Sacubitril 2 hours- LBQ657 1.5 hours
  - Volume of Distribution: 103 L 75 L
  - Metabolism: Sacubitril converted to active LBQ657 ~20%
  - Excretion in Urine: 52-68% 13%
  - Half Life: 1.4 hours- Sacubitril 11.5 hours- LBQ657 9.9 hours

Dosing

- **Starting dose in patients not treated with ACEI or ARB**: initiate at sacubitril 24mg/ valsartan 26mg by mouth twice daily
  - Double dose every 2-4 weeks to target dose of sacubitril 97mg/valsartan 103mg by mouth twice daily
- **Max dose in adults and geriatric patients**: sacubitril 97mg/ valsartan 103mg by mouth twice daily

Conversion from ACEI to Entresto

- Allow 36 hours after last dose of ACEI before beginning Entresto
- **Starting dose in patients previously treated with ACEI or ARB**: sacubitril 49mg/ valsartan 51mg tablet by mouth twice daily.
  - After 2-4 weeks, increase to target dose of sacubitril 97mg/ valsartan 103mg by mouth twice daily

Special Populations

- **Hepatic Impairment**
  - Mild impairment- no dosage adjustment needed
  - Moderate impairment- Initiate therapy at 24mg/26mg PO twice daily
  - Severe impairment- not recommended
- **Renal Impairment**
  - eGFR<30: initiate 24mg/26mg PO twice daily and double every 2-4 weeks until target dose
Contraindications

- Black Box Warning for use during Pregnancy
- Contraindications
  - Patients with hypersensitivity to any component
  - History of ACEI induced angioedema

Precautions

- Precautions
  - Patients with hypovolemia, signs of hypotension
  - Patients with risk factors for hyperkalemia
  - Severe hepatic disease
  - Breast feeding not recommended

Adverse Reactions

- Most Common Adverse Reactions
  - Hyperkalemia (12%)
  - Hypotension (18%)
  - Cough (9%)
  - Dizziness (6%)
- Most Severe Adverse reactions
  - Hyperkalemia (12%)
  - Renal Failure (5%)
  - Angioedema (<1%)

Drug-Drug Interactions

- Aliskiren
- Angiotensin II receptor antagonists
- ACEI
- Dasabuvir, Ombitasivir, Paritaprevir, Ritonavir
- Eltrombopag
- Lithium
- NSAIDS
- Potassium Sparing Diuretics

Price

- The wholesale acquisition cost for Entresto is about $12.50 per day

<table>
<thead>
<tr>
<th>Number of pills</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 pills</td>
<td>$375</td>
</tr>
<tr>
<td>180 pills</td>
<td>$1125</td>
</tr>
<tr>
<td>Blister packs of 100</td>
<td>$625</td>
</tr>
</tbody>
</table>

Place in therapy

- Entresto should be used in chronic heart failure patients with NYHA class II-IV heart failure and reduced ejection fraction
- Entresto should be used in place of an ACEI or ARB
- Entresto may be combined with other heart failure therapies
Additional information

• Entresto can be taken with or without food
• Patients should stay well hydrated on Entresto

Learning Assessment

Which two drug classes should Entresto NOT be combined with?

A. ACEI
B. Beta Lactam Antibiotics
C. Angiotensin Receptor II Antagonists
D. SSRI’s

References

Genvoya
(elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide)
Erin Buse
Pharm.D. Candidate class of 2017
University of Nebraska Medical Center
College of Pharmacy

Learning Assessment
What disease is Genvoya indicated for?
A. HIV-2
B. Hepatitis B
C. HIV-1
D. A and C
E. All of the above

Speaker Disclosure
• Erin Buse has no relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This information will not include a discussion of non-FDA approved (off-label) medication use.

Indication
• GENVOYA (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) is indicated as complete regimen for the treatment of HIV-1 infection in patients 12 years and older
• FDA approved November 5, 2015
• There are currently no unapproved uses

Overview of HIV-1
• HIV-1 stands for Human Immunodeficiency Virus-1 and if left untreated can develop into AIDS (Acquired Immunodeficiency Syndrome)
• HIV attacks your CD4 cells (T cells)
  – CD4 cells helps the immune system fight off infections
• HIV reduces your CD4 counts and makes you more likely to develop atypical infections

Stages of HIV
• Acute Infection
  – Produce large amounts of virus
  – “worst flu ever”
• Clinical latency
  – Produce low levels of virus
  – Produce no symptoms and last decades
• AIDS
  – CD4 < 200 cells/mm3
  – People typically survive 3 years
The HIV Life Cycle

Drug Formulation

- Oral tablet combination of four medications:
  - Elvitegravir 150 mg
  - Cobicistat 150 mg
  - Emtricitabine 200 mg
  - Tenofovir Alafenamide (TAF) 10 mg

Image source: Gilead Sciences

Mechanism of Action

- Elvitegravir
  - HIV-1 integrase inhibitor, which is required for viral replication
- Cobicistat
  - CYP3A4 inhibitor
  - Pharmacokinetic enhancer of Elvitegravir
- Emtricitabine
  - HIV-1 reverse transcriptase inhibitor, necessary enzyme for viral replication
- Tenofovir Alafenamide (TAF)
  - Prodrug of Tenofovir
  - Competitive inhibitor of DNA- and RNA-directed reverse transcriptase

Pharmacokinetics

- See Genvoya package insert absorption table

Pharmacokinetics

- See Genvoya package insert distribution and metabolism tables

Pharmacokinetics

- See Genvoya package insert elimination table
**Dosing**

- Recommended and Max dosing
  - 1 tablet once daily with food

**Special Populations**

- Pregnancy: Use if benefit outweighs risk
- Nursing: Not to breastfeed due to the potential for HIV transmission
- Pediatric
  - 12 years and ≥ 35 Kg: 1 tablet/day
  - < 12 years and < 35 Kg: Safety and Efficacy not established
- Geriatric
  - 1 tablet/day

**Special Populations**

- Hepatic Impairment
  - No dose adjustment needed for mild or moderate impairment
  - Child-Pugh Class A and B
  - Not recommended with people with severe impairment
  - Child-Pugh Class C
- Renal Impairment
  - CrCl ≥ 30 mL/min: No dose adjustment needed
  - CrCl < 30 mL/min: Safety and efficacy is not established

**Contraindications**

- Medications that are highly dependent of CYP3A4 metabolism and are associated with severe or life-threatening events
  - Ex: lovastatin, simvastatin, alfuzosin, ergotamine, cisapride, triazolam, and sildenafil
- Strong CYP3A inducers
  - Ex: rifampin, carbamazepine, phenytoin, and phenobarbital
- Avoid administering to patients with CrCl < 30 mL/min

**Precautions**

- Lactic acidosis/Severe Hepatomegaly with Stenosis
  - Risk factors: Obesity and prolonged nucleoside exposure
- Patients coinfected with HIV-1 and HBV
  - Genvoya not approved for treatment of HBV
- Loss of virological response due to drug interactions

**Precautions**

- Avoid use with other antivirals
- New onset or worsening renal impairment
- Bone loss and mineralization effects
- Fat redistribution
Adverse Reactions

- The most common:
  - Nausea (10%)
  - Diarrhea (7%)
  - Fatigue (5%)
  - Headache (6%)

- The more severe:
  - Renal failure (<1%)
  - Hypercholesteremia (2%)
  - Immune Reconstitution Syndrome

Drug-Drug Interactions

- Acid reducing agents ↓ Elvitegravir
- Antiarrhythmics
  - ↑ digoxin and amiodarone
- Antibacterials
  - ↑ clarithromycin and telithromycin
- Anticonvulsants
  - ↑ ethosumixide
  - ↓ elvitegravir, cobicistat, and TAF
- Antidepressants
  - ↑ SSRIs except sertraline
  - ↑ TCAs
  - ↑ trazadone
- Antifungals
  - ↑ elvitegravir, cobicistat, itraconazole, ketoconazole, and voriconazole

Drug-Drug Interactions

- Calcium channel Blockers
  - ↑ amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil
- Corticosteroid
  - Systemic: dexamethasone
  - ↑ elvitegravir and cobicistat
- Anti-gout
  - ↑ Colechicine
- Antipsychotics
  - ↑ quetiapine
- Benzodiazepines
  - ↑ diazepam and midazolam
- Beta-blockers
  - ↑ metoprolol and timolol
- Endothelin Receptor Antagonists
  - ↑ bosentan
- HMG-CoA Reductase inhibitors
  - ↑ atorvastatin
- Immunosuppressants
  - ↑ cyclosporine, sirolimus, and tacrolimus
  - ↑ elvitegravir and cobicistat
- Narcotics
  - ↑ buprenorphine
  - ↑ naltrexone
- Neuroleptics
  - ↑ perphenazine
  - ↑ risperidone
  - ↑ thioridazine
- Phosphodiesterase-5 inhibitors
  - ↑ sildenafil
  - ↑ tadalafil
  - ↑ vardenafil

Drug-Drug Interactions

- Inhaled Beta Agonists
  - ↑ Salmeterol
- Neurontics
  - ↑ perphenazine
  - ↑ risperidone
  - ↑ thioridazine

Drug-Drug Interactions

- Inhaled Nasal
  - ↑ fluticasone
- HMG-CoA Reductase inhibitors
  - ↑ atorvastatin
- Hormonal contraceptives
  - ↑ norgestimate
  - ↓ ethinyl estradiol
- Narcotics
  - ↑ buprenorphine
  - ↑ norbuprenorphine
  - ↓ nalaxone

Drug-Drug Interactions

- Cyclosporine, sirolimus, and tacrolimus
  - ↑ elvitegravir and cobicistat
- NARCOTICS
  - ↑ buprenorphine
  - ↑ norbuprenorphine
  - ↓ nalaxone

Price

- WAC of Genvoya is $31,362 per year
Place in therapy

• Treatment-naïve patients with HIV-1
  – ≥ 12 years of age
  – ≥ 35 Kg
• Virologically-suppressed (RNA < 50 copies/mL) patients that switched to Genvoya
  – ≥ 6 months of stable therapy
  – No treatment failure
  – No resistance to any of the individual drugs in Genvoya

Additional information

• Genvoya does not cure HIV or AIDS
  – It will not stop the spread of HIV to others
• Test for Hepatitis B before starting Genvoya
  – Worsen Hepatitis B infections
• Before taking Genvoya tell your physician if you have:
  – Liver problems, kidney problems, or bone problems

Learning Assessment

What disease is Genvoya indicated for?
A. HIV-2
B. Hepatitis B
C. HIV-1
D. A and C
E. All of the above

References

Nucala (mepolizumab)
Sarah Bailey
Pharm.D. Candidate class of 2017
UNMC College of Pharmacy

Speaker Disclosure
• Sarah Bailey has no relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This information will not include a discussion of non-FDA approved (off-label) medication use.

Learning Assessment
Nucala is indicated for:
A. Mild/Moderate asthma in adults
B. Mild/Moderate asthma in children 12 years or older
C. Severe eosinophilic asthma in adults and children 12 years or older
D. Severe atopic asthma in adults and children 12 years or older
E. A and B

Indication
• Nucala is indicated as an add-on medication for maintenance treatment of patients with severe eosinophilic asthma

- There are currently no unapproved uses
- Approved November 4th, 2015

Eosinophilic Asthma
• Eosinophilic asthma appears more often in late-onset asthma than childhood onset, which is more commonly atopic/allergic
• Also known as Th2-like or Type 2 asthma, likely arises due to persistent elevations in interleukin (IL) 4, 5, and 13
• Peripheral blood eosinophils are good predictors of response to Type 2 targeted asthma therapy

Current Asthma Treatment
• Treatment table
Drug Formulation

- Nucala is supplied as a powder
  - Subcutaneous injection
  - Reconstitution necessary
    - 1.2 mL of sterile water for injection, USP
    - Swirl for 10 seconds at 15-second intervals until powder is dissolved
    - Solution will contain 100 mg/mL of mepolizumab

Mechanism of Action

- Fully humanized monoclonal antibody against Interleukin-5
  - IL-5 is responsible for growth, differentiation, recruitment, activation and survival of eosinophils which leads to airway inflammation in asthma patients
  - Mepolizumab binds to IL-5 and prevents it from binding to the IL-5 receptor complex on eosinophils
  - reduces production and survival of eosinophils via inhibition of IL-5 signaling

Pharmacokinetics

- Absorption
  - 80% bioavailable
  - 2-fold accumulation of drug at steady-state
- Distribution
  - Vd is ~3.6 L for a 70 kg patient

Pharmacokinetics (cont.)

- Metabolism
  - Proteolytic enzymatic degradation
  - Does not affect/is not affected by P450 enzymes
- Excretion
  - Clearance is estimated to be 0.28 L/day for a 70 kg patient
  - Half-life of 16-22 days

Dosing

- Children 12 years and older
  - 100 mg SQ every 4 weeks
- Adults
  - 100 mg SQ every 4 weeks
- There are no dose adjustments for age, renal dysfunction or hepatic dysfunction

Special Populations

- Pregnant/Nursing
  - Mepolizumab is expected to cross the placenta
  - Unknown if it enters breast milk
- Pediatric
  - Age 0-11 years has no established safety or efficacy
- Geriatric
  - No dose adjustments
- Hepatic/Renal Impairment
  - No dose adjustments
Contraindications

- Patients with hypersensitivity to mepolizumab or its excipients
  - Hypersensitivity reactions have occurred from hours to days after injection

Precautions

- Herpes zoster
  - Consider Varicella vaccine prior to starting therapy if medically appropriate
- Existing helminth infection
  - Thought that eosinophils help fight against parasitic infections and are impaired during the use of this drug

Adverse Reactions

- The most common
  - Headache
  - Back pain
  - Fatigue
  - Injection site reaction
- The more severe
  - Angioedema
  - Bronchospasm
  - Hypersensitivity
  - Herpes Zoster

Drug-Drug Interactions

- There are currently no known drug interactions!

Price

- Wholesale Acquisition Cost (WAC)
  - $2,500.00 for each 100 mg dose

Place in therapy

- Add-on maintenance therapy for treatment of severe asthma in children and adults 12 years and older
Comparison to Cinqair

- Reslizumab (Cinqair) is another available IL-5 antagonist
  - Indicated as add-on for severe eosinophilic asthma in **adults only**
  - Available as **IV infusion only**
  - 3 mg/kg every 4 weeks

- Black Box Warnings
  - Requires specialized care setting
  - Requires experienced clinician
  - Risk of serious hypersensitivity reactions or anaphylaxis

Additional information

- Patient Counseling tips
  - Do not shake the reconstituted solution
  - Inject into upper arm, thigh, or abdomen
  - Will not relieve acute bronchospasm or status asthmaticus
  - It is important not to abruptly discontinue use of inhaled or systemic corticosteroids

- No black box warnings

Learning Assessment

Nucala is indicated for:
A. Mild/Moderate asthma in adults
B. Mild/Moderate asthma in children 12 years or older
C. Severe eosinophilic asthma in adults and children 12 years or older
D. Severe ectopic asthma in adults and children 12 years or older
E. A and B

References

Available at: Clinical Pharmacology.

Available at: Clinical Pharmacology.

Available at: UpToDate.


Available at: Nucala.
Onzeta Xsail  
(sumatriptan nasal powder)

Brittany League  
Pharm.D. Candidate class of 2017  
Creighton University School of Pharmacy

Learning Assessment

Onzeta is approved for which of the following:
- A. Prevention of migraine headaches
- B. Treatment of acute migraine headaches
- C. Treatment of cluster headaches
- D. Treatment of tension headaches
- E. A and B

Speaker Disclosure

- Brittany League has no relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This information will not include a discussion of non-FDA approved (off-label) medication use.

Indication

- ONZETRA (sumatriptan) is indicated for the acute treatment of migraine with or without aura in adults.
- FDA approved on January 27, 2016
  - Via 505(b)(2) regulatory pathway
- Currently there are no unapproved uses

Overview of Migraines

- Pathophysiology
  - Primary neuronal dysfunction leading to a sequence of changes intracranially and extracranially
  - Two major subtypes: with or without aura

- Epidemiology
  - Affects up to 12% of general population
  - More common in women than in men
  - Most prevalent in both men and women ages 30 to 39
  - Often genetically inherited, but all persons susceptible

Overview of Migraines

- Clinical Presentation
  - Throbbing unilateral pain
  - Lasts from 4-72 hours
  - Many patients experience nausea and vomiting

- Treatment
  - 5HT is an important neurotransmitter mediator
  - Triptans are agonists of 5HT and most widely prescribed for acute treatment
**Drug Formulation**
- Intranasal medication delivery system consisting of a low-dose (22mg) of sumatriptan powder
- Sumatriptan powder is delivered via the novel Xsail Breath Powered Delivery Device
- NOT a nasal spray or inhaler

**Mechanism of Action**
- Exerts its therapeutic action through agonist effects at the 5-HT1B/1D receptors on intracranial blood vessels and sensory nerves of the trigeminal system
- Results in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release

**Xsail Breath Powered Delivery Device**
- User exhales into device to deliver sumatriptan into nasal cavity
- Exhaled breath carries sumatriptan deep into nose
- Closure of soft palate helps to prevent swallowing and reduce GI absorption

**Pharmacokinetics**
- Absorption and Bioavailability
  - Peak plasma concentration: 45 min average (10 minutes to 2 hours)
  - Onzetra has 19% bioavailability vs SQ
- Distribution
  - Protein binding 14% to 21%
  - Effect of protein binding compared to other drugs has not been evaluated

**Pharmacokinetics**
- Metabolism
  - Metabolized by MAO (predominately A isoenzyme)
- Excretion
  - Half life is 3 hours (similar to sumatriptan nasal spray)

**Dosing**
- Recommended dosage is 22mg of sumatriptan nasal powder (2 nosepieces)
  - Given as 11mg in each nostril
- If migraine has not resolved by 2 hours after or returns after transient improvement, a second dose of 22 mg may be administered 2 hours after the first dose
- Max dose is two doses in 24 hours (44 mg/4 nosepieces)
### Special Populations

- **Pregnant/Nursing**
  - Pregnancy Category C
  - Minimize infant exposure by avoiding breastfeeding for 12 hours after treatment
- **Pediatric**
  - Safety and effectiveness has not been established in patients younger than 18 years of age

### Contraindications

- Ischemic coronary artery disease (CAD)
- Wolff-Parkinson-White syndrome or arrhythmias
- History of stroke, transient ischemic attack, hemiplegic or basilar migraine
- Peripheral vascular disease
- Ischemic bowel disease
- Uncontrolled Hypertension

### Precautions

- Cardiovascular
  - MI, Prinzmetal’s Angina, Arrhythmias, increase in blood pressure, cerebrovascular events
- Chest, Throat, Neck, and/or Jaw Pain/Tightness/Pressure
- Medication Overuse Headache
- Serotonin syndrome
- Seizures

### Adverse Reactions

- The most common:
  - Abnormal Taste 20%
  - Nasal Discomfort 11%
  - Rhinorrhea 5%
  - Rhinitis 2%

### Contraindications

- Recent use (within 24 hours) of ergotamine-containing medication or another 5HT1 agonist
- Concurrent administration of an MAO-A inhibitor or recent use (within 2 weeks)
- Hypersensitivity to sumatriptin (angioedema and anaphylaxis)
- Severe hepatic impairment

### Precautions

- Cardiovascular
  - MI, Prinzmetal’s Angina, Arrhythmias, increase in blood pressure, cerebrovascular events
- Chest, Throat, Neck, and/or Jaw Pain/Tightness/Pressure
- Medication Overuse Headache
- Serotonin syndrome
- Seizures
Drug-Drug Interactions

- Ergot-containing Drugs
- MAO-A inhibitors
- Other 5-HT1 Agonists
- SSRIs or SNRIs
- TCAs

Price

- WAC of ONZETRA is $30.50 per unit or $488 per package

Place in therapy

- Can be used for patients who:
  - Vomit with migraine attacks
  - Need rapid relief from pain
  - Don’t like injections
  - Don’t like nasal spray that can go down throat

Additional information

- How supplied
  - Disposable nosepiece containing a capsule and a reusable breath-powdered delivery device
  - 8 dose kit
    - Containing 2 nosepieces (22mg sumatriptan) per pouch
    - Each nosepiece contains 11mg sumatriptan
    - 2 breath-powered delivery system bodies

Learning Assessment

Onzetra is approved for which of the following:
A. Prevention of migraine headaches
B. Treatment of acute migraine headaches
C. Treatment of cluster headaches
D. Treatment of tension headaches
E. A and B

References

- Press release. Avanir Pharmaceuticals Announces FDA Approval of ONZETRA(TM) Xsail(TM)
  (AVP-825) for the Acute Treatment of Migraine in Adults. Available at:
  http://www.avanir.com/press/avanir-pharmaceuticals-announces-fda-approval-of-onzetraxsail-
- UpToDate, Inc. Pathophysiology, clinical manifestations, and diagnosis of migraine in adults.
  UpToDate[database online]. Waltham, MA. Available at:
- Cady RK, McAllister PJ, Spierings ELH, et al. A Randomized, Double-Blind, Placebo-
  Controlled Study of the Breath Powered Nasal Delivery of Sumatriptan Powder (AVP-825) in
- Obaidi M, Offman Elliot, Messina J, Carothers J, et al. Improved Pharmacokinetics of
  53(8): 1323-1333.
Praluent (alirocumab)
Taylor Pick
Pharm.D. Candidate class of 2017
Creighton University School of Pharmacy

Learning Assessment
Praluent is indicated for which of the following:
A. Add on to diet and max tolerated statin therapy
B. Heterozygous familial hypercholesterolemia
C. Clinical atherosclerotic cardiovascular disease
D. Individuals who require lower LDL-C levels
E. All of the above

Speaker Disclosure
- Taylor Pick has no relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This information will not include a discussion of non-FDA approved (off-label) medication use.

Indication
- Praluent is indicated for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic disease.
  - FDA approved July 24, 2015.
  - There are currently no unapproved uses.

Familial Hypercholesterolemia
- Heterozygous FH is an autosomal dominant disorder which renders the liver incapable of metabolizing excess LDL resulting in very high LDL levels
- High levels of LDL lead to increased risk of premature cardiovascular disease

Drug Formulation
- Pre-filled pen or syringe
  - 75 mg/mL or 150 mg/mL
  - Single use
  - Storage

http://products.sanofi.us/praluent/PRALUENT_Prefilled_Pen_IFU_75%20mg.pdf
Mechanism of Action

- Human monoclonal antibody that binds to Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9)
- PCSK9 promotes the degradation of LDL receptors within the liver by binding with LDL receptors on hepatocytes
- LDL receptors clear circulating LDL

Pharmacokinetics

- Absorption
  - Subcutaneous injection
  - Peak concentration 3-7 days

- Distribution
  - Vd: 0.04 to 0.05 L/kg

Pharmacokinetics

- Metabolism
  - No CYP450 enzymes
  - Low concentrations eliminated through saturable binding to PCSK9
  - Higher concentrations eliminated through non-saturable proteolytic pathway
- Excretion
  - Half life 17-20 days
  - Reduced to 12 days with statins

Dosing

- Administered every 2 weeks
- Measure LDL-C concentrations 4 to 8 weeks following initiation or titration

Special Populations

- Pregnant/Nursing
  - Risk vs. benefit
- Pediatric
  - Not studied in individuals less than 18 years old
- Geriatric
  - No difference between adults

Special Populations

- Hepatic Impairment
  - No dosage adjustments for mild to moderate
- Renal Impairment
  - No dosage adjustments for mild to moderate
Contraindications
• Those who have had a serious hypersensitivity reaction to Praluent

Precautions
• Those who are pregnant or breastfeeding

Adverse Reactions
• The most common:
  – Nasopharyngitis 11.3%
  – Injection site reactions 7.2%
  – Influenza 5.7%

• The more severe:
  – Hypersensitivity reactions including vasculitis

Drug-Drug Interactions
• No clinically significant drug reactions have been documented

Place in therapy
• Adjunct therapy to diet and maximally tolerated statin therapy in those with heterozygous FH or clinical atherosclerotic cardiovascular disease

Price
• WAC of Praluent is $560 per pen

<table>
<thead>
<tr>
<th>Course of therapy</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 week course of therapy</td>
<td>$1,120</td>
</tr>
</tbody>
</table>
### Additional information

- The effect of Praluent on cardiovascular morbidity and mortality has not been determined.

### Learning Assessment

Praluent is indicated for which of the following:

A. Add on to diet and max tolerated statin therapy  
B. Heterozygous familial hypercholesterolemia  
C. Clinical atherosclerotic cardiovascular disease  
D. Individuals who require lower LDL-C levels  
E. All of the above

### References

Available at: Sanofi and Regeneron Pharmaceuticals. Praluent.  
Available at: FDA.  
Available at: Clinical Pharmacology.  
Accessed at: FH Foundation.  
Praxbind  
(idarucizumab)  

Hailey Soukup  
Pharm.D. Candidate class of 2017  
Creighton University School of Pharmacy

Learning Assessment
Which of the following agents may be reversed with idarucizumab?  
a) Enoxaparin  
b) Rivaroxaban  
c) Dabigatran  
d) Apixaban  
e) All of the above

Speaker Disclosure
- Hailey Soukup has no relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This information will not include a discussion of non-FDA approved (off-label) medication use.

Indication
- Humanized monoclonal antibody indicated in patients treated with dabigatran when reversal is needed  
  - Emergency surgery/urgent procedures  
  - Life-threatening or uncontrolled bleeding

Bleeding on Novel Oral Anticoagulants (NOAC)
- NOACs a welcome alternative to Vitamin K antagonists  
- A major issue with NOACs was lack of reversal agents  
- Idarucizumab a major breakthrough  
  - First NOAC reversal agent approved by FDA  
  - Only will reverse dabigatran  
  - Will not reverse other NOACs

Drug Formulation
- Solution for injection  
  - Provided as two separate vials, each containing 2.5g/50mL
<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Pharmacokinetics</th>
</tr>
</thead>
</table>
| • Neutralizes the anticoagulant effect of dabigatran and its acylglucuronide metabolites | • Absorption
  - IV only |
| • Binds with higher affinity to dabigatran than dabigatran to thrombin | • Distribution
  - Limited extravascular distribution after infusion
  - Most remains intravenous |

<table>
<thead>
<tr>
<th>Pharmacokinetic</th>
<th>Dosing</th>
</tr>
</thead>
</table>
| • Metabolism
  - Biodegradation of antibody to smaller peptides or amino acids | • For intravenous use only |
| • Excretion
  - Initial half-life of 47 minutes
  - Terminal half-life of 10.3 hours
  - 32.1% of dose recovered in urine within a collection period of 6 hours | • Recommended dose is 5g |
  • Limited data on repeated dosing |

<table>
<thead>
<tr>
<th>Special Populations</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age, sex, and race had no clinically important effect on exposure</td>
<td>• No known contraindications to date</td>
</tr>
<tr>
<td>• Safety and efficacy have not been established in pediatrics, pregnant or nursing patients</td>
<td></td>
</tr>
<tr>
<td>• No recommendations for dosage adjustments in hepatic and renal impairment are available</td>
<td></td>
</tr>
<tr>
<td>• Patients with renal impairment may have reduced clearance</td>
<td></td>
</tr>
</tbody>
</table>
### Precautions
- Reversal may predispose to thromboembolic risk
  - Resume anticoagulant therapy as soon as medically appropriate
  - May initiate dabigatran 24 hours after administering idarucizumab
- Hypersensitivity reactions
- Hereditary fructose intolerance
  - Serious adverse events due to sorbitol excipient

### Adverse Reactions
- The most common:
  - Hypokalemia (7%)
  - Delirium (7%)
  - Infection (6%)
  - Constipation (7%)
  - Fever (6%)
- As with all proteins, there is a potential for antibody formation

### Drug-Drug Interactions
- No drug-drug interactions
- Not affected by coagulation factor concentrates

### Price
- WAC of idarucizumab is $1750 per 2.5g/50mL vial
- Single dose (5g)
  - Two vials, $3500

### Place in therapy
- Need for urgent reversal of dabigatran
  - Emergency surgery
  - Urgent procedure
  - Life-threatening or uncontrolled bleeding
- Only direct reversal agent available for dabigatran
- Is not to be used for other NOACs

### Learning Assessment
Which of the following agents may be reversed with idarucizumab?
- a) Enoxaparin
- b) Rivaroxaban
- c) Dabigatran
- d) Apixaban
- e) All of the above
References


Tresiba
(insulin degludec [rDNA] injection)
Jarred Vogel
Pharm.D. Candidate class of 2016
UNMC College of Pharmacy

Learning Assessment
If a patient realizes they have missed their nightly dose of their Tresiba (insulin degludec) basal insulin last night, what should they do next?
A. Increase meal time rapid acting insulin doses until the next scheduled Tresiba dose
B. Use their normal dose upon realizing, and resume normal nightly schedule as long as there is >8hr between doses
C. Use their normal dose upon realizing, and switch their daily doses to that new time thereafter
D. It’s easiest to just skip that dose – it won’t have any affect on their blood sugars since the duration of action is >42 hrs

Indication
• Tresiba is a long-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus
• FDA approved September 25, 2015
• Limitations of Use
  – Not recommended for treating diabetic ketoacidosis
  – Not to be used IV, IM or in an infusion pump

Overview of Diabetes
• Unable to properly use/store glucose
• Type 1 (insulin-dependent) – body stops producing insulin
• Type 2 (non insulin-dependent) – body does not produce enough insulin or unable to use insulin properly
• Insulin hormone is the ‘key’ for glucose uptake
• Type 2 insulin resistance over time will eventually result in insulin dependence
• Complications: neuropathy, cardiovascular, vision, kidney, blood vessels, etc…

Mechanism of Action
• Tresiba = insulin = regulation of glucose metabolism
• Stimulates peripheral glucose uptake (fat, muscle), and decreases hepatic glucose production
• Forms multi-hexamers in SQ tissue resulting in degludec depot
  – Slow release into systemic circulation
  – Binding of insulin-degludec to circulating albumin

Speaker Disclosure
• Jarred Vogel has no relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This information will not include a discussion of non-FDA approved (off-label) medication use
Pharmacokinetics

- Absorption – reach steady state after 3-4 days of regular administration
- Distribution – >99% plasma protein binding. In vitro protein binding shows no clinically relevant interaction with other protein bound drugs
- Elimination – half-life is determined by the rate of absorption from SQ tissue. Average t1/2 is 25 hours independent of dose. Mean apparent clearance is 0.03L/kg/hr after single SQ dose of 0.4 U/kg
- Effect – >42 hours

Dosing

- Individualize dose based on type on diabetes (I/II), metabolic needs, blood glucose monitoring results and glycemic control
- Rotate injection sites to reduce the risk of lipodystrophy
- Do not dilute or mix with any other insulin solution
- Administer subcutaneously at any time of the day
- Starting Dose in Insulin Naïve Patients
  - Type 1 DM: 1/3-1/2 total daily insulin dose (0.2-0.4u/kg)
  - Type 2 DM: 10u/day
- Starting Dose in Patients Already on Insulin Therapy
  - Type 1 & 2 DM: same unit dose as the total daily long or intermediate-acting insulin unit dose

Storage

- Unopened
  - Refrigerate between 36-46°F, discard when expired
- Open (in-use)
  - Do NOT refrigerate, keep at room temperature (below 86°F)
  - May be used for up to 56 days (8 weeks) after being opened
- Keep out of direct light
- Only use if solution is clear and colorless with no particles visible

Contraindications

- During episodes of hypoglycemia
- Hypersensitivity to Tresiba or one of its excipients
  - Rash, pruritis, SOB, wheezing, hypotension, tachycardia, and diaphoresis
  - Minor, local sensitivity with redness, swelling or itching at injection site is not considered hypersensitivity

Special Populations/Precautions

- Pregnancy Category C – no well-controlled clinical studies of the use of insulin degludec in pregnant
- Nursing Mothers – unknown if secreted in milk, exercise caution
- Pediatric – use under the age of 18 has not been established
- Geriatric – hypoglycemia may be more difficult to recognize in elderly
- Renal Impairment – no clinically relevant PK differences, but intensify glucose monitoring
- Hepatic Impairment – no PK differences identified, but intensify glucose monitoring

Adverse Reactions

- Type 1 Diabetes (n=1102)
  - Nasopharyngitis 23.9%
  - Upper respiratory tract infection 11.9%
  - Headache 11.8%
  - Sinusitis 5.1%
  - Gastroenteritis 5.1%
- Type 2 Diabetes Mellitus (n=2713)
  - Nasopharyngitis 12.9%
  - Headache 8.8%
  - Upper respiratory tract infection 8.4%
  - Diarrhea 6.3%

*Hypoglycemia was the most common adverse reaction, with rates depending on definition of hypoglycemia used, diabetes type, insulin dose, intensity of glucose control, background therapies, and other extrinsic factors – but is comparable to insulin glargine
Drug-Drug Interactions

- **Drugs that May Increase the Risk of Hypoglycemia**
  - Antidiabetic agents, ACE/ARB inhibitors, disopyramide, fibrates, fluoxetine, MAOIs, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics, GLP-1 receptor agonists, DDP-4 inhibitors, SGL T-2 inhibitors
  - Intervention – Dose reductions and increased frequency of glucose monitoring may be required when Tresiba is co-administered with these drugs

- **Drugs that May Decrease the Blood Glucose Lowering Effect of Tresiba**
  - Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestins (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones
  - Intervention – Dose increases and increased frequency of glucose monitoring may be required when co-administered with Tresiba

- **Drugs that May Increase or Decrease the Blood Glucose Lowering Effect of Tresiba**
  - Alcohol, BBs, clonidine, lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia
  - Intervention – Dose adjustment and increased frequency of glucose monitoring may be required when Tresiba is co-administered with these drugs

- **Drugs that May Blunt Signs and Symptoms of Hypoglycemia**
  - BBs, clonidine, guanethidine, and reserpine
  - Intervention – Increased frequency of glucose monitoring may be required when Tresiba is co-administered with these drugs

---

Price (WAC)

- U-100 = $443/box (5x3mL pens)
- U-200 = $533/box (3x3mL pens)

---

Place in therapy

- First or second line basal insulin therapy
- Patient unable to use basal insulin at same time each day
- Needing >80u/day of insulin glargine or 2 doses of glargine per day
- Vs insulin glargine T2DM – similar blood sugar congrool with no clinically important differences in hypoglycemia risk
- Vs insulin glargine T1DM + fast-acting – similar blood sugar control

- Table 6 and Table 8 from Tresiba package insert

---

Additional Information

- Do NOT perform dose conversion when using the FlexTouch pens – the pen window shows the number of insulin units being delivered
- The recommended days between dose increases is 3-4 days
- Patient can use their long-acting insulin any time in the day*
  - *encouraged to use at the same time every day
  - Can vary by 8-40 hr without compromising blood sugar control
  - Needs to be at least 8 hr between doses
- 1 dose maximum of 160 units vs insulin glargine 80 units

---

Learning Assessment

If a patient realizes they have missed their nightly dose of their Tresiba (insulin degludec) basal insulin last night, what should they do next?

A. Increase meal time rapid acting insulin doses until the next scheduled Tresiba dose
B. Use their normal dose upon realizing, and resume normal nightly schedule as long as there is >8hr between doses
C. Use their normal dose upon realizing, and switch their daily doses to that new time thereafter
D. It’s easiest to just skip that dose – it won’t have any affect on their blood sugars since Tresiba’s duration of action is >42 hrs
References

Zepatier (elbasvir/grazoprevir)
Megan Wachter
Pharm.D. Candidate class of 2017
Creighton University School of Pharmacy

Learning Assessment
Zepatier requires dosage adjustment for:
- a.) patients with any degree of renal impairment
- b.) patients with a Child-Pugh score of A
- c.) patients with a Child-Pugh score of B or C
- d.) all of the above
- e.) none of the above

Speaker Disclosure
- Megan Wachter has no relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This information will not include a discussion of non-FDA approved (off-label) medication use.

Indication
- Zepatier (elbasvir/grazoprevir) is indicated for the treatment of chronic hepatitis C genotypes 1 and 4 infections in adults.
- It was FDA-approved on January 28, 2016
- There are no unapproved uses for Zepatier

Disease State
- Hepatitis C is a liver infection caused by the hepatitis C virus (HCV)
- A majority of patients become infected by sharing needles
- It can be a short-term illness, but for most it develops into a chronic infection
- This could also lead to cirrhosis or cancer

Drug Formulation
- Available as an oral tablet
- Consists of 50mg of elbasvir and 100mg of grazoprevir
Mechanism of Action

- Elbasvir is an HCV NS5A protein inhibitor.
  - Mechanism is not completely understood
  - Believe it prevents HCV replication by blocking viral hyperphosphorylation
- Grazoprevir is an HCV NS3/4A protease inhibitor
  - Inhibits viral replication by blocking NS3/4A protease enzyme
  - Enzyme needed to produce mature viral proteins

Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Elbasvir</th>
<th>Grazoprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>99.9% plasma protein bound; peak concentration is obtained in 3-6 hours</td>
<td>98.8% plasma protein bound; peak concentration is obtained in 30 minutes – 6 hours</td>
</tr>
<tr>
<td>Distribution</td>
<td>Distributes into most tissues (Vd = 680 L)</td>
<td>Vd = 1250 L, most of goes to the liver</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Oxidative metabolism, primarily via CYP3A enzymes</td>
<td>Oxidative metabolism, also by CYP3A enzymes</td>
</tr>
<tr>
<td>Excretion</td>
<td>Excreted through feces (&gt;90%). Half-life for 50mg is 24 hours</td>
<td>Mainly through feces (&gt;90%). Half-life for 100mg is 31 hours.</td>
</tr>
</tbody>
</table>

Dosing

- 1 tablet by mouth daily
- Treatment duration can either be 12-16 weeks depending on the presence of polymorphisms or treatment experience

Special Populations

- Pregnant/Nursing
  - Both grazoprevir and elbasvir have an unclear risk to a developing fetus
  - Both cross the placenta; it is not known if excreted in breast milk
- Pediatric
  - PK in patients <18 yoa have not been established
- Geriatric
  - Elbasvir and grazoprevir AUC’s are 16% and 45% higher in those > 65 yoa

Special Populations

- Hepatic Impairment
  - No dosage adjustment needed for those with mild hepatic impairment
  - Contraindicated in those with moderate-severe impairment
- Renal Impairment
  - No dosage adjustment is needed for patients with any degree of renal impairment

Contraindications

- Child Pugh class B or C
- Concurrent use with strong CYP3A4 inducers, OATP1B1/3 transport inhibitors, and efavirenz
### Precautions

- ALT elevations have been reported
  - $>5x$ ULN – week 8 of treatment
  - Mostly asymptomatic, resolved with ongoing or completed therapy
  - Females, Asians, and patients $\geq 65$ are more likely to experience this
  - Monitor LFT’s at baseline, week 8, and as clinically indicated
  - Discontinue of ALT $>10x$ ULN persistently

### Adverse Reactions

- The most common:
  - Fatigue (7-11%)
  - Headache (11%)
  - Nausea (5-11%)

### Drug-Drug Interactions

- Co-administration with CYP3A4 inhibitors or inducers is not recommended
  - Antibiotics: nafcillin decreases Zepatier levels
  - Antifungals: ketoconazole increases Zepatier levels
  - Concomitant use with tacrolimus will ↑ tacrolimus levels

- Concomitant use with various HMG-CoA reductase inhibitors will increase statin drug levels
- HIV regimens containing cobicistat will increase Zepatier levels
- Modafinil + Zepatier = ↓ levels of elbasvir and grazoprevir

### Place in therapy

- Zepatier can be used with or without concomitant medications, such as ribavirin
- In comparison to Gilead Science’s Harvoni or Sovaldi, it is significantly cheaper and has comparable efficacy and side effects

### Price

- WAC is $650/tablet
- Developed by Merck pharmaceuticals
- Much lower compared to other HCV treatment
Additional information

- Take Zepatier at the same time each day; do not take it out of the blister pack until you are ready to take your dose
- Medication can be taken without regard to food

Learning Assessment

Zepatier requires dosage adjustment for:
- a.) patients with any degree of renal impairment
- b.) patients with a Child-Pugh score of A
- c.) patients with a Child-Pugh score of B or C
- d.) all of the above
- e.) none of the above

References

Zurampic (lesinurad)
Christopher Zaleski
Pharm.D. Candidate class of 2017
University of Nebraska Medical Center – College of Pharmacy

Speaker Disclosure
• Christopher Zaleski has no relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This information will not include a discussion of non-FDA approved (off-label) medication use.

Learning Assessment
Zurampic is indicated for which of the following:
A. 60 yo male with eCrCl of 63 mL/min on current allopurinol therapy
B. 49 yo female with eCrCl of 29 mL/min on current febuxostat therapy
C. 58 yo male with eCrCl of 93 mL/min not on current anti-gout therapy

Indication
• Zurampic (lesinurad) is approved for the treatment of hyperuricemia associated with gout, in combination with a xanthine oxidase inhibitor, in those patients who have not achieved target serum uric acid levels on xanthine oxidase inhibitor therapy alone.
• FDA approved in December 2015.
• There are currently no unapproved uses of Zurampic (lesinurad).

Overview of Gout
• Hyperuricemia:
  − A metabolic disorder in which excessive concentrations of uric acid in the blood leads to the deposition of urate crystals in and around the joints and connective tissues, primarily in the first metatarsophalangeal joint, or big toe.
  − The accumulation of urate crystals leads to chronic inflammation, which in turn may lead to acute gout flares, arthritis, joint damage, disfiguring tophi, kidney stones, and chronic kidney disease.
  − Hyperuricemia is mainly caused by inefficient uric acid excretion.
  − Other comorbid conditions such as hypertension, cardiovascular disease, kidney disease, and diabetes mellitus may contribute to hyperuricemia.

Current Chronic Gout Therapies
• Xanthine oxidase inhibitors:
  − Zyloprim (allopurinol) and Uloric (febuxostat)
• Benemid (probenecid)
• Krystexxa (pegloticase)
• Zurampic (lenisurad)
Mechanism of Action

• Zurampic (lesinurad) works by inhibiting the function of transporter proteins involved in renal uric acid reabsorption, specifically the uric acid transporter 1 (URAT1) and organic anion transporter 4 (OAT4). This lowers serum uric acid levels and increases renal clearance and fractional excretion of uric acid in patients suffering from gout.

Pharmacokinetics

• Absorption
  – Zurampic (lesinurad) exhibits rapid absorption after oral administration.
  – Maximal concentration (Cmax) is seen within 1 to 4 hours.
  – Bioavailability is nearly 100%.
• Distribution
  – Exhibits extensive protein binding, > 98%, primarily to albumin.
  – Steady state volume of distribution is approximately 20 L.

Pharmacokinetics

• Metabolism
  – Zurampic (lesinurad) is primarily metabolized via oxidation by CYP2C9.
  – Plasma exposure of the metabolites is minimal and the metabolites are not known to contribute to the uric acid lowering effects of the parent drug.
  – Major substrate for CYP2C9, weak inducer of CYP3A4
• Excretion
  – 63% excreted in the urine, with ~30% remaining unchanged.
  – 32% excreted in the feces.
  – The elimination half-life is approximately 5 hours.

Dosing

• One 200 mg tablet by mouth once daily.
  – Special considerations:
    • Administer in the morning with food and water. Advise patients to stay well-hydrated (~2L of fluids/day).
    • Should not be used as monotherapy, must be used in combination with a xanthine oxidase inhibitor (eg allopurinol or febuxostat).
    • If treatment with the xanthine oxidase inhibitor is interrupted, Zurampic therapy should also be held.
  – Max dose is 200 mg per day.

Special Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Impairment</td>
<td>eGFR &gt; 60 mL/min: no dosage adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>eGFR 30-59 mL/min: limited experience in clinical trials, use should not be initiated</td>
</tr>
<tr>
<td></td>
<td>eGFR &lt; 30 mL/min: use is contraindicated</td>
</tr>
<tr>
<td></td>
<td>End-stage renal disease or peritoneal dialysis: use is contraindicated</td>
</tr>
<tr>
<td></td>
<td>Renal recently diagnosed: if eGFR &lt; 45 mL/min, treatment should be discontinued</td>
</tr>
<tr>
<td>Hepatic Impairment</td>
<td>Mild to moderate (Child-Pugh Score A and B): no dosage adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>Severe (Child-Pugh Score C): use is not recommended due to lack of efficacy.</td>
</tr>
<tr>
<td>Geriatric</td>
<td>Follow normal adult dosing and monitoring parameters.</td>
</tr>
<tr>
<td>Pediatric</td>
<td>Safety and efficacy have not been established in neonates, infants, children, or adolescents.</td>
</tr>
<tr>
<td>Pregnant/Nursing</td>
<td>There is currently no human data available to support the use of Zurampic (lesinurad) **in pregnant or breastfeeding females. Animal studies on rabbits and rats demonstrated no clinically relevant effects on the embryo/fetal. **</td>
</tr>
</tbody>
</table>

Contraindications

• Zurampic (lesinurad) should not be used in the following:
  - Severe renal impairment (CrCl < 30 mL/min)
  - End-stage renal disease
  - Dialysis patients
  - Kidney transplant recipients
  - Patients suffering from tumor lysis syndrome
  - Patients with Lesch-Nyhan syndrome
**Precautions**

- Cardiovascular events: cardiac adverse events including cardiovascular deaths, non-fatal MI, and non-fatal strokes occurred during clinical trial; a causal relationship to Zurampic use was not established.
- Gout flare: following initiation of therapy.
- Nephrotoxicity: Black Box Warning when Zurampic is given alone versus given concomitantly with a xanthine oxidase inhibitor.
- CYP2C9 poor metabolizers: increased [Zurampic]

**Adverse Reactions**

- Cerebrovascular accident, myocardial infarction
- Headache (5%)
- GERD (3%)
- Influenza (5%)
- Renal:
  - Increased SCr (3% to 7%)
  - Renal failure (< 4%)  
  - Nephrolithiasis (3%)
  - Acute renal failure

**Drug-Drug Interactions**

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Risk</th>
<th>Effect</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>D</td>
<td>CYP3A4 inducers &lt; serum predominantly</td>
<td>Double arquiprazole dose and dose may be increased</td>
</tr>
<tr>
<td>Aspirin</td>
<td>C</td>
<td>May effect of Zurampic</td>
<td>Monitor therapy</td>
</tr>
<tr>
<td>Contraception (estrogens and progestins)</td>
<td>D</td>
<td>Use back-up, nonhormonal contraception</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>C</td>
<td>Zurampic may interact (nephrotoxic)</td>
<td>Monitor therapy</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>C</td>
<td>Zurampic may interact (nephrotoxic)</td>
<td>Monitor therapy</td>
</tr>
<tr>
<td>Valproate Products</td>
<td>X</td>
<td>May &lt; serum [Zurampic]</td>
<td>Avoid combination</td>
</tr>
</tbody>
</table>

**Price**

- Pricing is currently unavailable as Zurampic has yet to reach the market.

**Place in therapy**

- Zurampic (lesinurad) should only be used in combination with a xanthine oxidase inhibitor; monotherapy should be avoided.
- Can be initiated in those patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone.

**Additional information**

- Counseling tips:
  - Patients should take Zurampic in the morning with food and water, at the same time as their xanthine oxidase inhibitor.
  - Patients should remain well hydrated while taking Zurampic (~2L/fluids per day).
Learning Assessment

Zurampic is indicated for which of the following:

A. 60 yo male with eCrCl of 63 mL/min on current allopurinol therapy
B. 49 yo female with eCrCl of 29 mL/min on current febuxostat therapy
C. 58 yo male with eCrCl of 93 mL/min not on current anti-gout therapy

References