Pharmacotherapy Update 2016: General Health

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Disclaimer

• I have no conflicts of interest to disclose

• Given the nature of this presentation, trade (brand) names will be used to introduce medications; this is not an endorsement for any particular entity or company and should not be taken as such

• All information comes from product labeling except where otherwise noted

Objectives

• Identify medications that were approved and came to market in 2016

• Develop a general understanding of each medication’s indication, dosing, potential adverse effects, place in therapy, and unique characteristics

• Discuss key updates in treatment guidelines that occurred in 2016
Infectious diseases

**HIV**
- Odefsey®
  - Emtricitabine/tenofovir alafenamide
- Descovy®
  - Emtricitabine/tenofovir alafenamide

**Hepatitis C**
- Viekeira XR
  - dasabuvir/om替avir/paritaprevir/ritonavir
- Zepatier
  - Elbasvir/grazoprevir
- Epclusa
  - Sofosbuvir/velpatasvir

Infectious disease
- Cardiovascular
- Pulmonology
- Diabetes
- Neurology
- Gastrointestinal

Infectious disease
- Human immunodeficiency virus (HIV-1)
- Hepatitis C
- Cardiovascular
- Pulmonology
- Diabetes
- Neurology
- Gastrointestinal
Infectious diseases

HIV
- Odefsey®
  - Emtricitabine/rilpivirine/tenofovir alafenamide
- Descovy®
  - Emtricitabine/tenofovir alafenamide

Hepatitis C
- Viekeira XR
  - dasabuvir/ombitasvir/paritaprevir/ritonavir
- Zepatier
  - Elbasvir/grazoprevir
- Eclusa
  - Sofosbuvir/velpatasvir

**Odefsey®**
emtricitabine/rilpivirine/tenofovir alafenamide

- Approved March 1, 2016 (priority review)
- Indicated for treatment of HIV-1 infection as a complete regimen
  - Adults and children ≥12 years old
  - Initial therapy [HIV-1 RNA ≤100,000 copies/mL]
  - Replacing stable therapy [HIV-1 RNA ≤50 copies/mL], at least 6 months, no treatment failures, and no known anti-viral resistance
- **One pill, once-a-day regimen**

**Individual Components**

- **Emtricitabine**
  - Nucleoside reverse transcriptase inhibitor
  - 200mg
- **Rilpivirine**
  - Non-nucleoside reverse transcriptase inhibitor
  - 25mg
- **Tenofovir alafenamide**
  - Nucleotide reverse transcriptase inhibitor
  - 25mg
- **Inhibit viral replication**
Odefsey® emtricitabine/rilpivirine/tenofovir alafenamide

Clinical Considerations
- Should be taken with a meal
- Not recommended with CrCl <30 mL/min
- Contraindicated with proton pump inhibitors, carbamazepine, and rifampin
- Tenofovir
  - Black box warning for lactic acidosis and hepatomegaly
  - Risk of renal toxicity and/or Fanconi syndrome
- Not approved for Hepatitis B

Descovy® emtricitabine/tenofovir alafenamide

- Approved April 4, 2016 (standard review)
- Indicated for treatment of HIV-1 infection
  - Adults and children ≥12 years old
  - Must be used in combination with other antiretrovirals

Descovy® emtricitabine/tenofovir alafenamide

Individual Components/Dosing
- Emtricitabine
  - Nucleoside reverse transcriptase inhibitor
  - 200mg
- Tenofovir alafenamide
  - Nucleotide reverse transcriptase inhibitor
  - 25mg
- Inhibit viral replication
- One tablet once daily

Must be taken with other anti-retrovirals
Descovy®
emtricitabine/tenofovir alafenamide

Clinical Considerations
• Not recommended with CrCl <30 mL/min
• Tenofovir
  • Black box warning for lactic acidosis and hepatomegaly
  • Risk of renal toxicity and/or Fanconi syndrome
• Not approved for hepatitis B

Infectious diseases

HIV
• Odefsey®
  • Emtricitabine/rilpivirine/tenofovir alafenamide
• Descovy®
  • Emtricitabine/tenofovir alafenamide

Hepatitis C
• Viekira XR
  • dasabuvir/ombitasvir/paritaprevir/ritonavir
• Zepatier
  • Elbasvir/grazoprevir
• Epclusa
  • Sofosbuvir/velpatasvir

Viekira XR®
dasabuvir/ombitasvir/paritaprevir/ritonavir

• Approved July 22, 2016 (standard review)
• Indicated for adults with chronic hepatitis C virus
  • Genotype 1a or 1b
  • Without cirrhosis or with compensated cirrhosis
  • Not approved for those with decompensated cirrhosis
• Cure rates
  • Genotype 1a: 95-96% (with ribavirin)
  • Genotype 1b: 100% (without ribavirin)
• Once-daily formulation to replace Viekira Pak®
### Individual Components

<table>
<thead>
<tr>
<th>Agent</th>
<th>Inhibits</th>
<th>Interferes with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasabuvir 200mg</td>
<td>RNA-dependent RNA polymerase on NS5B gene</td>
<td>Viral RNA replication</td>
</tr>
<tr>
<td>Ombitasvir 8.33mg</td>
<td>HCV NS5A</td>
<td>Viral RNA replication and virion assembly</td>
</tr>
<tr>
<td>Paritaprevir 50mg</td>
<td>HCV NS3/4A protease</td>
<td>HCV coded polyprotein cleavage</td>
</tr>
<tr>
<td>Ritonavir 33.33mg</td>
<td>CYP3A4</td>
<td>Not active against Hepatitis C virus</td>
</tr>
</tbody>
</table>
Viekira XR®
dasabuvir/ombitasvir/paritaprevir/ritonavir

Dosing
• Three pills once daily; must be taken with a meal

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a, without cirrhosis</td>
<td>Viekira XR + ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1a, with compensated cirrhosis</td>
<td>Viekira XR + ribavirin</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Genotype 1b, with or without compensated cirrhosis</td>
<td>Viekira XR</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

Clinical Considerations
• Contraindications
  • Moderate to severe hepatic impairment
  • Coadministration with strong CYP2C8 inducers/inhibitors, CYP3A inducers, and drugs highly dependent upon CYP3A for clearance
  • Discontinue ethinyl estradiol-containing medications before initiating treatment
  • Monitor closely for ALT elevations
• Adverse effects include:
  • Nausea, pruritus, insomnia, and fatigue
  • Anemia with RBV

Zepatier®
elbasvir/grazoprevir
• Approved January 28, 2016 (priority review)
• Indicated for adults with chronic hepatitis C virus
  • Genotype 1 or genotype 4
  • Use with ribavirin indicated in certain patient populations
• Cure rates:
  • Genotype 1: 95%
  • Genotype 4: 97%
• In genotype 1a, testing for presence of NS5A resistance-associated polymorphisms is recommended
**Individual Components**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Inhibits</th>
<th>Interferes with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbasvir 50mg</td>
<td>NS5A</td>
<td>Viral RNA replication, Virion assembly</td>
</tr>
<tr>
<td>Grazoprevir 100mg</td>
<td>NS3/4A</td>
<td>Proteolytic cleavage of HCV encoded polyprotein</td>
</tr>
</tbody>
</table>

**Dosing**

- One tablet once daily with or without food

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced without baseline NS5A polymorphisms</td>
<td>Zepatier</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced with baseline NS5A polymorphisms</td>
<td>Zepatier + ribavirin</td>
<td>16 weeks</td>
</tr>
<tr>
<td>Genotype 1b: Treatment-naïve or PegIFN/RBV-experienced</td>
<td>Zepatier</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 4: Treatment-naïve</td>
<td>Zepatier</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 4: PegIFN/RBV-experienced</td>
<td>Zepatier + ribavirin</td>
<td>16 weeks</td>
</tr>
</tbody>
</table>

PegIFN: peginterferon alfa; RBV: ribavirin; PI: protease inhibitor

**Clinical Considerations**

- Contraindications:
  - Moderate to severe hepatic impairment
  - OATP1B1/3 inhibitors, strong CYP3A inducers/inhibitors, and efavirenz
  - Monitor for ALT elevations at baseline, 8 weeks, (12 weeks), and as clinically indicated
  - Adverse effects include:
    - Fatigue, headache, and nausea
Epclusa®
sofosbuvir/velpatasvir

- Approved June 28, 2016 (Priority review)
- Indicated for adults with chronic Hepatitis C
  - Genotype 1, 2, 3, 4, 5, or 6
  - Without cirrhosis or with compensated cirrhosis
  - With decompensated cirrhosis when used in combination with ribavirin
- Cure rates: 97-100%
- One pill, once daily for 12 weeks for all genotypes
  - Unless decompensated: requires ribavirin

Epclusa®
sfosbuvir/velpatasvir

Individual Components

<table>
<thead>
<tr>
<th>Agent</th>
<th>Inhibits</th>
<th>Interferes with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir 400mg</td>
<td>NS5B RNA-dependent RNA polymerase</td>
<td>Viral replication</td>
</tr>
<tr>
<td>Velpatasvir 100mg</td>
<td>NS5A</td>
<td>Viral replication</td>
</tr>
</tbody>
</table>

Dosing

- One tablet once daily with or without food
- Dosing is the same for genotypes 1, 2, 3, 4, 5, and 6

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient without cirrhosis and patients with compensated cirrhosis (Child-Pugh A)</td>
<td>Epclusa</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Patients with decompensated cirrhosis (Child-Pugh B and C)</td>
<td>Epclusa + ribavirin</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>
Epclusa®
sofosbuvir/velpatasvir

Clinical Considerations
• Coadministration with amiodarone (bradycardia) and PPIs (decreased absorption) are not recommended
• Coadministration with P-glycoprotein inducers and/or moderate to potent CYP inducers is not recommended
• No dosage recommendation given in renal dysfunction (CrCl <30 mL/min)
• Adverse effects most commonly include:
  • Headache and fatigue

New Agent Comparison

<table>
<thead>
<tr>
<th>Agent</th>
<th>Genotype</th>
<th>Compensated Cirrhosis?</th>
<th>Decompensated Cirrhosis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasabuvir/ombitasvir/pitravir/ritonavir (Viekira XR®)</td>
<td>1</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Elbasvir/grazoprevir (Zepatier®)</td>
<td>1 &amp; 4</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir (Epclusa®)</td>
<td>1, 2, 3, 4, 5, 6</td>
<td>Yes</td>
<td>Yes (with ribavirin)</td>
</tr>
</tbody>
</table>

Hepatitis C Guidelines
Initiation of Treatment in Treatment-Naïve Patients

Genotype 1a without cirrhosis (Class I, Level A)
• Elbasvir/grazoprevir
• Ledipasvir/sofosbuvir
• Daily paritaprevir/ritonavir/ombitasvir + BID dasabuvir (**Viekira Pak)
• Simeprevir/sofosbuvir
• Sofosbuvir/velpatasvir

Genotype 1a with compensated cirrhosis (IA)
• Elbasvir/grazoprevir
• Ledipasvir/sofosbuvir
• Sofosbuvir/velpatasvir

www.hcvguidelines.org (February 20, 2017); all treatments x12 weeks
Hepatitis C Guidelines
Initiation of Treatment in Treatment-Naïve Patients

Genotype 1b without cirrhosis (1A)
- Elbasvir/grazoprevir
- Ledipasvir/sofosbuvir
- Daily paritaprevir/ritonavir/ombitasvir + BID dasabuvir (**Viekira Pak)
- Simeprevir/sofosbuvir
- Sofosbuvir/velpatasvir

Genotype 1b with compensated cirrhosis (1A)
- Elbasvir/grazoprevir
- Ledipasvir/sofosbuvir
- Daily paritaprevir/ritonavir/ombitasvir + BID dasabuvir (**Viekira Pak)
- Sofosbuvir/velpatasvir

Genotype 1b without cirrhosis (1A)

Genotype 1b with compensated cirrhosis (1A)

Genotype 2 without cirrhosis (1A)
- Sofosbuvir/velpatasvir

Genotype 2 with compensated cirrhosis (1A)
- Sofosbuvir/velpatasvir

Genotype 3 without cirrhosis (1A)
- Daclatasvir/sofosbuvir
- Sofosbuvir/velpatasvir

Genotype 3 with compensated cirrhosis (1A)
- Sofosbuvir/velpatasvir

Genotype 4 with or without cirrhosis (1A)
- Sofosbuvir/velpatasvir
- Paritaprevir/ritonavir/ombitasvir + ribavirin

Genotype 5/6 with or without cirrhosis (1A)
- Ledipasvir/sofosbuvir
- Sofosbuvir/velpatasvir

www.hcvguidelines.org (February 20, 2017); all treatments x12 weeks
• Infectious disease
• Cardiovascular
• Pulmonology
• Diabetes
• Neurology
• Gastrointestinal

Byvalson® nebivolol/valsartan
• Approved June 3, 2016 (standard review)
• Indicated for the treatment of hypertension to lower blood pressure
• The only commercially available beta blocker + angiotensin II receptor blocker (ARB) combination therapy

Individual Components
• Nebivolol 5mg
  • Highly-selective inhibitor of beta-1-adrenergic receptors
  • Endothelium-derived nitric oxide-dependent vasodilation
• Valsartan 80mg
  • Blocks binding of angiotensin II to AT1 receptor
  • Prevents vasoconstrictor and aldosterone-secreting effects of angiotensin II
• Individual agent also approved for heart failure
Byvalson®
nebivolol/valsartan

Dosing
• One tablet once daily
  • Initial therapy
  • Patients not adequately controlled on valsartan 80mg or nebivolol at ≤10mg
  • Maximum effects are obtained within 2 to 4 weeks
  • Increased dosing does not result in any meaningful further reduction in blood pressure

Byvalson®
nebivolol/valsartan

Clinical Considerations
• Do not administer in women who are pregnant due to possible injury/death to fetus
• Contraindications:
  • Severe bradycardia, heart block greater than 1st degree, sick sinus syndrome
  • Decompensated heart failure or cardiogenic shock
  • History of hypersensitivity to either individual product
• Caution/Monitoring:
  • Diabetics
  • Potassium
  • Do not abruptly discontinue

Yosprala®
aspirin/omeprazole

• Approved September 14, 2016 (standard review)
• Indicated for patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events who are at risk of developing aspirin-associated gastric ulcers
  • age ≥55 years old
  • documented history of gastric ulcers
Yosprala® aspirin/omeprazole

**Individual Components**
- Aspirin 81mg or 325mg
- Delayed release
- Omeprazole 40mg
- Immediate release

**Dosing**
- Aspirin dosage dependent upon indication
- One tablet once daily at least 60 minutes prior to a meal

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Yosprala® aspirin/omeprazole

**Clinical Considerations**
- Not for use as initial dose of aspirin during onset of ACS/AMI or before PCI
- Not labeled to be interchangeable with individual products
- Warnings, contraindications, and adverse events mirror the individual products

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Qbrelis® lisinopril

**Approved July 29, 2016 (standard review)**
- Indicated treatment of hypertension (adults and pediatric patients ≥6 years old), adjunct therapy for heart failure, and acute myocardial infarction
- Not recommended in children <6 years old
- Available as 1 mg/mL aqueous solution with a sweet taste
- Only commercially available lisinopril liquid preparation
Qbrelis® (lisinopril)

<table>
<thead>
<tr>
<th>Qbrelis®</th>
<th>Compounded lisinopril suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved</td>
<td>Yes</td>
</tr>
<tr>
<td>Meets FDA standards for potency and purity</td>
<td>Yes</td>
</tr>
<tr>
<td>FDA-approved labeling</td>
<td>Yes</td>
</tr>
<tr>
<td>Required compliance with FDA’s current good manufacturing practices</td>
<td>Yes</td>
</tr>
<tr>
<td>Source of active ingredients approved by FDA</td>
<td>Yes</td>
</tr>
<tr>
<td>Shaking required</td>
<td>No</td>
</tr>
<tr>
<td>Shelf life stability</td>
<td>24 months</td>
</tr>
<tr>
<td>Refrigeration required</td>
<td>No</td>
</tr>
<tr>
<td>Available at retail pharmacies</td>
<td>Yes</td>
</tr>
<tr>
<td>Covered by Medicaid</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Dosing**
- Starting dose: 0.07 mg/kg (up to 5mg) once daily
  - Adjust according to blood pressure response
  - Doses above 0.61 mg/kg (40mg) have not been studied in pediatric patients

**Clinical Considerations**
- No refrigeration or shaking required
- Not recommended in patients with CrCl <30 mL/min
- Warnings, contraindications, and adverse events mirror standard lisinopril labeling
  - Angioedema
  - Hypotension
  - Hyperkalemia
  - Pregnancy
**Stage C Heart Failure with Reduced Ejection Fraction (HFrEF)**

**Pharmacological Treatment:**
Renin-angiotensin system inhibition with angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) or angiotensin receptor-neprilysin inhibitor (ARNI)

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACE: A</td>
<td>Clinical strategy of inhibition of the renin-angiotensin system with ACE-I or ARBs or ARNI in conjugation with evidence-based beta blockers, and aldosterone antagonists in selected patients, is recommended in patients with HFrEF to reduce morbidity and mortality</td>
</tr>
<tr>
<td></td>
<td>ARB: A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARNI: B-R</td>
<td></td>
</tr>
</tbody>
</table>

Circulation. 2016;134.
Stage C Heart Failure with Reduced Ejection Fraction (HFrEF)

Pharmacological Treatment:

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACE-A</td>
<td>ACE-Is are recommended in HFrEF to reduce morbidity and mortality</td>
</tr>
<tr>
<td>I</td>
<td>ARB-A</td>
<td>ARBs are recommended in HFrEF to reduce morbidity and mortality in those intolerant to ACE-Is (angioedema, cough)</td>
</tr>
<tr>
<td>IIa</td>
<td>ARNI-B-R</td>
<td>In those with HFrEF NYHA class II or III symptoms, replacement with ARNI is recommended to further reduce morbidity and mortality</td>
</tr>
</tbody>
</table>

Circulation. 2016;134.

Stage C Heart Failure with Reduced Ejection Fraction (HFrEF)

Pharmacological Treatment: Ivabradine (Sinoatrial node I-channel inhibitor)

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>Ivabradine can be beneficial to reduce HF hospitalizations for patients with symptomatic NYHA class II-III stable chronic HFrEF (LVEF ≤35%) who are receiving goal-directed therapy, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a resting heart rate of 70 bpm or greater</td>
</tr>
</tbody>
</table>

Circulation. 2016;134.

2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease

Developed in Collaboration with American Association for Thoracic Surgery, American Society of Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons

Endorsed by Preventive Cardiovascular Nurses Association and Society for Vascular Surgery

© American College of Cardiology Foundation and American Heart Association

Circulation. 2016;133.
Duration of DAPT in CAD

**Key Points**
- Aspirin 81mg daily is almost always continued indefinitely in patients with CAD
- In SIHD following PCI, DAPT should be continued for >1 month and >6 months for BMS and DES, respectively
  - May discontinue at 3 months with high risk of bleeding (oral anticoagulation, major intracranial surgery, develop significant overt bleeding)
- With acute/recent ACS, DAPT should be continued for >12 months
  - May discontinue at 6 months with high risk of bleeding

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Infectious disease
- Cardiovascular
- Pulmonology
- Diabetes
- Neurology
- Gastrointestinal
Cinqair® reslizumab

- Approved March 23, 2016 (standard review)
- Indicated as add-on maintenance therapy in adult patients with severe asthma
  - Must have an eosinophilic phenotype
  - Should not be used for acute bronchospasm, status asthmaticus, or other eosinophilic conditions
- Available as 100 mg/10 mL single-use vials

Mechanism

- Monoclonal antibody
- Interleukin-5 (IL-5) antagonist
  - Growth, differentiation, recruitment, activation, and survival of eosinophils
  - Theoretically decreases inflammation in asthma
  - True mechanism of action not definitely established

Dosing

- 3 mg/kg as intravenous infusion in healthcare setting every 4 weeks
  - Administer over 20 to 50 minutes
  - Not for IV push/bolus
  - Requires in-line filter for administration

Patients requiring 3 vials of Cinqair®

<table>
<thead>
<tr>
<th>Patient Weight (kg)</th>
<th>Cinqair® Dose (mg)</th>
<th>Total Volumes of Cinqair® Solution (mL)</th>
<th>Number of Vials Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>61</td>
<td>251</td>
<td>20.1</td>
<td>3</td>
</tr>
<tr>
<td>68</td>
<td>254</td>
<td>20.4</td>
<td>3</td>
</tr>
<tr>
<td>69</td>
<td>251</td>
<td>20.1</td>
<td>3</td>
</tr>
<tr>
<td>72</td>
<td>210</td>
<td>21.0</td>
<td>3</td>
</tr>
<tr>
<td>71</td>
<td>219</td>
<td>21.3</td>
<td>3</td>
</tr>
<tr>
<td>73</td>
<td>216</td>
<td>21.6</td>
<td>3</td>
</tr>
<tr>
<td>75</td>
<td>219</td>
<td>21.9</td>
<td>3</td>
</tr>
<tr>
<td>74</td>
<td>222</td>
<td>22.2</td>
<td>3</td>
</tr>
<tr>
<td>75</td>
<td>225</td>
<td>22.5</td>
<td>3</td>
</tr>
</tbody>
</table>

www.cinqair.com
Cinqair®
reslizumab

Clinical Considerations
• Black box warning: anaphylaxis
  • Seen in 0.3% of patients in placebo-controlled trials
  • Can occur as early as second dose
  • Administration should occur in healthcare setting with healthcare professional prepared to treat anaphylaxis
• Warnings include
  • Malignancy (0.6% vs 0.3% in clinical trials; varying types)
  • Do not abruptly stop or discontinue steroids upon initiation; do so gradually
  • Treat parasitic infections prior to initiation or discontinue therapy

Bevespi Aerosphere®
glycopyrrolate/formoterol fumarate

• Approved April 25, 2016 (standard review)
• Indicated as a twice-daily, long-term treatment for adults with chronic obstructive pulmonary disease (COPD)
• Not a rescue inhaler or used to treat sudden symptoms
• Not indicated for the treatment of asthma
• First inhaler to utilize Co-suspension Delivery Technology

Co-suspension Delivery Technology

www.cosuspenddeliverytechnology.com
Bevespi Aerosphere®
glycopyrrolate/formoterol fumarate
Co-suspension Delivery Technology

Individual Components
- Glycopyrrolate 9mcg
  - Long-acting antimuscarinic agent; anticholinergic
- Formoterol fumarate 4.8mcg
  - Long-acting beta₂-adreneric agonist (LABA)
- Together, relax smooth muscle around airways and prevent those muscles from constricting leading to bronchodilation

Dosing
- Two puffs, twice daily, every day
Bevespi Aerosphere®
glycopyrrolate/formoterol fumarate

Clinical Considerations
• Do not initiate in acutely deteriorating COPD or in combination with other medications containing LABA
• Avoid beta-blockers and other anticholinergics
• If bronchospasm occurs, discontinue use
• Worsening narrow-angle glaucoma and urinary retention may occur
• Most common adverse effects (>2%):
  • urinary tract infection
  • cough

Jentadueto XR®
linagliptin/metformin

• Approved May 27, 2016 (standard review)
  • Standard release formulation January 2012
• Indicated as adjunct to diet and exercise in adults with type 2 diabetes mellitus (DM)
  • Not to be used in patients with type 1 DM
• Extended release formulation allowing for once-daily administration
Jentadueto XR®
linagliptin/metformin

Individual Components and Dosing
• Linagliptin 2.5mg or 5mg
  • Dipeptidyl peptidase IV (DPP-IV) inhibitor
  • Prevents inhibition of incretin hormones (glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide)
  • Increase insulin synthesis and decrease glucagon secretion
• Metformin 1000mg
  • Decreases hepatic glucose production
  • Decreases intestinal absorption of glucose
  • Improves insulin sensitivity

Jentadueto XR®
linagliptin/metformin

Individual Components and Dosing
• Linagliptin 2.5mg or 5mg
• Metformin 1000mg
• Dosing based on patient’s current doses of individual products or Jentadueto IR
• Maximum daily dose of linagliptin 5mg and metformin 2000mg
• Decreased doses of insulin and/or sulfonylureas may be required when used concomitantly
Jentadueto XR®
linagliptin/metformin

Clinical Considerations
• Expect ~1.7% reduction in Hgb A1C
• up to 3% in patients with high baseline (8.5-12.0%)
• Black box warning for lactic acidosis
• Metformin labeling recommends dosage adjustment for renal dysfunction
• Primary adverse effects:
  • Diarrhea (6%)
  • Nasopharyngitis (6%)

Invokamet XR®
canagliflozin/metformin

• Approved September 20, 2016 (standard review)
• Standard release formulation August 2014
• Indicated as adjunct to diet and exercise in adults with type 2 diabetes mellitus (DM)
• Not to be used in patients with type 1 DM
• Extended release formulation allowing for once-daily administration
Invokamet XR®
canagliflozin/metformin

Individual Components and Dosing
• Canagliflozin 50mg, 100mg, or 150mg
• Sodium-glucose cotransporter 2 (SGLT2) inhibitor
  • Reduces reabsorption of glucose in proximal tubule thereby increasing urinary glucose excretion
• Metformin 500mg or 1000mg
  • Decreases hepatic glucose production
  • Decreases intestinal absorption of glucose
  • Improves insulin sensitivity

Clinical Considerations
• Expect ~1.8% reduction in Hgb A1C
• Black box warning for lactic acidosis
• Metformin labeling recommends dosage adjustment for renal dysfunction
• Canagliflozin requires increased dosing with UDP-glucuronosyl transferase (UGT) inducers
  • Rifampin, phenytoin, ritonavir
• Warnings for bone fracture, increased yeast infections, increased urinary tract infections, and hypotension
**Synjardy XR®**  
*empagliflozin/metformin*  
- Approved December 9, 2016 (standard review)  
- Standard formulation approved August 2015  
- Indicated as adjunct to diet and exercise in adults with **type 2 diabetes mellitus (DM)**  
  - Not to be used in patients with type 1 DM  
  - Also combination of SGLT2 inhibitor and metformin  
  - Similar labeling for warnings and adverse effects  
- Dosing ranges from empagliflozin 5 to 25mg/day and metformin 500 to 2000mg/day

**Adlyxin®**  
*lixisenatide*  
- Approved July 27, 2016 (standard review)  
- Indicated as adjunct to diet and exercise in adults with **type 2 diabetes mellitus (DM)**  
  - Not to be used in patients with type 1 DM  
  - Non-insulin injectable glucagon-like peptide-1 (GLP-1) agonist

**Mechanism and Dosing**  
- GLP-1 receptor agonist  
  - Increases glucose-dependent insulin release  
  - Decreases glucagon secretion  
  - Slows gastric emptying  
- Available as 50 mcg/mL and 100 mcg/mL prefilled pens (3mL - contains 14 pre-set doses)  
  - Initiate at 10mcg once daily x14 days  
  - On day 15, increase to 20 mcg once daily  
  - Administer within one hour before the first meal of the day  
  - Inject into abdomen, thigh, or upper arm
Adlyxin®
lixisenatide

Clinical Considerations
• Expect ~0.8% reduction in Hgb A1C
• Decreased doses of insulin and/or sulfonylureas may be required when used concomitantly
• Administration interactions:
  • Oral contraceptives should be taken >1 hour before or 11 hours after lixisenatide
  • Others concentration-dependent drugs should be given >1 hour prior to lixisenatide
• Adverse effects include nausea, vomiting, headache, diarrhea, dizziness, and hypoglycemia

Soliqua®
insulin glargine/lixisenatide

• Approved November 21, 2016 (priority review)
• Indicated as adjunct to diet and exercise in adults with type 2 diabetes mellitus (DM)
  • Not to be used in patients with type 1 DM
• Combination of long-acting insulin and a non-insulin injectable for those uncontrolled on either of the individual products
  • Between 15 and 60 units/day of long-acting insulin
• Has not been studied with short-acting insulins
Soliqua®
insulin glargine/lixisenatide

Individual Components and Dosing
- Insulin glargine (100 units/mL)
  - long acting insulin
- Lixisenatide (33 mcg/mL)
  - GLP-1 receptor agonist
    - Increases glucose-dependent insulin release
    - Decreases glucagon secretion
    - Slows gastric emptying
- Administer within one hour before the first meal of the day
- Inject into abdomen, thigh, or upper arm
Soliqua®
insulin glargine/lixisenatide

Individual Components and Dosing
- Insulin glargine (100 units/mL)
- Lixisenatide (33 mcg/mL)

### Starting Doses

<table>
<thead>
<tr>
<th>Current basal insulin dose</th>
<th>Soliqua® Dose</th>
<th>Insulin glargine content</th>
<th>Lixisenatide content</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30 units/day</td>
<td>15 units</td>
<td>15 units</td>
<td>5 mcg</td>
</tr>
<tr>
<td>30-60 units/day</td>
<td>30 units</td>
<td>30 units</td>
<td>10 mcg</td>
</tr>
</tbody>
</table>

- 1 unit Soliqua® = 1 unit insulin glargine = 0.33 mcg lixisenatide

### Dosage Titration (weekly)

<table>
<thead>
<tr>
<th>Fasting Plasma Glucose</th>
<th>Recommended Dosage Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above target range</td>
<td>+2 to +4 units</td>
</tr>
<tr>
<td>Within target range</td>
<td>0 units</td>
</tr>
<tr>
<td>Below target range</td>
<td>-2 to -4 units</td>
</tr>
</tbody>
</table>

- Maximum dose = 60 units
Clinical Considerations

- Approval trial demonstrated 1.1% average reduction in Hgb A1C
- Administration interactions:
  - Oral contraceptives should be taken >1 hour before or 11 hours after lixisenatide
  - Others concentration-dependent drugs should be given >1 hour prior to lixisenatide
- Adverse effects:
  - hypoglycemia, allergic reactions, nausea, nasopharyngitis, diarrhea, upper respiratory tract infections, headache

- Infectious disease
- Cardiovascular
- Pulmonology
- Diabetes
- Neurology
- Gastrointestinal
Nuplazid®
pimavanserin

- Approved April 29, 2016 (priority review)
- Atypical antipsychotic indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis
- Over 50% of patients with Parkinson's disease experience hallucinations and delusions
  - Majority of patients in approval trial experienced fewer and/or less severe symptoms at 6 weeks
- No effect on motor symptoms

Nuplazid®
pimavanserin

**Mechanism**
- Exact mechanism unknown
- Believed to be mediated through inverse agonist and antagonist activity at serotonin 5-HT₂A and (to lesser extent) 5-HT₂C receptors
  - Inverse agonism suppresses basal activity
  - Does not bind dopamine, histamine, muscarinic, or adrenergic receptors

Nuplazid®
pimavanserin

**Mechanism and Dosing**
- Exact mechanism unknown
- Believed to be mediated through inverse agonist and antagonist activity at serotonin 5-HT₂A and (to lesser extent) 5-HT₂C receptors
  - Inverse agonism suppresses basal activity
  - Does not bind dopamine, histamine, muscarinic, or adrenergic receptors
**Nuplazid®]**

**Mechanism**
- Exact mechanism unknown
- Believed to be mediated through inverse agonist and antagonist activity at serotonin 5-HT_{2A} and (to lesser extent) 5-HT_{2C} receptors
  - Inverse agonism suppresses basal activity
- Does not bind dopamine, histamine, muscarinic, or adrenergic receptors

**Dosing**
- 34mg (taken as two 17mg tablets) once daily
- Does not require dosage titration
- With or without food

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**Clinical Considerations**
- Not recommended in renal (CrCl <30 mL/min) or hepatic impairment
- Should not be used for dementia-related psychosis
- QT interval prolongation
  - Should be avoided with other QT prolonging agents
  - Requires dosage adjustment to 17mg once daily when administered with strong CYP3A4 inhibitors
  - May require increased dose with strong 3A4 inducers
- Adverse effects: peripheral edema and confusion

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**Zinbryta®**

- Approved May 27, 2016
- Previously marked as Zenapax® to prevent acute rejection in kidney transplant recipients (discontinued in 2009 due to lack of market demand)
- Indicated for the treatment of adults with relapsing forms of multiple sclerosis (MS)
  - Should be reserved for patients who have had inadequate response to ≥2 other MS therapies
  - Decreases flare-ups and reduces development of new brain lesions
- Only available through a restricted distribution program called the Zinbryta REMS Program
Zinbryta®
daclizumab

Mechanism
• Exact mechanism in MS unknown
• Believed to be related to modulation of IL-2-mediated activation of lymphocytes
  • Binds to CD25 subunit of IL-2 receptor

Dosing
• 150mg injected subcutaneously once monthly
  • Prefilled syringe
  • Inject into thigh, abdomen, or back of upper arm

Clinical Considerations
• Black box warnings
  • Hepatic injury (liver failure, autoimmune hepatitis)
  • Monitor LFTs at baseline and then monthly to 6 months after completion of therapy
  • Other immune-mediated disorders (skin reactions, lymphadenopathy, non-infectious colitis)

• Risk Evaluation and Mitigation Strategy (REMS) Program
  • Prescribers must enroll and complete training to be certified
  • Patients must enroll and comply with ongoing monitoring
  • Pharmacies must be certified

Clinical Considerations
• Contraindications
  • Preexisting hepatic disease (ALT/AST >2x ULN)
  • History of autoimmune hepatitis
  • Warnings for anaphylaxis, angioedema, and depression/suicide
  • Screen for tuberculosis and other infections prior to initiation
  • Ensure vaccinations up to date
  • Live vaccines not recommended during therapy and up to 4 months after completion
Briviact®
brivaracetam (C-V)

• Approved February 18, 2016 (standard review)
• Indicated as part of combination therapy to treat partial-onset seizures in people ≥16 years old with epilepsy
• Federally controlled substance (Class-V) due to ability to be abused or lead to dependence

Briviact®
brivaracetam (C-V)

Mechanism
• Exact mechanism not known
• Highly selective for synaptic vesicle protein 2A in the brain (affect neurotransmitter release?)

Dosing
• Starting dose = 50mg BID
• Based on tolerability and therapeutic response, dosing ranges 25mg BID to 100mg BID
• Available as 1:1:1 dosing conversion:
  • Tablets (10mg, 25mg, 50mg, 75mg, and 100mg)
  • Oral solution (10 mg/mL)
  • Injection (50mg/5mL single-dose vial)

Briviact®
brivaracetam (C-V)

Clinical Considerations
• Does not require pharmacokinetic monitoring
• For all stages of hepatic impairment, start at 25mg BID with a maximum dose of 75mg BID
• Dose should be increased when used with CYP3A4 inducers (including phenytoin and carbamazepine)
• Warnings for suicidal ideation, somnolence/fatigue, negative psychiatric/behavioral reactions
• Adverse effects: somnolence/sedation, dizziness, fatigue, nausea/vomiting
Onzetra Xsail®
sumatriptan nasal powder

- Approved January 27, 2016
  - New dosage form for most commonly prescribed treatment of migraine headaches (initial approval 1992)
- Indicated for the **acute treatment of migraine** with or without aura in adults
  - Not indicated for migraine prophylaxis or for cluster headaches
- Marketed as a quick option in those experience nausea and vomiting with migraines
  - Rapidly absorbed nasal powder delivered to the back of the nose with a breath-powered delivery system

Onzetra Xsail®
sumatriptan nasal powder

Onzetra Xsail®
sumatriptan nasal powder
Onzetra Xsail®
sumatriptan nasal powder

Mechanism
- 5-HT₁B/1D receptor agonist in intracranial blood vessels and sensory nerves of the trigeminal system
- Cranial vessel vasoconstriction
- Inhibition of proinflammatory neuropeptide release

Dosing
- 22mg – administer via one nosepiece in each nostril (11mg each)
- Maximum dose in a 24-hour period = two doses (44mg)

Clinical Considerations
- Contraindications:
  - Coronary artery disease/vasospasm, Wolff-Parkinson-White syndrome, history of stroke/TIA, hemiplegic migraine, peripheral vascular disease, ischemic bowel disease, uncontrolled hypertension
  - Recent (last 24 hours) use of 5-HT₁ agonist or ergotamine
  - Recent (last 2 weeks) use of MAO-inhibitors
  - Severe hepatic impairment
- Adverse effects:
  - abnormal taste, nasal discomfort, rhinorrhea, rhinitis
Xtampza ER (oxycodone; C-II)
• DETERx Microsphere formulation (lipophilic salt)
• Only ER oxycodone paid for by UnitedHealthcare

Troxyca ER (oxycodone/naltrexone; C-II)
• Only oxycodone product that contains opioid antagonist naltrexone

Probuphine (buprenorphine; C-III)
• Partial opioid agonist used for maintenance treatment of opioid dependence in those who have sustained clinical stability on low/moderate dose transmucosal buprenorphine
• Four subdermal implants in upper arm that last for 6 months; can repeat for an additional 6 months
• Must be prescribed/inserted by certified physician

Infectious disease
Cardiovascular
Pulmonology
Diabetes
Neurology
Gastrointestinal
Ocaliva®

Approved May 27, 2016 (priority review)
First treatment approved for primary biliary cholangitis (PBC) in almost 20 years
In combination with ursodeoxycholic acid (UDCA), indicated for the treatment of PBC in adults with inadequate response to UDCA
Monotherapy in adults unable to tolerate UDCA
Accelerated approval
- Based upon reduction in alkaline phosphatase (ALP)
- Benefit in survival or disease-related symptoms has not been established

Mechanism
- Farnesoid X receptor (FXR) agonist
- Nuclear receptor expressed in liver and intestine
- Key regulator of bile acid, inflammatory, fibrotic, and metabolic pathways
- Decreases intracellular hepatocyte bile acid concentrations
  - suppresses de novo synthesis of bile acids from cholesterol
  - increases transport of bile acids out of hepatocytes

Dosing
- Recommended starting dose = 5mg once daily
  - Intolerant to UDCA or have not achieved adequate response to 1 year of UDCA therapy
  - Can increase to 10mg daily at 3 months
    - If adequate reduction in ALP and/or total bilirubin not achieved
    - If tolerating
  - Take at least 4 hours before or after bile acid binding resins
- Available as 5mg and 10mg tablets
**Clinical Considerations**

- Severe pruritus
  - Antihistamine or bile acid binding resin
  - Cut dose in half
  - Temporarily discontinue for up to 2 weeks
- Hepatic impairment
  - Starting dose in Child-Pugh B/C is 5mg once weekly
  - Can increase at 3 months to 5mg twice weekly and max of 10mg twice weekly
  - Decreases INR in patients on warfarin
- Adverse effects: pruritus, fatigue, abdominal pain, rash, dizziness, constipation, arthralgia, eczema

**Medication Access**

- No matter how well medications are prescribed, patients have to obtain and take them as prescribed
- Copay assistance cards/coupons/vouchers
- Patient Assistance Programs
- Encourage questions
  - “What questions do you have for me?”
  - “What could I explain better for you?”
- Compliance

**Pharmacotherapy Update 2016: General Health**

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Clinical Pharmacist Advanced, Palmetto Health
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Charleston, South Carolina
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