NEW DRUG UPDATE
SUNDAY/8:00-9:30AM

ACPE UAN: 0107-9999-17-011-L01-P 0.15 CEU/1.5 hr
0107-9999-17-011-L04-T 0.15 CEU/1.5 hr

Activity Type: Application-Based

Learning Objectives for Pharmacists & Pharmacy Technicians: Upon completion of this CPE activity participants should be able to:
1. Identify therapeutic indications of drugs recently approved by the FDA
2. Discuss the pharmacological properties of the new medications
3. List side effects, warnings, precautions and significant drug interactions associated with each medication
4. Identify the normal dose and dosage forms of the drugs presented
5. Describe limitations to implementing the new medications into clinical practice

Speaker: Joe Strain, PharmD
Dr. Joe Strain is a clinical pharmacist residing in Rapid City, SD. He currently practices at Rapid City Regional Hospital where he has primarily worked with the hospitalist program since 2004. Joe also serves as Professor of Pharmacy Practice for the South Dakota State University College of Pharmacy. Joe received his Doctorate in Pharmacy from South Dakota State University and then completed a Pharmacy Practice Residency at the University of Utah Hospitals and Clinics in Salt Lake City, UT.

Speaker Disclosure: Joe Strain reports no actual or potential conflicts of interest in relation to this CPE activity. Off-label use of medications will not be discussed during this presentation.
New Drug Update 2017

Joe Strain, Pharm.D.
SDSU College of Pharmacy – Rapid City Regional Hospital

Disclosure

- Joe Strain reports no actual or potential conflicts of interest associated with this presentation
Learning Objectives

- Upon successful completion of this activity, participants should be able to:
  - Identify therapeutic indications of drugs recently approved by the FDA.
  - Discuss pharmacological properties of the new medications.
  - List side effects, warnings, precautions and significant drug interactions associated with each medication.
  - Identify the normal dose and dosage forms of the drugs presented.
  - Describe limitations to implementing the new medications into clinical practice.

New Drug Approval Trends
Agenda

- Sugammadex (Bridion®)
- Pimavanserin (Nuplazid™)
- Sofosbuvir/velpatasvir (Epclusa®)
- Elbasvir/grazoprevir (Zepatier™)
- Obeticholic acid (Ocaliva™)
- Brivaracetam (Briviact®)
- Patiromer (Veltassa®)
- Lesinurad (Zurampic®)
- Insulin degludec/liraglutide (Xultophy®)
- Insulin glargine/Lixisenatide (Soliqua™)
- Bezlotoxumab (Zinplava™)
- Andexanet alfa (AndexXa™)

Sugammadex (Bridion®)

- Indication
  - Reversal of rocuronium and vecuronium

- Pharmacology
  - Gamma-cyclodextrin
  - 8 sugar ring with negatively charged side chains
  - Binds free rocuronium & vecuronium in plasma → remaining NMBA shifts from NMJ back to plasma
Rocuronium

Vecuronium

Succinylcholine

Sugammadex

Cisatracurium besylate

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**Sugammadex (Bridion®)**

- Pharmacokinetics
  - Onset in 2-3 minutes
  - T ½ ~ 2 hours
  - Excreted unchanged in the urine (95%)
  - T ½ prolonged in renal impairment
    - 19 hours in severe renal impairment
Sugammadex (Bridion®)

- Contraindications
  - Hypersensitivity reactions (0.3% incidence)
  - Reports of prolonged hospitalization and need for respiratory support
- Warnings/precautions
  - Severe renal impairment (CrCl < 30 ml/min)
  - No data for reversal in ICU
  - Limited data in pediatrics
  - No data in pregnancy or nursing mothers

- Warnings/precautions
  - Bradycardia → cardiac arrest within minutes of administration
    - Treat with atropine
- Drug interactions
  - Progestin-containing contraceptives
    - Must use alternative contraception for 7 days
### Common Adverse Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Sugammadex</th>
<th>Placebo</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 mg/kg (N = 895)</td>
<td>4 mg/kg (N = 1921)</td>
<td>16 mg/kg (N = 98)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11%</td>
<td>12%</td>
<td>15%</td>
</tr>
<tr>
<td>Pain</td>
<td>48%</td>
<td>52%</td>
<td>36%</td>
</tr>
<tr>
<td>Nausea</td>
<td>23%</td>
<td>26%</td>
<td>23%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4%</td>
<td>5%</td>
<td>13%</td>
</tr>
<tr>
<td>Headache</td>
<td>7%</td>
<td>5%</td>
<td>10%</td>
</tr>
</tbody>
</table>

### Median Recovery Time to T4/T1 Ratio to 0.9 after Rocuronium

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Recovery Time (Minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugammadex 2mg/kg (N = 48)</td>
<td>1.4</td>
</tr>
<tr>
<td>Neostigmine 50 mcg/kg (N = 48)</td>
<td>21.5</td>
</tr>
</tbody>
</table>
Sugammadex (Bridion®)

- Dosing post surgery
  - Train of four = 2 twitches
    - 2 mg/kg IV bolus
  - Post-tetanic count = 1-2 twitches and no TOF responses
    - 4 mg/kg IV bolus
- Dosing 3 minutes post 1.2 mg/kg of rocuronium
  - 16 mg/kg bolus

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Re-administration of rocuronium or vecuronium after sugammadex administration (up to 4 mg/kg)

<table>
<thead>
<tr>
<th>Renal function</th>
<th>Wait Time</th>
<th>Dose to Administer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>5 minutes to 4 hours</td>
<td>1.2 mg/kg rocuronium</td>
</tr>
<tr>
<td></td>
<td>&gt; 4 hours</td>
<td>0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium</td>
</tr>
<tr>
<td>Mild to moderate impairment</td>
<td>&lt; 24 hours</td>
<td>1.2 mg/kg rocuronium</td>
</tr>
<tr>
<td></td>
<td>&gt; 24 hour*</td>
<td>0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium</td>
</tr>
</tbody>
</table>

*Bridion PI 2015*
## Sugammadex (Bridion®)

- **Cost**
  - 200mg ~ $90
  - 500mg ~ $166
- **Availability**
  - 200mg and 500mg vials (100mg/ml)

### Expense Comparison for a 70 kg Patient

<table>
<thead>
<tr>
<th>Indication</th>
<th>Sugammadex</th>
<th>Neostigmine + Glycopyrrolate</th>
<th>Succinylcholine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post surgery TOF = 2</td>
<td>$90</td>
<td>$84</td>
<td>NA</td>
</tr>
<tr>
<td>Post surgery TOF = 0</td>
<td>$166</td>
<td>$115</td>
<td>NA</td>
</tr>
<tr>
<td>Rapid Sequence Intubation</td>
<td>$278</td>
<td>NA</td>
<td>$21</td>
</tr>
</tbody>
</table>

(includes rocuronium 100mg = $4.50)

NA = not applicable
Sugammadex (Bridion®)

• Bottom line
  • Fast, effective, safe reversal agent for rocuronium and vecuronium
  • Will NOT reverse other NMB’s
  • Watch for rare allergic reactions
  • ? Potential to replace succinylcholine

• Additional review

Bezlotoxumab (Zinplava™)

• Indication
  • Reduce recurrence of *Clostridium difficile* infection (CDI)
  • Patients MUST be receiving treatment for *Clostridium difficile* and at high risk of recurrence
  • NOT indicated for the treatment of CDI

• Pharmacology
  • Human monoclonal antibody
  • Binds to *Clostridium difficile* toxin B
  • Not fully understood why it prevents recurrence

• Pharmacokinetics
  • T ½ ~ 19 days
Bezlotoxumab (Zinplava™)

- Contraindications
  - None

- Warnings and Precautions
  - Heart failure exacerbations
    - 12.7% (15/118) bezlotoxumab vs. 4.8% (5/104) placebo
  - Deaths in patients with a history of heart failure
    - 19.5% (23/118) bezlotoxumab vs. 12.5% (13/104) placebo

- Risk vs. benefit

- Drug interactions
  - None identified

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### Adverse Reactions from Modify I and II Trials

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Bezlotoxumab N = 786</th>
<th>Placebo N = 781</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall infusion-related</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Nausea</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Headache</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.3%</td>
<td>1%</td>
</tr>
</tbody>
</table>
## MODIFY I and MODIFY II Efficacy Results

<table>
<thead>
<tr>
<th>Recurrent CDI</th>
<th>Bezlotoxumab N = 781</th>
<th>Placebo N = 781</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong>*</td>
<td>16.5% (129/781)</td>
<td>26.6% (206/773)</td>
</tr>
<tr>
<td>Hx of CDI in past 6 month</td>
<td>25% (54/216)</td>
<td>41.1% (90/219)</td>
</tr>
<tr>
<td>Hypervirulent strain</td>
<td>22% (22/100)</td>
<td>32.1% (35/109)</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>15.4% (60/390)</td>
<td>31.4% (127/405)</td>
</tr>
</tbody>
</table>

*primary endpoint; NNT = 10; p-value < 0.0001
All subjects received vancomycin, metronidazole or fidaxomicin for 10-14 days

http://ofid.oxfordjournals.org/content/2/suppl_1/67.full.html

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### Bezlotoxumab (Zinplava™)

- **Dosing**
  - Administer during treatment for CDI
  - Single dose, 10 mg/kg IV infusion over 1 hour

- **Availability/storage**
  - 1000mg/40ml (25mg/ml) vial stored in refrigerator
  - Dilute in NS or D5 to 1 mg/ml to 10 mg/ml prior to infusion
  - Allow bag to come to room temp prior to use (stable x 16 hours)

- Expected first quarter 2017
- Cost???
Bezlotoxumab (Zinplava™)

• Bottom line
  • Reduced rate of recurrent CDI
  • Only in conjunction with antibiotic treatment
  • Consider for high risk populations
  • Well-tolerated in trials
  • Caution in heart failure

• Additional review

Pimavanserin (Nuplazid™)

• Indication
  • Treatment of hallucinations & delusions associated with Parkinson’s disease psychosis

• Pharmacology
  • Mechanism “unknown”
  • Selective serotonin inverse agonist
Pimavanserin (Nuplazid™)

• Pharmacokinetics
  • T ½ 75h, active metabolite 200h

• Metabolism
  • CYP3A4/5

• Elimination
  • Minimal renal clearance

Pimavanserin (Nuplazid™)

• Warnings & precautions
  • Black Box: increased mortality in elderly dementia patients treated with antipsychotics
  • QT prolongation (~ 5-8 msec)

• Drug interactions
  • CYP3A4 inhibitors & inducers
    • Ketoconazole increased AUC 3X
    • Phenytoin, rifampin will decrease levels
### Common Adverse Reactions from 6-week Placebo-Controlled Trials

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Pimavanserin N = 202</th>
<th>Placebo N = 231</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Constipation</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>Hallucination</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Confusion</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>2%</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

Nuplazid PI. 2016

### Efficacy Results from Phase 3 Clinical Trial

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Pimavanserin N = 95</th>
<th>Placebo N = 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPS-PD Mean score change from baseline</td>
<td>-5.79*</td>
<td>-2.73</td>
</tr>
</tbody>
</table>


*P = 0.0014
Pimavanserin (Nuplazid™)

• Dosing
  • 34 mg once daily with or without food

• Availability
  • 17 mg tablets

• Cost
  • ~ $2,000 per month

Pimavanserin (Nuplazid™)

• Bottom line
  • First agent formally approved for Parkinson’s psychosis
  • Lacks dopamine antagonist effects of other antipsychotics
  • Unknown if it is superior to clozapine

• Additional review
Elbasvir/Grazoprevir (Zepatier®)

- **Indication**
  - Genotype 1 or 4 Hepatitis C
    - With or without Ribavirin
- **Pharmacology**
  - Elbasvir
    - HCV NS5A inhibitor
  - Grazoprevir
    - HCV NS3/4A protease inhibitor

### Genotype 1 Studies

<table>
<thead>
<tr>
<th>Genotype 1 Studies</th>
<th>Population</th>
<th>SVR12</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-EDGE TN</td>
<td>Treatment Naïve +/- cirrhosis</td>
<td>95% (273/288)</td>
<td></td>
</tr>
<tr>
<td>C-EDGE CO-INFXN</td>
<td>Treatment Naïve +/- cirrhosis + HIV-1 Co-infection</td>
<td>95% (179/189)</td>
<td>Zepatier 12 weeks</td>
</tr>
<tr>
<td>C-SURFER</td>
<td>Treatment Naïve / Treatment Experienced +/- cirrhosis + severe renal impairment</td>
<td>94% (115/122)</td>
<td></td>
</tr>
<tr>
<td>C-EDGE TE</td>
<td>Treatment Experienced +/- cirrhosis +/- HIV-1 co-infection</td>
<td>94% (90/96) 97% (93/96)</td>
<td>Zepatier 12 weeks Zepatier + RBV 16 weeks</td>
</tr>
<tr>
<td>C-Salvage</td>
<td>Treatment Experienced +/- cirrhosis</td>
<td>96% (76/79)</td>
<td>Zepatier + RBV 12 weeks</td>
</tr>
<tr>
<td>Genotype 4 Studies</td>
<td>Population</td>
<td>SVR12</td>
<td>Treatment Duration</td>
</tr>
<tr>
<td>--------------------</td>
<td>------------</td>
<td>-------</td>
<td>--------------------</td>
</tr>
<tr>
<td>C-EDGE TN</td>
<td>Treatment Naïve +/- cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-EDGE CO-INFXN</td>
<td>Treatment Naïve +/- cirrhosis + HIV-1 Co-infection</td>
<td>97% (64/66)</td>
<td>Zepatier 12 weeks</td>
</tr>
<tr>
<td>C-SCAPE</td>
<td>Treatment Naïve without cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-EDGE TE</td>
<td>Treatment Experienced +/- Cirrhosis</td>
<td>100% (8/8)</td>
<td>Zepatier + RBV 16 weeks</td>
</tr>
</tbody>
</table>

Elbasvir/Grazoprevir (Zepatier®)

- **Contraindications**
  - Moderate or severe hepatic impairment
  - Strong CYP3A inducers (carbamazepine, phenytoin, rifampin)
  - Atazanavir, darunavir, lopinavir, saquinavir, cyclosporine, efavirenz

- **Drug Interactions**
  - Avoid co-administration:
    - CYP3A inducers (decreased concentrations)
    - CYP3A inhibitors (increased concentrations)
  - Do not exceed atorvastatin 20 mg daily or rosuvastatin 10 mg daily, use lowest statin dose necessary.
Elbasvir/Grazoprevir (Zepatier®)

- Adverse effects
  - Headache, nausea, fatigue

- Dosage and Administration
  - One tablet once daily with or without food
  - 50 mg elbasvir /100 mg grazoprevir

- No adjustments in renal dysfunction or dialysis

Elbasvir/Grazoprevir (Zepatier®)

- Bottom line
  - One tablet, once daily treatment for HCV genotypes 1 or 4 infections
  - Cure rates of >94%
  - Duration of 12 weeks for most patient groups
  - NS5A polymorphism testing recommended
  - Approved in renal failure

- Additional review
Sofosbuvir and Velpatasvir (Epclusa®)

• **Indication**
  • Genotype 1, 2, 3, 4, 5, or 6 HCV infection
    • Without cirrhosis or with compensated cirrhosis
    • With decompensated cirrhosis in combination with ribavirin

• **Pharmacology**
  • Sofosbuvir: NS5B polymerase inhibitor
  • Velpatasvir: NS5A inhibitor

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### ASTRAL-1 Trial
Response to 12 weeks of sofosbuvir-velpatasvir

<table>
<thead>
<tr>
<th>Any genotype</th>
<th>99% (618/624)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>98% (206/210)</td>
</tr>
<tr>
<td>1b</td>
<td>99% (117/118)</td>
</tr>
<tr>
<td>2</td>
<td>100% (104/104)</td>
</tr>
<tr>
<td>4</td>
<td>100% (116/116)</td>
</tr>
<tr>
<td>5</td>
<td>97% (34/35)</td>
</tr>
<tr>
<td>6</td>
<td>100% (41/41)</td>
</tr>
</tbody>
</table>

Drug interactions

- P-gp inducers and CYP inducers decrease concentrations of sofosbuvir and velpatasvir
- Amiodarone may lead to bradycardia when given with sofosbuvir
- Acid-reducing drugs decrease velpatasvir absorption
- Avoid proton pump inhibitors
Sofosbuvir and Velpatasvir (Epclusa®)

• Dosing
  • One tablet orally once daily
  • 400 mg sofosbuvir / 100 mg velpatasvir
  • With or without food
• No dosage recommendations for patients with severe renal impairment (CrCl < 30 ml/min)
### Hepatitis C Dosage and Cost Summary

<table>
<thead>
<tr>
<th>HCV Infection</th>
<th>Treatment</th>
<th>Duration</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotypes 1,4,5,6</td>
<td>Harvoni®</td>
<td>12 weeks</td>
<td>$94,500</td>
</tr>
<tr>
<td>Genotype 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Viekira Pak™ + ribavirin</td>
<td>12 weeks&lt;sup&gt;1&lt;/sup&gt;</td>
<td>$83,300</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>Sofosbuvir + ribavirin</td>
<td>12 weeks</td>
<td>~ $84,000</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>Sofosbuvir + ribavirin</td>
<td>24 weeks</td>
<td>~ $168,000</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>Sofosbuvir + daclatasvir</td>
<td>12 weeks</td>
<td>~ $150,000</td>
</tr>
<tr>
<td>Genotype 4</td>
<td>Technivie™ + ribavirin</td>
<td>12 weeks</td>
<td>~ $77,000</td>
</tr>
<tr>
<td>Genotypes 1 &amp; 4</td>
<td>Zepatier™</td>
<td>12 weeks&lt;sup&gt;d&lt;/sup&gt;</td>
<td>~ $54,000</td>
</tr>
<tr>
<td>Genotypes 1,2,3,4,5,6</td>
<td>Epclusa®</td>
<td>12 weeks&lt;sup&gt;e&lt;/sup&gt;</td>
<td>~$74,760</td>
</tr>
</tbody>
</table>

- <sup>a</sup> For genotype 1 patients receiving prior treatment and having cirrhosis 24 weeks is recommended
- <sup>b</sup> For genotype 1b without cirrhosis ribavirin not needed
- <sup>c</sup> For 1a with cirrhosis 24 weeks recommended
- <sup>d</sup> Patients with polymorphism or who are treatment experienced may require ribavirin and/or 16 weeks of treatment
- <sup>e</sup> Patients with decompensated cirrhosis

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### Obeticholic acid (Ocaliva™)

- **Indication**
  - Primary biliary cholangitis with or without ursodiol

- **Pharmacology**
  - Farnesoid X receptor agonist
  - Decreases amount of bile acids in hepatocytes by suppressing synthesis
  - Increases transport of bile acids from the hepatocytes

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<sup>Ocaliva PI 2016.</sup>
Obeticholic acid (Ocaliva™)

- Pharmacokinetics/dynamics
  - Clinical effects on AlkPO4 plateau at ~3 months
  - Metabolized by conjugation in the liver
    - Severe hepatic impairment increases level 17X
  - Primarily excreted through biliary system

Obeticholic acid (Ocaliva™)

- Contraindications
  - Complete biliary obstruction
- Warnings and precautions
  - Liver enzyme elevations
  - Severe pruritus
  - HDL reduction
Obeticholic acid (Ocaliva™)

• Drug interactions
  • Bile acid binding resins may decrease absorption
  • Take 4 hours before or 4 hour after
  • Increases warfarin exposure but decreases INR???

Obeticholic acid Adverse Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Obeticholic acid titration N = 70</th>
<th>Obeticholic acid 10 mg N = 73</th>
<th>Placebo N = 73</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>56%</td>
<td>68%</td>
<td>38%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16%</td>
<td>23%</td>
<td>14%</td>
</tr>
<tr>
<td>Abdominal pain &amp; discomfort</td>
<td>19%</td>
<td>10%</td>
<td>14%</td>
</tr>
<tr>
<td>Rash</td>
<td>7%</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Eczema</td>
<td>6%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Discontinuation rate</td>
<td>10%</td>
<td>12%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Ocaliva PI 2016
Results from the POISE Trial

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Obeticholic acid titration N = 70</th>
<th>Obeticholic acid 10 mg N = 73</th>
<th>Placebo N = 73</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint responder rate</td>
<td>46%**</td>
<td>47%**</td>
<td>10%</td>
</tr>
<tr>
<td>ALP &lt; 1.67 ULN*</td>
<td>47%</td>
<td>55%</td>
<td>16%</td>
</tr>
<tr>
<td>Decrease in ALP of ≥ 15%*</td>
<td>77%</td>
<td>77%</td>
<td>29%</td>
</tr>
<tr>
<td>Tbili ≤ ULN*</td>
<td>89%</td>
<td>82%</td>
<td>78%</td>
</tr>
</tbody>
</table>


*component of primary endpoint  ** p < 0.001 vs. placebo

ALP = alkaline phosphate; ULN = upper limit of normal

Obeticholic acid (Ocaliva™)

- **Dosing**
  - 5 mg once daily, increase to 10 mg in 3 months if further decrease in AlkPO4 or total bilirubin is needed
  - Do not start at 10 mg due to incidence of pruritus
  - If pruritus develops
    - Decrease dose to 5 mg daily or 5 mg every other day
    - Discontinue for up to 2 weeks then restart at lower dose
    - Add antihistamine or bile acid binding resin
Obeticholic acid (Ocaliva™)

• Availability
  • 5 or 10 mg tablets
  • Specialty pharmacies will supply

• Cost
  • ~ $69,000 per year

Obeticholic acid (Ocaliva™)

• Bottom line
  • First approval for primary biliary cholangitis in 20 years
  • Unique mechanism of action
  • Ongoing research for non-alcoholic steatohepatitis

• Additional review
  • Bowlus C. Hepat Med. 2016;8:89-95.
Brivaracetam (Briviact®)

• **Indication**
  - Adjunctive therapy for partial onset seizures in patients ≥ 16 years old

• **Pharmacology**
  - Binds to synaptic vesicle protein 2A in the brain
  - Similar to levetiracetam but with higher affinity for the receptor

Brivaracetam (Briviact®) Briviact PI 2016.

Brivaracetam (Briviact®)

• **Pharmacokinetics**
  - Peaks in 1 hour
  - Metabolized primarily by hydrolysis to inactive compounds
    - Secondary via CYP2C19
  - T ½ ~ 9 hours
  - Elimination primarily via kidneys (95%)
Brivaracetam (Briviact®)

• Contraindications
  • Hypersensitivity

• Warnings and precautions
  • Suicidal thoughts/behavior
  • Driving due to fatigue
  • Psychiatric reactions
  • Withdrawal seizures

Brivaracetam increases phenytoin & carbamazepine levels
  • Monitor levels

Rifampin decreases levels
  • Double the dose of brivaracetam
  • No additional benefit if used with levetiracetam
### Adverse Reactions from Placebo-Controlled Trials

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Brivaracetam</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 803</td>
<td>N = 459</td>
</tr>
<tr>
<td>Somnolence &amp; sedation</td>
<td>15.2%</td>
<td>8.5%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11.2%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8.7%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4%</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

*Neurology* 2016; 87:314-323

### Clinical Efficacy

<table>
<thead>
<tr>
<th>Brivaracetam</th>
<th>50 mg</th>
<th>100 mg</th>
<th>200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>% seizure reduction over placebo per 28 days</td>
<td>19.5%</td>
<td>24.4%</td>
<td>24%</td>
</tr>
</tbody>
</table>

*Bar-Meir et al.* 2016; *Neurology* 87:314-323
Brivaracetam (Briviact®)

• Dosing
  • Start with 50 mg BID
  • Adjust to 25 mg BID or 100 mg BID based on tolerability & response
  • If hepatic impairment start at 25 mg BID with max 75 mg BID
  • Avoid abruptly stopping

Brivaracetam (Briviact®)

• Availability & Cost
  • Tablets (10, 25, 50, 75, 100 mg)
    • ~ $900/month
  • Oral Solution (10 mg/ml)
    • ~ $900/month
  • Injection (50 mg/5ml)
    • ~$80/day
  • DEA Schedule V
Brivaracetam (Briviact®)

- **Bottom line**
  - Similar to levetiracetam with higher potency for the SV2A receptor
  - No direct comparison to levetiracetam
  - Controlled substance
- **Additional review**

Patiromer (Veltassa®)

- **Indication**
  - Treatment of hyperkalemia
  - Not for emergent treatment
- **Pharmacology**
  - Non-absorbed, potassium-binding, anionic polymer
  - Calcium ions exchange for potassium ions in the colon thus facilitating fecal elimination
Patiromer (Veltassa®)

- Pharmacokinetics
  - Not absorbed
  - Onset of action 7 hours
- Contraindications
  - Hypersensitivity
- Warnings and precautions
  - Avoid in severe constipation or bowel obstructions
  - Hypomagnesemia

- Drug interactions
  - Binds to other drugs in the GI tract (Black Box Warning)
  - Take all other medications at least 6 hours before or after patiromer
  - FDA now requiring drug interaction studies for sodium polystyrene sulfonate
## Adverse Reactions in Clinical Trials

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Patiromer N = 666</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypomagnesemia (&lt; 1.4 mg/dl)</td>
<td>9%</td>
</tr>
<tr>
<td>Constipation</td>
<td>7.2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.8%</td>
</tr>
<tr>
<td>Hypokalemia (&lt; 3.5 mEq/L)</td>
<td>4.7%</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2%</td>
</tr>
</tbody>
</table>

## Patiromer Use in Patients with Renal Disease and taking RAAS inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Patiromer starting dose 8.4 g daily N = 90</th>
<th>Patiromer starting dose 16.8 g daily N = 147</th>
<th>Overall Population N = 237</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline potassium (mmol/L)</td>
<td>5.31</td>
<td>5.74</td>
<td>5.58</td>
</tr>
<tr>
<td>Mean change from baseline at week 4</td>
<td>-0.65 (-0.074, -0.55)</td>
<td>-1.23 (-1.31, -1.16)</td>
<td>-1.01 * (-1.07, -0.95)</td>
</tr>
</tbody>
</table>

*P < 0.001
Patiromer (Veltassa®)

- **Dosing**
  - 8.4 g once daily
  - Titrate weekly to goal potassium
  - Max recommended dose = 25.2 g
  - Mix into 30 ml of water, stir, then add 60 ml of water and stir; Do not heat
  - Store in fridge; stable at room temp x 3 months
- **Cost is ~ $20-30 per dose**

- **Monitoring**
  - Potassium and magnesium

**Bottom line**
- Alternative hyperkalemic agent
- Not for emergent use
- No direct comparison against sodium polystyrene sulfonate
- Separate other drugs by 6 hours

**Additional review**
Lesinurad (Zurampic®)

• **Indication**
  - Hyperuricemia with gout in patients taking a xanthine oxidase inhibitor

• **Pharmacology**
  - Uric acid transporter 1 (URAT1) inhibitor
  - Blocks uric acid reabsorption in the kidney thus facilitating excretion

Lesinurad (Zurampic®)

• **Pharmacokinetics**
  - Well-absorbed (~ 100%)
  - 98% protein bound
  - T ½ ~ 5 hours
  - Metabolism
    - CYP2C9
  - Elimination
    - Majority via kidneys
Lesinurad (Zurampic®)

- **Contraindications**
  - Severe renal impairment (CrCl < 30 ml/min)
  - Tumor lysis syndrome

- **Warnings and precautions**
  - Not for use as monotherapy
  - Do not initiate if CrCl < 45 ml/min
  - Monitor renal function closely if CrCl < 60 ml/min

---

### Adverse Reactions from Phase 3 Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>Placebo N = 516</th>
<th>Lesinurad 200mg N = 511</th>
<th>Lesinurad 400mg N = 510</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scr ≥ 1.5X baseline</td>
<td>12 (2.3%)</td>
<td>29 (5.7%)</td>
<td>85 (16.7%)</td>
</tr>
<tr>
<td>Resolution of Scr by end of study</td>
<td>9/12 (75%)</td>
<td>26/29 (90%)</td>
<td>68/85 (80%)</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>1.7%</td>
<td>0.6%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Headache</td>
<td>4.1%</td>
<td>5.3%</td>
<td>NR</td>
</tr>
<tr>
<td>GERD</td>
<td>0.8%</td>
<td>2.7%</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = not reported
Lesinurad (Zurampic®)

- Drug interactions
  - CYP2C9 inhibitors (e.g. fluconazole, amiodarone)
    - Use caution
  - CYP2C9 inducers (e.g. rifampin, carbamazepine)
    - Monitor for reduced efficacy
  - Lesinurad is a weak inducer of CYP3A4
    - Hormonal contraceptives, sildenafil, amlodipine may be reduced

---

Efficacy with Allopurinol

Month 6

<table>
<thead>
<tr>
<th>% with Uric Acid Level of &lt; 6 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLEAR 1 Trial</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>28</td>
</tr>
<tr>
<td>54</td>
</tr>
</tbody>
</table>

- Allopurinol
- Lesinurad + allopurinol

P < 0.0001
Efficacy with Febuxostat

Month 6

% with Uric Acid Level of < 5 mg/dl

- Febuxostat
- Lesinurad + Febuxostat

CRYSral Trial

Lesinurad (Zurampic®)

• Dosing
  • Add when not reaching goal uric acid level on allopurinol or febuxostat
  • 200mg once daily with food and water
  • Hydrate with 2L per day

• Cost
  • ~$350
Lesinurad (Zurampic®)

• Bottom line
  • Unique option for gout patients not reaching goal uric acid levels with xanthine oxidase inhibitors
  • Do not use as monotherapy or in renal failure
• Additional review
  • Hoy S. Drugs 2016;76:509-16.

Insulin degludec/Liraglutide (Xultophy®)

• Indication
  • Type 2 diabetes mellitus inadequately controlled on basal insulin (< 50 units) or liraglutide (≤ 1.8 mg daily)
• Pharmacology
  • Ultra long acting insulin
  • GLP-1 agonist
    • Increases glucose-dependent insulin release
    • Decreases glucagon secretion
    • Slows gastric emptying
### DUAL V Trial

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Glargine ( N = 279 )</th>
<th>Liraglutide/degludec ( N = 278 )</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A_1C ) reduction at 26 weeks*</td>
<td>1.13%</td>
<td>1.81%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>( A_1C &lt; 7% )</td>
<td>47%</td>
<td>71.6%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypoglycemia (events/patient-year)</td>
<td>5.05</td>
<td>2.23</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Weight change</td>
<td>+ 1.8 kg</td>
<td>- 1.4 kg</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>


---

### Insulin degludec/Liraglutide (Xultophy®)

- **Dosing**
  - Start at 16 units (16 units of degludec and 0.58 mg of liraglutide)
  - Titrate every 3-4 days by 2 units
  - Max dose of 50 units (50 units of degludec and 1.8 mg of liraglutide)

- **Availability**
  - Only available as a 3 ml pen; packs of 5 pens
  - 100 units of degludec and 3.6 mg of liraglutide
Insulin degludec/Liraglutide (Xultophy®)

• Administration
  • Attach needle
  • Select priming symbol “∙∙—” prior to each use
  • Press button until liquid comes out of needle (may repeat up to 6 times)
  • Then select dose and administer similar to insulin shot
  • Hold button until dose says “0” then count to 6

• Stability/storage
  • Refrigerator until first use then at room temp or refrigerator; protect from light/direct heat
  • Discard 21 days after first use

Insulin glargine/Lixisenatide (Soliqua™)

• Indication
  • Type 2 diabetes mellitus uncontrolled on lixisenatide or basal insulin (< 60 units daily)

• Pharmacology
  • Long acting insulin
  • GLP-1 agonist
    • Increases glucose-dependent insulin release
    • Decreases glucagon secretion
    • Slows gastric emptying
### LixiLan-L Trial

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Glargine N = 365</th>
<th>Glargine/Lixi N = 366</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C reduction at 30 weeks*</td>
<td>0.6%</td>
<td>1.1%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>A1C &lt; 7%</td>
<td>30%</td>
<td>55%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Hypoglycemia (events/patient-year)</td>
<td>4.22</td>
<td>3.03</td>
<td>NR</td>
</tr>
<tr>
<td>Weight change</td>
<td>+ 0.7 kg</td>
<td>- 0.7 kg</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

* Primary outcome

---

### Insulin glargine/Lixisenatide (Soliqua™)

- **Starting dose**
  - If on lixisenatide or less than 30 units of basal insulin
    - Insulin glargine 15 units/ 5 mcg lixisenatide
    - Displayed as “15” in the dosing window
  - If on 30-60 units of basal insulin
    - Insulin glargine 30 units/10mcg lixisenatide
    - Displayed as “30” in the dosing window

- **Availability**
  - Only available as a 3 ml pen; packs of 5 pens
  - 100 units/ml of glargine, 33 mcg/ml lixisenatide
Insulin glargine/Lixisenatide (Soliqua™)

• Administration
  • Alcohol swab to rubber seal prior to attaching needle
  • Select “2” units prior to each use
  • Press button until liquid comes out of needle (may repeat up to 3 times)
  • Then select dose and administer similar to insulin shot
  • Hold button until dose says “0” then count to 10

• Stability/storage
  • Store in refrigerator until first use then at room temperature; Protect from light
  • Discard 14 days after first use

Pricing

• Insulin glargine/Lixisenatide (Soliqua)
  • $120 for each 3ml pen

• Insulin degludec/Liraglutide (Xultophy)
  • TBD
Insulin glargine/Lixisenatide (Soliqua™)
Insulin degludec/Liraglutide (Xultophy®)

- Bottom line
  - Combination, once-daily injections
  - Lowers A1C vs. insulin monotherapy
  - Useful for patients not controlled on basal insulin and oral agents
  - Rare pancreatitis
  - Weight loss vs. weight gain with insulin monotherapy

- Additional review

Andexanet alfa (AndexXa™)

- Indication
  - Pending approval for reversal of factor Xa inhibitors

- Pharmacology
  - Protein produced in Chinese hamster ovary cells
  - Three structural modifications from Factor Xa
  - Serves as decoy to bind to Factor Xa inhibitors

Andexanet alfa (AndexXa™)

- Pharmacokinetics
  - Onset
    - 2-10 minutes
  - T ½ ~ 1 hour
  - Duration
    - Effects maintained for 2 hours after the bolus dose or end of the infusion


Andexanet alfa (AndexXa™)

- Contraindications
  - Allergy
- Warnings and precautions
  - Non-neutralizing antibodies (17%)
- Drug interactions
  - No data

### Adverse Reactions with Andexanet

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bolus N = 24</td>
<td>Bolus+Inf N = 24</td>
<td>Bolus N = 27</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Feeling hot</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Flushing</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Urticaria</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Inf = infusion

---

### Andexanet alfa (AndexXa™)

- ANNEXA-A and ANNEXA-R Trials
  - Healthy volunteers, 50-75 years old
  - Apixaban or rivaroxaban for ~4 days
  - Andexanet bolus or bolus + 2-hour infusion
  - 92-97% reduction in anti-Xa activity
  - ~2 hours after the dose or infusion, anti-Xa activity similar to placebo group
Results

Interim analysis of 67 patients with acute bleeding after Factor Xa inhibitor
Bolus followed by 2 hour infusion
12 hours after andexanet 79% (37/47) achieved excellent or good hemostasis
18% thrombotic event (12/67); 15% (10/67) died

Clinical Efficacy-ANNEXA 4

Andexanet alfa (AndexXa™)

- **Dosing**
  - Varies based on agent reversing and possibly timing of anti-Xa agent
  - Likely a bolus followed by an infusion
- **Cost**
  - ???
- **FDA letter**
  - Additional manufacturing data requested
  - Data to include enoxaparin and edoxaban
  - Review other post-marketing commitments

Bottom line

- Reversal agent for Xa inhibitors
- Most published data in healthy volunteers
- Preliminary data with clinical bleeding
- Will dosing vary based on agent?

Additional review

- http://www.doacresources.org/
Aspirin/Omeprazole (Yosprala™)

- Indication
  - Secondary prevention of cardiovascular and cerebrovascular events in patients at risk for aspirin-associated ulcers

- Dosage form
  - Intelli-COAT system
  - Immediate release omeprazole 40mg
  - Delayed-release, enteric-coated aspirin (dissolves at pH > 5.5)

Cumulative Incidence of Gastric Ulcers

<table>
<thead>
<tr>
<th>Months</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASA + OME N = 265</td>
<td>EC ASA N = 625</td>
</tr>
<tr>
<td>0-1</td>
<td>1.1%</td>
<td>3.8%</td>
</tr>
<tr>
<td>0-3</td>
<td>3%</td>
<td>6.8%</td>
</tr>
<tr>
<td>0-6</td>
<td>3.8%*</td>
<td>8.7%</td>
</tr>
</tbody>
</table>

ASA = aspirin; OME = omeprazole; EC = enteric coated

* p-value = 0.02; ** p-value 0.005
Aspirin/Omeprazole (Yosprala™)

• Dosing
  • 81/40 mg
  • 325/40 mg

• Price
  • ~$140 per month
  • ~ $40 for a month of omeprazole 40mg + ASA E.C. 325 mg

• Compliance vs. Cost