New Drugs of 2016

Amy M. Lugo, PharmD, BCPS, BC-ADM, FAPhA
Clinical Pharmacy Specialist
Director, Managed Care Residency
Defense Health Agency
Pharmacy Operations Division
Formulary Management Branch
San Antonio, Texas

LCDR Kendra N. Jenkins, USPHS
PharmD, BCPS
Program Management Officer
Immigration and Customs Enforcement (ICE) Enforcement and Removal Operations
ICE Health Service Corps
Washington, DC

CPE Information and Disclosures

Amy Lugo declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

Kendra Jenkins declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

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CPE Information

• Target Audience: Pharmacists & Technicians
• ACPE#: 0202-0000-16-172-L01-P/T
• Activity Type: Knowledge-based

Learning Objectives – Pharmacist

1. List new therapeutic agents that were approved by the Food and Drug Administration (FDA) in 2016.
2. Describe the mechanism of actions and indications for new therapeutic drugs.
3. Compare and contrast the new therapeutic agents with products available with similar indications.
4. Discuss important patient education and therapeutic monitoring parameters for new therapeutic agents.
5. Summarize the adverse effects and patient safety considerations for new therapeutic agents.

Learning Objectives – Technician

1. List new therapeutic agents that were approved by the Food and Drug Administration (FDA) in 2016.
2. Recognize the new therapeutic agents and discuss how they compare with currently available products that have similar indications.
3. State the indication and adverse effects for each new therapeutic drug.

Self-Assessment Question 1

1. What is the mechanism of action of ixekizumab?
   - a) IL-2 inhibitor
   - b) BCL-2 inhibitor
   - c) IL-17a receptor antagonist
   - d) Tyrosine kinase inhibitor
Self-Assessment Question 2

2. Tumor lysis syndrome is a concern with which drug?
   a) lifitegrast
   b) pimavanserin
   c) cabozantanib
   d) venetoclax

Self-Assessment Question 3

3. Which drug : indication pairing is correct?
   a) Elbasvir/grazoprevir: cholera
   b) Glycopyrrolate/formoterol fumarate: COPD
   c) Lifitegrast: erectile dysfunction
   d) Fluciclovine F18: breast cancer

Drug to be Reviewed

- Endocrinology (1)
- Dermatology (1 of 2)
- Hematology/Oncology (2 of 4)
- Neurology/Psychiatry (3)
- Gastrointestinal (1)
- Infectious Disease (4)
- Ophthalmology (1)
- Pulmonology (1 of 2)
- Nuclear (1 of 2)
- Miscellaneous

Endocrinology

Lixisenatide

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic</td>
<td>Lixisenatide</td>
</tr>
<tr>
<td>Brand</td>
<td>Adlyxin</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Sanofi</td>
</tr>
<tr>
<td>FDA-Approval Date</td>
<td>July 2016</td>
</tr>
<tr>
<td>Approval Type</td>
<td>NDA</td>
</tr>
<tr>
<td>Type of drug</td>
<td>Glucagon-like peptide-1 (GLP-1) receptor agonist</td>
</tr>
<tr>
<td>FDA Indications</td>
<td>To improve glycemic control in type II diabetics</td>
</tr>
<tr>
<td>Dosing</td>
<td>Initiate at 10 mcg once daily for 14 days; On Day 15, increase dose to 20 mcg once daily</td>
</tr>
<tr>
<td>Available preparations</td>
<td>Injection: 50 mcg/mL and 100 mcg/mL in 3 mL in prefilled pen</td>
</tr>
</tbody>
</table>
**Lixisenatide**

**Administration & Dosing**

- **Dosage forms**
  - 50 mcg/mL in 3 mL, in green prefilled pen (for 14 pre-set doses; 10 mcg per dose)
  - 100 mcg/mL in 3 mL, in burgundy prefilled pen (for 14 pre-set doses; 20 mcg/dose)

- **Clear and colorless**

- **Inject into the abdomen, thigh or upper arm; rotate sites**

- **Dose:** 10 mcg daily x 14 days then ↑ to 20 mcg daily

**GLP-1 RA Adverse Events**

<table>
<thead>
<tr>
<th>ADR</th>
<th>DUAL 5.73 mcg (%)</th>
<th>ALBI 1.8 mcg (%)</th>
<th>EQW (%)</th>
<th>ExBID (%)</th>
<th>LIRA (%)</th>
<th>LIXI (%)</th>
<th>Insulin Glargine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>12.4</td>
<td>21.1</td>
<td>11.1</td>
<td>14.4</td>
<td>34.7</td>
<td>20.7</td>
<td>25.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.7</td>
<td>12.6</td>
<td>13.1</td>
<td>10.5</td>
<td>8.6</td>
<td>13.1</td>
<td>8.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.3</td>
<td>12.7</td>
<td>4.2</td>
<td>5.8</td>
<td>14.2</td>
<td>10.7</td>
<td>10.0</td>
</tr>
</tbody>
</table>

**Lixisenatide**

**Results**

- **Study:** GetGoal-Mono
- **Weeks:** 24
- **Treatment Arms:** Basal Insulin +/- SU Lixisenatide vs placebo
- **Δ HbA1c (%):** -0.77
- **Δ FPG (mg/dL):** -2.2
- **Wt (kg):** 86.5
- **Δ Wt (kg):** -2.3

**Summary**

- **Lixisenatide** is the 6th available GLP1RA and the 2nd once daily agent.
- **Lixisenatide** has been compared head to head with liraglutide and exenatide twice daily.
  - There are no clinically significant differences between agents in terms of glycemic control.
  - Warnings and precautions with lixisenatide are similar to the rest of the class except there is no increased risk of MTC or MEN2.
  - As with all GLP1RAs, there is an increased risk of hypoglycemia when combined with a sulfonylurea.
  - Lixisenatide does not increase or decrease cardiovascular risk (ELIXA trial).

**Parameters**

- **Parameter:** Drug Information
- **Background:** Lixisenatide is available in 60 countries worldwide as LixiSyra.
- **ADRs:** N/V/D, HA, dizziness, and hypoglycemia.
- **Contraindications:** Hypersensitivity including anaphylaxis.
- **Warnings/Precautions:** Anti-lixisenatide antibodies.
- **Black Box Warning:** None; only exenatide BID and lixisenatide do NOT have the BBW for medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2).
Lixisenatide

Summary

• When adding lixisenatide to background therapy, or when using as monotherapy, A1c may improve ~0.5% to 1%
• When used in combination with metformin, patients may observe weight loss
• Lixisenatide offers no compelling advantages over existing GLP1RAs

Dermatology

Ixekizumab (Taltz)

Parameter Drug Information
Generic Ixekizumab
Brand Taltz
Manufacturer Eli Lilly & Company
Approval Date March 2016
Approval Type BLA 351(a)
Type of drug Humanized monoclonal antibody (mAb) against IL-17A; IL-17A receptor antagonist
FDA
Indications Treatment of adults with moderate-severe plaque psoriasis who are candidate for systemic therapy or phototherapy
Dosing SQ administration: 160 mg at Week 0; followed by 80mg at Weeks 2, 4, 6, 8, 10 and 12; then 80mg q4 weeks
Available preparations Auto-injector – 80 mg/mL Prefilled Syringe – 80 mg/mL

Immunobiologics

• Numerous agents approved for plaque psoriasis
  – Adalimumab (TNF)
  – Etanercept (TNF)
  – Certolizumab (TNF)
  – Golimumab (TNF)
  – Ustekinumab (IL 12/23)
  – Apremilast (PDE-4)
  – Secukinumab (IL-17A)
  – Ixekizumab (IL-17A)

Background

Plaque Psoriasis (PsO)

Parameter Rare Disease
Background • Most prevalent autoimmune condition
  > 7.5 million Americans (2 to 4% of population)
  > 20 to 30% will have moderate to severe dz requiring systemic Rx
  > 10 to 30% patient will develop psoriatic arthritis
Diagnosis & Severity • Diagnosed by visual inspection; rare skin biopsy
  Severity depends on body surface area involved
    Mild = < 3%
    Moderate = 3 to 10%
    Severe = > 10%
Age of onset • Any age but typically 15 to 25 years of age
Guidelines • Medical board of the National Psoriasis Foundation (NPF) guideline for moderate - severe psoriasis
  – First line systemic agent = MTX, etanercept, adalimumab & ustekinumab (2012)
  – Combine biologics with other systemic treatments (2014)
Assessing Severity of Psoriasis

Severity of psoriasis can be assessed using:

- **BSA** (Body Surface Area)
- **PASI** (Psoriasis Area and Severity Index)
- **IGA/PGA** (Investigator/Physician’s Global Assessment)

- BSA (Body Surface Area) - Estimate of amount of skin affected by psoriasis (hand equals about one percent of the skin)
- PASI (Psoriasis Area and Severity Index) - Assessment tool used to determine severity and extent of psoriasis
- The affected area and lesion characteristics are used in a formula that results in score of 0-72
- A 75% improvement in PASI score or PASI 75 is a standard endpoint in psoriasis clinical trials
- IGA/PGA (investigator/physician’s global assessment) - A 5-, 6-, or 7-point rating that ranges from “clear” to “very severe psoriasis”

Ixekizumab Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Treatments</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNCOVER-2</td>
<td>N = 1,224</td>
<td>Ixekizumab 80 mg SC Q2W</td>
<td>PASI 75 88% sGPA 82%</td>
</tr>
<tr>
<td>UNCOVER-3</td>
<td>N = 1,346</td>
<td>Ixekizumab 80 mg SC Q4W</td>
<td>PASI 75 81% sGPA 74%</td>
</tr>
<tr>
<td>UNCOVER-1</td>
<td>N = 1,296</td>
<td>Ixekizumab 80 mg SC Q2W</td>
<td>PASI 75 89% sGPA 82%</td>
</tr>
</tbody>
</table>

Both doses of ixekizumab were more effective in achieving PASI 75 & sGPA 0/1 compared to placebo.

Ixekizumab

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background</strong></td>
<td>2nd agent to target the IL-17 cytokine pathway for the treatment of plaque psoriasis – competitor to secukinumab. Ixekizumab has similar PASI 75 to secukinumab, possibly higher PASI90. Both ixekizumab &amp; secukinumab have NO malignancy warnings.</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>Long term efficacy and safety not fully characterized.</td>
</tr>
<tr>
<td><strong>Adverse Reactions</strong></td>
<td>Injection site reactions (17%), upper respiratory infections (14%), nausea (2%) and tinea infections (2%).</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Serious hypersensitivity reaction to ixekizumab or to any of the excipients.</td>
</tr>
</tbody>
</table>
| **Warning and Precautions** | Life
care: none. |
| | Infected: discontinue ixekizumab until infection resolves. |
| | Tuberculosis (TB): Evaluate prior to starting treatment. |
| | Inflammatory bowel disease (IBD): Ixekizumab may exacerbate IBD (seen in trials). Monitor closely. |

Ixekizumab Summary

- Second available IL-17A receptor antagonist
- Only indicated for plaque psoriasis
- Similar mechanism of action, PASI 75 and safety profile compared to secukinumab
- Lack of long-term safety data
- No black box warning or REMS
- Indirect comparisons
  - Ixekizumab may have a higher PASI 90 than other immunobiologics (secukinumab, ustekinumab or adalimumab)

Hematology/Oncology

- Category C
- Safety / effectiveness has not been established
- None
- CYP450 enzymes can be altered – monitor narrow therapeutic index drugs
- No drug interaction studies have been conducted
**Hematology/Oncology Drugs**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Route</th>
<th>MFR</th>
<th>Indication</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defibrotide sodium (Defitelio)</td>
<td>IV</td>
<td>Jazz Pharma</td>
<td>Adults &amp; children who develop hepatic veno-occlusive disease (VOD) with additional kidney or lung abnormalities s/p a HSCT</td>
<td>March 2016</td>
</tr>
<tr>
<td>Venetoclax (Venclexta)</td>
<td>PO</td>
<td>AbbVie</td>
<td>CLL pts who have a 17p deletion and have been tx with at least 1 prior therapy</td>
<td>April 2016</td>
</tr>
<tr>
<td>Cabozantinib (Cabometyx)</td>
<td>PO</td>
<td>Exelixis</td>
<td>Advanced RCC after receiving prior anti-angiogenic therapy</td>
<td>April 2016</td>
</tr>
<tr>
<td>Atezolizumab (Tecentriq)</td>
<td>IV</td>
<td>Genentech</td>
<td>Urothelial carcinoma, locally advanced or metastatic who have progression during/ following platinum-containing chemo, or have progression within 12 mo of neoadjuvant or adjacent tx with platinum-containing chemo</td>
<td>May 2016</td>
</tr>
</tbody>
</table>

**Venetoclax (Venclexta)**

**Parameter**
- Drug Information

**Generic**
- venetoclax

**Brand**
- Venclexta

**Manufacturer**
- AbbVie (marketed by AbbVie/Genentech)

**Approval Date**
- April 2016

**Approval Type**
- New molecular entity, NDA (Breakthrough therapy, Priority Review, Accelerated Approval, Orphan)

**Type of drug**
- BCL-2 inhibitor, Oral Oncologic Agent for Chronic lymphocytic leukemia (CLL)

**FDA Indications**
- Chronic lymphocytic leukemia with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy, accelerated approval based on ORR and contingent upon verification and description of clinical benefit in a confirmatory trial

**Formulation**
- 10, 50, 100 mg tab

**Dosage**
- Weekly ramp-up schedule over 5 wks to 400 mg/day (Wk 1-20 mg, Wk 2-50 mg, Wk 3-100 mg, Wk 4-200 mg, Wk 5 and beyond - 400 mg)

**Background Chronic Lymphocytic Leukemia**

**Parameter**
- Rare Disease

**Rare Disease**
- One of most common types of leukemia in adults
- B cells are found mostly in blood, BM, LN
- Normal B cells make antibodies that mark germs to be destroyed

**Patho-physiology**
- Pt with CLL who have 17p deletion lack a portion of the chromosome that acts to suppress cancer growth

**Prevalence**
- 19K new CLL cases 2016; 4.6K deaths/year
- 17p deletion found in 3-10% in previously untreated; 30-50% refractory

**Age of onset**
- Median age at diagnosis 70

**Presentation**
- Can be fast or slow growing, often slow growing
- Staging useful to predict prognosis, but no standard system
- Assessments include lymphocyte counts, adenopathy, hepatosplenomegaly, anemia, thrombocytopenia
- Pancytopenia, hemorrhage, infection are major cause of death

**Venetoclax Efficacy**

**Study Overview**
- Treatment Arms

**Treatment Arms**
- Phase 2, OL, SA, MC study in previously treated CLL with 17p deletion (n=106)
  - Duration: median 12 months
  - Patients had at least 1 prior therapy

**Patientcharacteristics**
- Median age 66 yo (29-85), 95% white, 69% male
- Median 8 therapies was 3 (1-12)
- Median tx duration=10.3 mo (0-34 mo)
- 46% received >48 weeks
- D/C due to ADRs was 8.3%; 9.6% required dose adjustment

**Efficacy Measures**
- Venetoclax oral daily via weekly ramp-up schedule until disease progression or unacceptable toxicity
- No placebo group

**Venetoclax Results**

**Efficacy Measure**
- Defined as a partial remission or better

**Overall response rate**
- 80.2%
- 95% CI (71% – 87%)

**Complete remission**
- 5.7%

**Partial remission**
- 69.8%

**Median time to 1st response**
- 0.8 months (0.1-8.1)

**Median duration of response: not reached Range: 2-19+mo**

**Safety**
- Tumor lysis is primary concern, particularly early on
- Most common ADRs (>20%): neutropenia, nausea, diarrhea, anemia, upper respiratory tract infection, fatigue


**Venetoclax (Venclexta) Product labeling. AbbVie. April 2016.**

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**Venetoclax (Venclexta) Product labeling. AbbVie. April 2016.**
**Venetoclax**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
</table>
| Background | 17p deletion is detected by FDA-approved companion diagnostic test  
Up to ½ of progressed CLL have 17p del making disease difficult to treat |
| Comments |Selective inhibitor of BCL-2 protein, which supports cancer cell growth  
& is overexpressed in CLL; binding BCL-2 protein displaces pro-cancer proteins |
| Adverse Reactions |Tumor lysis syndrome (TLS) due to rapid reduction in tumor with risk based on multiple factors including tumor burden and comorbidities  
Most common: neutropenia (40%), nausea, diarrhea, anemia (18%), thrombocytopenia (15%), URTI, fatigue, infection (20%) |
| Contraindications |Concomitant use with strong inhibitors of CYP3A at initiation and during ramp-up phase (azole antifungals, conivaptan, clarithromycin, indinavir) |
| Warning/Precautions/Pregnancy |Tumor Lysis Syndrome: Prophylaxis with IV/PO hydration, antihyperuricemics, in/outpatient mgmt as appropriate for risk  
Neutropenia (41%): Monitor blood counts and for infection; adjust dose per label  
Immunization: No live attenuated vaccines  
Embryo-Fetal toxicity: May cause embryo-fetal harm |

**Venetoclax Summary**

- First treatment to target BCL-2 protein and indicated for CLL patients who have failed one prior therapy
- Candidates should be assessed to ensure appropriateness for outpatient initiation and closely monitored for tumor lysis syndrome
- Full approval contingent upon findings from confirmatory study
  - Two ongoing phase 3 trials assessing venetoclax in combination with anti-CD20 antibodies
  - NCCN guidelines recommend for relapsed, refractory CLL, not for first-line therapy
- Novel mechanism of action
- Promising new therapy for high risk subset of patients with relapsed CLL and poor prognostic factors

**Cabozantinib (S)-malate (Cabometyx)**

**Background Renal Cell Carcinoma**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rare Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>5th most common type of cancer</td>
</tr>
</tbody>
</table>
| Patho-physiology | 50% of renal tumors are RCC, with 80% being clear cell  
Risk factors: smoking, obesity, and occupational exposures  
Several hereditary subtypes: VHL  
Most important prognostic factors: tumor stage, grade, local extent of tumor, presence of regional nodal metastases, evidence of metastatic disease (MSKCC is most widely used model) |
| Prevalence |Estimated 61K diagnosed in 2015; 14K will die; 3.8% of all new cancers |
| Age of onset | Median age 64, 30% advanced at diagnosis |
| Presentation/Management |Typically with a suspicious mass involving kidney seen on imaging  
Less common triad of symptoms: hematuria, flank mass, flank pain  
5yr survival rate advances from 1992-1995 to 2004-2010: 7 to 12% in advanced, 88 to 91% in localized  
Localized disease is treated with surgical intervention  
Advanced: surgery, radiation, chemo, cytokine, targeted therapy |

**Cabozantinib**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic</td>
<td>cabozantinib</td>
</tr>
<tr>
<td>Brand</td>
<td>Cabometyx</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Exelixis</td>
</tr>
<tr>
<td>Approval Date</td>
<td>25 Apr 2016</td>
</tr>
<tr>
<td>Approval Type</td>
<td>NDA (Breakthrough therapy, Priority Review, Fast Track)</td>
</tr>
<tr>
<td>Type of drug</td>
<td>Tyrosine Kinase Inhibitor (targets VEGF, MET, AXL)</td>
</tr>
</tbody>
</table>
| FDA Indications |Treatment of patients with advanced renal cell carcinoma who have received prior antiangiogenic therapy  
Has approval with different dosing for progressive medullary thyroid cancer |
| Formulation |20, 40, 60 mg tabs |
| Dosing |60 mg orally daily |

**Cabozantinib (S)-malate (Cabometyx)**

<table>
<thead>
<tr>
<th>Issue</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactation</td>
<td>Discontinue breastfeeding</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>Not established</td>
</tr>
</tbody>
</table>
| Dose Adjustments |No specific data in severe renal/hepatic clinical trials available  
Metabolism does occur in the liver  
Patients with reduced renal function increase risk of TLS |
| Drug-drug Interactions |Avoid concomitant use with moderate CYP3A inhibitors, strong or moderate CYP3A inducers, P-gp inhibitors, or narrow therapeutic index P-gp substrates |
| Other |Females should undergo pregnancy testing, use contraception; male fertility may be compromised  
Being studied in lymphoma, multiple myeloma, acute leukemia |
Cabozantinib

**Parameter** | **Drug Information**
--- | ---
**Comments** | • Small molecule inhibitor of tyrosine kinases such as VEGF-receptor, c-MET and AXL; being examined in CELESTIAL for HCC  
• Novelty includes targeting of multiple pathways  
• VEGF (angiogenesis) and mTOR (nutrition, blood supply)

**Adverse Reactions** | • Treatment D/C due to ADRs 9% in cabozantinib vs 25% everolimus  
• Most common grade 3 or 4: Hypertension, diarrhea, fatigue, hyperglycemia

**Contraindications:** none

**Warning/Precautions** | • Hemorrhage (2.1%)  
• GI Perforation/Fistula (1.2%)  
• Thrombotic events (7.3%)  
• HTN (37%)/Crisis  
• Diarrhea (11%)  
• Palmar plantar erythrodysesthesia  
• Reversible Posterior Leukoencephalopathy  
• Embryo-fetal toxicity

**Pregnancy** | • No available human data, animal data suggests fetal harm  
• Advise effective contraception during treatment  
• Lactation: advise not to breast feed while taking

**Pediatrics** | • Not established

**Dose Adjustments** | • Mild to moderate hepatic impairment reduce dose, avoid in severe  
• Mild to moderate renal impairment no adjustment, no data severe

**Drug-drug Interactions** | • Strong CYP3A4 inhibitors: reduce cabozantinib dosage  
• Strong CYP3A4 inducers: increase cabozantinib dosage

**Other** | • Patients should not eat for at least 2 hrs before and 1 hour after taking cabozantinib  
• Approved in medullary thyroid carcinoma, dosage of 80 mg and 20 mg; Do not confuse with cabozantinib (Cometriq)

**Cabozantinib Efficacy**

**Study Design** | **Efficacy Measures** | **Results**
--- | --- | ---
Phase III, R, OL, MC METEOR study, pts with advanced RCC who had received prior anti-angiogenic therapy (TKI)  
Cabozantinib (n=330) vs everolimus (n=328) | Primary endpoint  
• Progression free survival (PFS) among 1st 375 randomized patients  
Secondary endpoints  
• OS and response rate | • Median PFS 7.4 vs 3.8 mos (HR 0.58, 0.45-0.78, p<0.0011)  
• Median OS in ITT 21.4 vs 16.5 mos (HR 0.66, 0.53-0.83, p<0.0003)  
• Confirmed response rate: 17% (13-22) vs 3% (2-6)

**Safety** | • Most common ADRs (>25%): diarrhea, fatigue, decreased appetite, erythrodysesthesia, HTN, vomiting, wt loss, constipation  
• Serious AE’s: abdominal pain, pleural effusion, diarrhea, nausea

**Cabozantinib Summary**

• Small molecule inhibitor of tyrosine kinases such as VEGF-receptor, c-MET and AXL  
• Approved for renal cell carcinoma  
• Also approved for medullary thyroid cancer and being studied in hepatocellular carcinoma  
• According to NCCN guidelines, use as subsequent therapy, not first-line  
• Advantage: targets multiple pathways

**Neurology/Psychiatry**

**Brivaracetam (Briviact)**
**Parameter** | **Drug Information**
--- | ---
| **Generic** | Brivaracetam |
| **Brand** | Briviact |
| **Manufacturer** | UCB |
| **Approval Date** | February 2016 |
| **Approval Type** | New molecular entity |
| **Type of drug** | Antiepileptic drug (AED) |
| **FDA Indications** | Adjunctive therapy in the treatment of partial-onset seizures in patients ≥16 years old |
| **Dosing** | 50 mg BID and titrate to 100 mg BID |
| **Available preparations** | Tablets: 10, 25, 50, 75, and 100 mg, Oral solution: 10 mg/mL, Injection for IV use: 50 mg/5 mL single-dose vial |

**Brivaracetam**

**Parameter** | **Drug Information**
--- | ---
| **Adverse Reactions** | Most common (≥5%): somnolence and sedation (16%), dizziness (12%), fatigue (9%), and nausea and vomiting (5%) |
| **Contraindications** | Hypersensitivity to brivaracetam or inactive ingredients (bronchospasm and angioedema have occurred) |
| **BBW or Significant Adverse Effects** | • Suicidal behavior and ideation • Neurological adverse reactions • Psychiatric adverse reactions |

**Parameter** | **Drug Information**
--- | ---
| **Indication** | • Adjunctive therapy in the treatment of partial-onset seizures in pts 16yo and older with epilepsy • Partial onset seizures in pts ≥1 mo of age with epilepsy • Myoclonic seizures in pts ≥12 yo with juvenile myoclonic epilepsy • Primary generalized tonic-clonic seizures in patients ≥6 yo with idiopathic generalized epilepsy |
| **Half Life** | 9 hours |
| **MOA** | High and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain, which may contribute to the anticonvulsant effect |
| **Strengths** | Tabs: 10, 25, 50, & 100 mg; Oral solution: 10 mg/mL; Injection for IV use: 50 mg/5 mL single-dose vial |
| **Chemical Structure** | ![Chemical Structure](image) |

**Brivaracetam Efficacy**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Treatment Arms</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three R, DB, PC, MC studies; Duration: 12 weeks Study 1 (n=398); Study 2 (n=398); Study 3 (n=760)</td>
<td>R (1:1:1:1) 3 doses (20mg, 50mg, 100mg)</td>
<td>Primary endpoint: Study 1 and 2: % ↓ in POS frequency over a 7-day period Study 3: % ↓ in POS frequency over PBO over a 28-day period; ≥50% responder rate</td>
</tr>
<tr>
<td>Baseline characteristics: • ≥ 8 partial onset seizures (POS) at baseline • Not adequately controlled with 1-2 concomitant AEDs</td>
<td>Brivaracetam BID vs Placebo</td>
<td></td>
</tr>
</tbody>
</table>

**Brivaracetam Results**

<table>
<thead>
<tr>
<th>Study</th>
<th>Endpoint</th>
<th>% decrease in POS over placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study 1</strong></td>
<td>% Dec in POS</td>
<td>-6.8%* -6.5% -11.7%*</td>
</tr>
<tr>
<td><strong>Study 2</strong></td>
<td>% Dec in POS</td>
<td>-0.9% -4.1% -12.8%*</td>
</tr>
<tr>
<td><strong>Study 3</strong> (n=760)</td>
<td>≥ 50% responder rates</td>
<td>38.9%* 37.8%*</td>
</tr>
</tbody>
</table>

POS = partial onset seizures; PBO = placebo
*Statistically significant (p < 0.001) compared to placebo
Brivaracetam Summary

- Discontinuation rates due to ADRs
  - 5% (50 mg/day)
  - 8% (100 mg/day)
  - 7% (200 mg/day)
  - 4% (placebo)
- Place in therapy
  - Similar in structure to levetiracetam
  - Less titration
  - Controlled substance (C-V) designation
  - No compelling advantage over levetiracetam

Pimavanserin (Nuplazid)

Parameter | Drug Information
---|---
Generic | Pimavanserin
Brand | Nuplazid
Manufacturer | Acadia Pharmaceuticals Inc.
FDA Approval Date | April 29, 2016
Approval Type | 505(b)
Type of drug | Atypical antipsychotic
FDA Indications | Hallucinations and delusions associated with Parkinson's disease psychosis (PDP)
Dosing | 34 mg (2 tabs) PO daily, without titration, with or without food
Available preparations | Oral IR tablets, 17 mg

Parameter | Drug Information
---|---
FDA agreed in 2013 to approve NDA on 1 positive study; 3 additional studies failed to show benefit
First AAP approved for psychosis in Parkinson’s disease
5-HT2A inverse agonist which lacks dopamine receptor interaction and the associated motor function effects

Pimavanserin

Parameter | Drug Information
---|---
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Parameter | Drug Information
---|---
FDA agreed in 2013 to approve NDA on 1 positive study; 3 additional studies failed to show benefit
First AAP approved for psychosis in Parkinson’s disease
5-HT2A inverse agonist which lacks dopamine receptor interaction and the associated motor function effects

Psychosis in Parkinson’s Disease (PDP) Current standards of care

- 2006 American Academy of Neurology
  - Recommend clozapine (Level B), quetiapine (Level C)
  - Clozapine requires frequent hematologic monitoring for potentially fatal agranulocytosis
- 2016 systematic review in the Journal of Geriatric Psychiatry and Neurology
  - Daily doses of 100 mg quetiapine do not provide significant symptom relief for PD psychosis
  - Available quetiapine efficacy studies have many limitations
Pimavanserin Efficacy

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Treatment</th>
<th>Efficacy Measures</th>
<th>Results: Δ SAPS-PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>R, DB, MC, OP, PC</td>
<td>R (1:1)</td>
<td>Primary SAPS-PD</td>
<td>Pimavanserin = -5.79</td>
</tr>
<tr>
<td>Duration: 6 weeks,</td>
<td>Pimavanserin 34mg PO</td>
<td>Secondary UPDRS</td>
<td>PBO = -2.73</td>
</tr>
<tr>
<td>n = 199</td>
<td>daily</td>
<td>CGI</td>
<td>Difference from PBO</td>
</tr>
<tr>
<td></td>
<td>vs PBO</td>
<td>Exploratory SCOPA-sleep CBS</td>
<td>= -3.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI (-4.9, -1.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NNT = 11</td>
</tr>
</tbody>
</table>

- R=randomized; DB=double-blind; OP=outpatient; PC=placebo-controlled; LSM=least-squares mean; PD=Parkinson's Disease; SAPS-PD=Scale for the Assessment of Positive Symptoms in Parkinson’s Disease; UPDRS=Unified Parkinson’s Disease Rating Scale (UPDRS); CGI=Clinical Global Impression scale; SCOPA=Scal es for Outcomes in Parkinson’s Disease; CBS=Caregiver Burden Scale.

Pimavanserin Safety

- Included data from 2 safety extension trials
- OR for serious adverse effects, including death
  - 2.4 (95% CI 1.0 to 5.7, p=0.05) for 34 mg vs. placebo
- Deaths considered class effect of antipsychotic use in the elderly dementia population
- Common adverse reactions
  - Peripheral edema (7% vs. 2% placebo)
  - Confusional state (6% vs. 3% placebo)
  - QT prolongation of 10-14 ms found at 68 mg, not studied at recommended 34 mg dose

Pimavanserin Summary

- First drug approved for the indication of PDP
- Unique mechanism of action
- Current recommendations include use ofquetiapine or clozapine first
- Very costly compared to generic AAPs
- No long-term safety data
- Place in therapy currently unclear

Daclizumab (Zinbryta)

- Background
  - Daclizumab was previously marketed as Zenapax for the prophylaxis of acute organ rejection in patients receiving renal transplants (discontinued in 2009 for commercial reasons)
- Pharmacokinetics
  - Protein binding (>99%) primarily to serum albumin and alpha-acid glycoprotein
  - Metabolism: Hepatic, primarily by CYP3A4 and CYP2D6; major metabolite, DM-3411 (inactive)
- Adverse Reactions
  - Nasopharyngitis, upper respiratory infections, rash, influenza, dermatitis, oropharyngeal pain, bronchitis, eczema, lymphadenopathy, tonsillitis, acne
- Serious Adverse Reactions
  - Risk of anaphylaxis and angioedema
  - Increased risk of infections
  - Increased risk of depression and suicide

Parameter Drug Information

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Daclizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic</td>
<td>Daclizumab</td>
</tr>
<tr>
<td>Brand</td>
<td>Zinbryta</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Biogen</td>
</tr>
<tr>
<td>Approval Date</td>
<td>May 27, 2016</td>
</tr>
<tr>
<td>Approval Type</td>
<td>BIA</td>
</tr>
<tr>
<td>Type of drug</td>
<td>Interleukin-2 (IL-2) inhibitor; Immunosuppressing monoclonal antibody</td>
</tr>
<tr>
<td>FDA Indications</td>
<td>Multiple Sclerosis, relapsing</td>
</tr>
<tr>
<td>Dosing</td>
<td>150 milligrams once monthly; self-injectable</td>
</tr>
<tr>
<td>Available preparations</td>
<td>150 mg/mL solution in a single-dose prefilled syringe Limited distribution; REMS</td>
</tr>
</tbody>
</table>

Parameter Drug Information

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Daclizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>Daclizumab was previously marketed as Zenapax for the prophylaxis of acute organ rejection in patients receiving renal transplants (discontinued in 2009 for commercial reasons)</td>
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<tr>
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</tr>
<tr>
<td>Serious Adverse Reactions</td>
<td>Risk of anaphylaxis and angioedema Increased risk of infections Increased risk of depression and suicide</td>
</tr>
</tbody>
</table>
Daclizumab

Parameter | Drug Information
--- | ---
Warnings & Precautions | • Autoimmune hepatitis, bilirubin elevation, skin reactions, lymphadenopathy, colitis, hypersensitivity, infections, depression, and suicide
Contraindications | • Pre-existing hepatic disease or hepatic impairment
| • History of autoimmune hepatitis or other autoimmune condition involving the liver
| • History of hypersensitivity to daclizumab or any other component of the formulation
BBW Or Significant Adverse Effects | • Hepatic injury including autoimmune hepatitis
| • Other immune-mediated disorders
Comments | • Available only through a Risk Evaluation and Mitigation Strategy (REMS) program

Daclizumab Efficacy

Parameter | Drug Information
--- | ---
Study Design | DECIDE Trial: Phase III, R, DB, AC (301), PC (201), PG, FD; n= 2462
Duration: 1-2 years
Patient characteristics | • Adults with relapsing MS
| • 41% had prior disease modifying therapy
| • 34% had prior interferon beta therapy
| • Baseline MSIS-29= 21.7
Primary Endpoints | Daclizumab vs Interferon beta-1a
1:1
ARR = annual relapse rate (ARR = [% relapse in treatment group]/[% relapse in placebo group]; NNT = number needed to treat 71
Clinical Results
ARR 0.216 0.393 < 0.0001
Relative reduction 45% N/A
Proportion relapse free (wk 144) 67% 51%
Proportion with 12-week confirmed disability progression 16% 20% 0.16
NNT 7
MRI Results
Mean number of new or newly enlarging T2 hyperintense lesions 4.31 9.44 < 0.0001
Relative reduction 54% N/A
Proportion of patients with clinically meaningful worsening of MSIS-29 score 19% 23%

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NNT 7
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Mean number of new or newly enlarging T2 hyperintense lesions 4.31 9.44 < 0.0001
Relative reduction 54% N/A
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Daclizumab Comparisons

Parameter | Zinbryta (daclizumab) | Avonex (Interferon Beta-1a) | Copaxone (Glatiramer acetate) | Betaseron (Interferon Beta-1b) | Plegridy (Peginterferon Beta-1a) | Tecfidera (Dimethyl Fumarate)
--- | --- | --- | --- | --- | --- | ---
Dosage form | SQ | IM | SQ | SQ | SQ | Capsule
Dosing | Monthly | Weekly | QD-3XW | QOD | Q2W | BID
Generic | No | No | No | No | No | No
Renal adjustments | No | No | No | No | No | No
Hepatic adjustments | Yes (BBW) | No | No | No | No | No
ARR 0.46 0.87 0.67 0.67 0.65 0.59
NNT 7 12 17 6 6 6

Daclizumab Summary

• Disease modifying monoclonal antibody
• Because of its safety profile, daclizumab should be reserved for patients who have had an inadequate response to 2 or more MS drugs
• Daclizumab is a costly injectable with a mandatory REMS program due to the risk of severe hepatic injury
• Daclizumab is the only once monthly self-injectable
  – Indicated for relapsing MS
  – Data from head to head trials have shown it to be more effective than interferon beta-1a and placebo in treating MS
**Gastrointestinal**

**Obeticholic acid (Ocaliva)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic</td>
<td>Obeticholic acid</td>
</tr>
<tr>
<td>Brand</td>
<td>Ocaliva</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Intercept Pharmaceuticals, Inc</td>
</tr>
<tr>
<td>Approval Date</td>
<td>May 27, 2016</td>
</tr>
<tr>
<td>Approval Type</td>
<td>New molecular entity: NDA 505(b)</td>
</tr>
<tr>
<td>Type of drug</td>
<td>Farnesoid X receptor (FXR) agonist</td>
</tr>
<tr>
<td>FDA Indications</td>
<td>Tx of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA</td>
</tr>
<tr>
<td>Dosing</td>
<td>5mg orally once daily in adults who have not achieved an adequate response to an appropriate dosage of UDCA for at least 1 year or are intolerant to UDCA; dose is titrated based on alk phos and/or Tfili; Max dose: 10mg once daily</td>
</tr>
<tr>
<td>Preparations</td>
<td>5mg and 10mg tablets</td>
</tr>
</tbody>
</table>

**Obeticholic acid (Ocaliva)**

**Drug Interactions**
- Warfarin = potential decreased INR
- CYP1A2 substrates with narrow therapeutic index (theophylline)

**Adverse Reactions**
(≥ 5%): pruritus, fatigue, abdominal pain and discomfort, rash, oropharyngeal pain, dizziness, constipation, arthralgia, thyroid function abnormality, and eczema

**Contraindications**
- Patients with complete biliary obstruction

**Warnings & Precautions**
- Liver-Related ADRs: Monitor for elevations in LFTs & development of liver-related ADRs; weigh the potential risk against the benefits of continuing tx. Do not exceed 10 mg qday. Adjust the dose for patients with moderate or severe hepatic impairment. D/C in patients who develop complete biliary obstruction
- Severe Pruritus: addition of bile acid binding resins or antihistamines; reduce dose and/or temporary dose interruption
- Reduction in HDL: Monitor for changes in serum lipid levels during tx

**Clinical Trial**
No improvement in survival or disease-related symptoms has been established

**POISE Trial:** R (1:1:1), DB, PC, 12 month trial (n=216) pts with PBC taking UDCA for ≥ 12mo or who could not tolerate UDCA

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP ≥ 1.67x ULN; Tfili between 1 and 2 x ULN</td>
<td></td>
</tr>
<tr>
<td>Excluded if other liver disease, MELD score ≥ 15</td>
<td></td>
</tr>
<tr>
<td>Primary endpoint: composite (↓ ALP number and %, ↓ Tfili)</td>
<td></td>
</tr>
</tbody>
</table>

**Primary composite endpoint**

<table>
<thead>
<tr>
<th>Obet acid titration (n=78)</th>
<th>Obet acid titration (n=70)</th>
<th>PBO (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder rate, (%) [95% CI]</td>
<td>48 [36, 60]</td>
<td>46 [34, 58]</td>
</tr>
</tbody>
</table>

**Components of Primary endpoint**

<table>
<thead>
<tr>
<th>ALP ≥ 1.67x ULN, n (%)</th>
<th>40 (55)</th>
<th>33 (47)</th>
<th>12 (16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dec in ALP at least 15%, n (%)</td>
<td>57 (78)</td>
<td>54 (77)</td>
<td>21 (29)</td>
</tr>
<tr>
<td>Total bil ≥ ULN, n (%)</td>
<td>60 (82)</td>
<td>62 (89)</td>
<td>57 (78)</td>
</tr>
</tbody>
</table>

**Obeticholic acid Summary**

- For primary biliary cholangitis (PBC) after UDCA therapy or those who cannot tolerate UDCA
- Not effective for alcoholic liver disease
- Not effective for NAFLD or NASH
### Infectious Disease

- Elbasvir/grazoprevir
- Sofosbuvir/velpatasvir
- Obiltoxaximab
- Cholera vaccine

### Hepatitis C (HCV) Direct Acting Antiviral (DAA) Drugs

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand (Manufacturer)</th>
<th>Strengths &amp; Formulations</th>
<th>FDA Approval</th>
<th>FDA Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir</td>
<td>Olysio (Janssen)</td>
<td>150mg</td>
<td>11/22/2013</td>
<td>GT 1, 4</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Sovaldi (Gilead)</td>
<td>400mg</td>
<td>12/6/2013</td>
<td>GT 1, 2, 3, 4</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>Harvoni (Gilead)</td>
<td>90mg/400mg</td>
<td>10/10/2014</td>
<td>GT 1, 2, 3, 4, 6</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/Ombitasvir/Dasabuvir</td>
<td>Viekira Pak (AbbVie)</td>
<td>75mg/50mg/12.5mg &amp; 250mg</td>
<td>12/19/2014</td>
<td>GT 1</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Daklinza (BMS)</td>
<td>30mg, 60mg oral tablets</td>
<td>7/24/2015</td>
<td>GT 1, 3</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/Ombitasvir</td>
<td>Tekvirox (AbbVie)</td>
<td>75mg/50mg/12.5mg oral tablet</td>
<td>7/24/2015</td>
<td>GT 1, 3</td>
</tr>
<tr>
<td>Grazoprevir/Elbasvir</td>
<td>Zepatier (Merck)</td>
<td>100mg/50mg tablet</td>
<td>02/01/2016</td>
<td>GT 1, 4</td>
</tr>
<tr>
<td>Velpatasvir/Sofosbuvir</td>
<td>Epclusa (Gilead)</td>
<td>100mg/400mg</td>
<td>06/28/2016</td>
<td>GT 1, 2, 3, 4, 5, 6</td>
</tr>
</tbody>
</table>

Simeprevir, Sofosbuvir and Daclatasvir are NOT used as monotherapy. AASLD/IDSA HCV guideline have the most up to date treatment recommendations.

### HCV Epidemiology

- Genotypes 1-6 in the US population
  - Genotype 1 is most common strain → 75%
  - Genotype 1a and 1b
    - 1a accounts for 70% of genotype 1 infections and is typically more difficult to treat
    - Genotype 2-3 → 20–25% of cases
  - Genotype 4-6 extremely rare

### Grazoprevir/Elbasvir

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic</td>
<td>Grazoprevir/elbasvir</td>
</tr>
<tr>
<td>Brand</td>
<td>Zepatier</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Merck &amp; Co., Inc.</td>
</tr>
<tr>
<td>FDA Approval</td>
<td>January 28, 2016</td>
</tr>
<tr>
<td>Approval Type</td>
<td>505 (b) NMA, priority review / breakthrough therapy designation</td>
</tr>
<tr>
<td>Type of drug</td>
<td>Hepatitis C virus; Direct Acting Antiviral (HCV DAA)</td>
</tr>
<tr>
<td>FDA Indications</td>
<td>Treatment of HCV genotypes (GT) 1 &amp; 4 in adults</td>
</tr>
<tr>
<td>Dosing</td>
<td>One tablet daily for 12 week (majority)</td>
</tr>
<tr>
<td>Available preparations</td>
<td>100mg grazoprevir / 50mg elbasvir single tablet</td>
</tr>
</tbody>
</table>

Grazoprevir/elbasvir (Zepatier), Merck & Co., Inc, Jan 2016
Grazoprevir/Elbasvir

**Parameter**

**Drug Information**

**Background**

- Grazoprevir = 2nd gen protease inhibitor (PI)
- Elbasvir = NS5A inhibitor
- Contraindicated in mod-severe liver disease; LFTs testing required
- Single daily tablet GT 1 & 4 for 12 weeks
- Difficult to treat patients – increase duration (16 wks) & + RBV
- Studied in advance kidney dz, & opiate sub. therapy
- SVR >90% (comparable to Harvoni or Viekira)

**Comments**

- Niche in severe kidney dz (CKD 4 or 5 on dialysis)
- Testing for NS5A resistance in HCV GT1a prior to treatment
- Hepatic testing prior and during treatment

**Adverse Reactions**

- Fatigue, headache and nausea
- Anemia and headache in ZEP + RBV for 16 weeks

**Warning and Precautions**

- ALT elevations: hepatic testing prior to treatment and 8 wks
- Risk associated with ribavirin combination treatment

**Contraindications**

- Moderate or severe hepatic impairment (Child-Pugh B or C)
- OAT1B1/3 inhibitors, strong CYP3A inducers and efavirenz

**Pregnancy Category B**

Pediatrics Safety and efficacy have not been established

**Dose Adjustments**

No dose adjustments are required for geriatric patients, or mild hepatic impairment (Child-Pugh A).

**Drug-drug interactions**

- OATP1B1/3 inhibitors (e.g. atazanavir, darunavir, lopinavir, saquinavir, tipranavir, cyclosporine)
- CYP3A Inducers (e.g. carbamazepine, phenytoin, rifampin, St. John’s Wort) efavirenz

**Grazoprevir/elbasvir  (Zepatier). Merck & Co., Inc., PI, Jan 2016**

**Grazoprevir/Elbasvir Efficacy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Entry Criteria</th>
<th>Study Design</th>
<th>Interventions with SVR12 Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-EDGE TN N=316 12 weeks</td>
<td>GT 1,4,5,6; TN + cirrhosis</td>
<td>RCT, DB, PC, MC 2:1</td>
<td>GZR/EBR PBO (followed by OL GZR/EBR)</td>
</tr>
<tr>
<td>C-EDGE CO-INFECION N=216 12 weeks</td>
<td>GT 1,4,5,6; TN + cirrhosis HIV co-inf</td>
<td>OL, SA, MC</td>
<td>GZR/EBR</td>
</tr>
<tr>
<td>C-EDGE TE N=420 12 and 16 weeks</td>
<td>GT 1,4,6; TE (RBV/IFN) + cirrhosis + RBV</td>
<td>RCT, DB, MC 1:1:1</td>
<td>12 weeks GZR/EBR GZR/EBR + RBV 16 weeks GZR/EBR GZR/EBR + RBV</td>
</tr>
<tr>
<td>C-SURFER N=237 12 weeks</td>
<td>GT 1; TN &amp; TE + cirrhosis; Advanced kidney dz (CKD 4 or 5)</td>
<td>RCT, DB, PC, MC 1:1</td>
<td>GZR/EBR pharmacokinetic GZR/EBR PBO (followed by OL GZR/EBR)</td>
</tr>
</tbody>
</table>

**C-EDGE TN**

- GT=genotype, RCT= randomized control trial, DB= double blind, PC=placebo controlled, GZR/EBR = grazoprevir/elbasvir, OL=open-label, TN=treatment naiive, TE=treatment experienced, PBO=Placebo

**Grazoprevir/Elbasvir Results**

<table>
<thead>
<tr>
<th>C-EDGE TN</th>
<th>C-EDGE CO-INFECION</th>
<th>C-EDGE TE</th>
<th>C-SURFER</th>
</tr>
</thead>
<tbody>
<tr>
<td>GZR/EBR</td>
<td>GZR/EBR</td>
<td>GZR/EBR</td>
<td>GZR/EBR+PK</td>
</tr>
<tr>
<td>w/o RBV</td>
<td>w/o RBV</td>
<td>w/o RBV</td>
<td>w/o RBV</td>
</tr>
<tr>
<td>316</td>
<td>218</td>
<td>105</td>
<td>104</td>
</tr>
<tr>
<td>Duration (weeks)</td>
<td>All pt SVR12</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td>12</td>
<td>16</td>
</tr>
</tbody>
</table>

**C-SURFER**

- PK=Pharmacokinetic
- *Modified full analysis set (FAS) with 2 lost to follow-up

**Grazoprevir/Elbasvir Summary**

- 5th highly potent oral DAA combination regimen for HCV genotype 1
- Ledipasvir/sofosbuvir combo and sofosbuvir alone based regimens are market leaders
- Comparable efficacy and safety to ledipasvir/sofosbuvir, paritaprevir/ritonavir/ombitasvir + dasabuvir
- No other regimen to treat patients with CrCl< 30 mL/min

**Sofosbuvir/Velpatasvir (Epclusa)**

10/30/2016
Sofosbuvir/Velpatasvir

Parameter | Drug Information
--- | ---
Generic | Sofosbuvir / velpatasvir
Brand | Epclusa
Manufacturer | Gilead Sciences, Inc.
FDA Approval Date | June 28, 2016
Approval Type | 505(b)(2) NDA, priority review / breakthrough therapy designation
Type of drug | Hepatitis C virus; Direct Acting Antiviral (HCV DAA)
FDA Indications | Treatment of HCV genotypes (GT) 1 - 6 in adults
Dosing | One tablet daily for 12 week
Available preparations | 100mg velpatasvir / 400 mg sofosbuvir

Efficacy Data:
- **SVR12 Rate**: 90% in all HCV genotypes
- Single daily tablet for 12 weeks
- Velpatasvir = 2nd generation NS5A replication complex inhibitor
- Hepatitis C virus; Direct Acting Antiviral (HCV DAA)

Safer tolerated with low SAE & discontinuation rates

**Comments**
- Pangenomic and improved resistance profile
- Inducers of P-gp and moderate inducers of CYP3A4 may reduce Epclusa therapeutic effect.
- P450 may reduce Epclusa therapeutic effect.
- Not recommended for severe renal impairment (eGFR <30 mL/min) or with ESRD
- No dosage adjustment for any hepatic impairment
- Drug-drug interactions: Inducers of P-gp and moderate inducers of P450 may reduce Epclusa therapeutic effect.
- • PPI, H2 antagonist, anticonvulsants, select HIV anti-retrovirals & rifampin

**Background**
- **Parameter**
  - Velpatasvir = 2nd generation NS5A replication complex inhibitor
  - Sofosbuvir = nucleotide analog inhibitor
  - Does not inhibit host DNA / RNA polymerases
  - Not recommended in advance kidney dose (crCl <30 ml/min)
  - Single daily tablet for 12 weeks
  - Add RBV to patients with decompensated cirrhosis
  - GT 1 TE CC, no longer need RBV compared to Harvoni + RBV
  - GT1-4 DC, improved efficacy compared to previous SOF regimen
  - GT 3 TN TE NC CC, improves SVR vs SOF + DVC
  - GT 2 patients, no longer need RBV
  - GT 1 TE CC, no longer need RBV compared to Harvoni + RBV 12 weeks
  - GT 1-4 DC, improved efficacy compared to previous SOF regimen
  - SVR >90% in all HCV genotypes
  - Single daily tablet for 12 weeks
  - Velpatasvir = 2nd generation NS5A replication complex inhibitor

**Efficacy**
- SVR rate >95% in diverse patient populations including decompensated cirrhosis / negative predictors of response
- Safety: Well tolerated with low SAE & discontinuation rates

**Indication**
- Treatment of HCV genotypes (GT) 1 - 6 in adults

**Study** | **Entry Criteria** | **Study Design** | **Interventions with SVR12 Primary Endpoint** | **ASTRAL-1** | **ASTRAL-2** | **ASTRAL-3** | **ASTRAL-4**
--- | --- | --- | --- | --- | --- | --- | ---
ASTRAL 1 | N=740 12 weeks | GT 1,4,5,6, TN, TE cirrhosis | RCT, DB, PC, MC 5:1 (GT5 excluded) | SOF/VEL vs RBV (followed by OL SOF/VEL) | SVR12 Rate (95% CI) 99.9% (95.9%, 100%) | 99.3% (95.5%, 100%) | 99.8% (98.4%, 99.7%) | 99.8% (98.4%, 99.7%)
ASTRAL 2 | N=268 12 weeks | GT 2; TN, TE cirrhosis | R, OL, MC 5:1 (GT5 excluded) | SOF/VEL vs SOF + RBV | 99.0% (97.9%, 99.6%) | 0% | 99.9% (95.5%, 100%) | 99.8% (98.4%, 99.7%)
ASTRAL 3 | N=552 12 or 24 weeks | GT 3; TN TE+ cirrhosis | R, OL, MC 1:1:1 | SOF/VEL vs SOF + RBV | 99.9% (95.9%, 100%) | 0% | 99.9% (95.5%, 100%) | 99.8% (98.4%, 99.7%)
ASTRAL 4 | N=267 12 or 24 weeks | GT 1 – 6; TN & TE Decompensated cirrhosis | R, OL, MC 1:1.1:1 | 12 weeks: SOF/VEL | 0% | 99.3% (95.5%, 100%) | 99.8% (98.4%, 99.7%)
ASTRAL 5 | N=104 12 weeks | GT 1-4; TN & TE cirrhosis; RBV co- | OL, SA, MC | 12 weeks: SOF/VEL | 0% | 99.3% (95.5%, 100%) | 99.8% (98.4%, 99.7%)

**Analysis**
- N=277
- SVR12: 99.0% (97.9%, 99.6%)
- 0%
- 99.9% (95.9%, 100%)

Sofosbuvir/Velpatasvir

Summary

- 1st pangenomic DAA available
- Well tolerated
- Incidence of AEs was similar in subjects with or without cirrhosis
- Most common AEs (>2%) in the trials were headache, fatigue, and nausea
- Low discontinuation and relapse rate
- One death in the trials – after subject completed 12 weeks of treatment and died post-treatment day

Obiltoxaximab (Anthim)

**Parameter** | **Drug Information**
---|---
Generic | Obiltoxaximab
Brand | Anthim
Manufacturer | Elusys Therapeutics
Approval Date | 18 Mar 2016
Approval Type | BLA 351(a)
Type of drug | Monoclonal antibody that binds the PA of B. anthracis

**FDA Indications**
- Injection: 600 mg/6 mL (100 mg/mL) in a single-dose vial

**Dosing**
- Dilute the injection in 0.9% Sodium Chloride Injection, USP, before administering as an intravenous infusion

**Background - Anthrax**

- Category A bioterrorism agent
- Bacterial infection caused by B. anthracis
- Inhalation of B. anthracis spores causes inhalational anthrax
- Protective antigen (PA) is a component of edema toxin and lethal toxin
- Fatality rate of 45-89%

**Pathophysiology**
- Toxins cause hemorrhage, edema, tissue necrosis and death
- Antibacterial drugs are the main treatment
- Raxibacumab and Anthrax immune globulin are used with antibacterial drugs
- Must be taken for a prolonged period of time

**Obiltoxaximab Efficacy**

**Study Overview**
- 4 studies compared obiltoxaximab vs PBO vs obiltoxaximab + antibacterial drugs

**Primary efficacy measure**
- Proportion of survival at day 28
**Obiltoxaximab Results**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>ANTHIM 16mg/kg IV</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NZW Rabbits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>0 (0/9)</td>
<td>93% (13/14)</td>
<td>0.0010</td>
</tr>
<tr>
<td>Study 2</td>
<td>0 (0/13)</td>
<td>62% (8/13)</td>
<td>0.0013</td>
</tr>
<tr>
<td>Cynomolgus Macaques</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 3</td>
<td>6% (1/16)</td>
<td>47% (7/15)</td>
<td>0.0068</td>
</tr>
<tr>
<td>Study 4</td>
<td>0 (0/17)</td>
<td>31% (5/16)</td>
<td>0.0085</td>
</tr>
</tbody>
</table>

Proportion of Survival at Day 28

1Survival assessed 28 days after spore challenge

2p-value is from 1-sided Boschloo Test (with Berger-Boos modification of gamma=0.001) compared to placebo

3Exact 95% confidence interval of difference in survival rates

4ANTHIM products manufactured at two different facilities were tested in two separate treatment arms

---

**Obiltoxaximab Summary**

- No human studies
- Current main treatments are antibacterial drugs, raxibacumab and Anthrax immune globulin
- Obiltoxaximab proves effective with or without antibacterial drugs
- Provides another treatment option for a fatal infection

---

**Cholera: Current Treatment**

- Mainstay of therapy is hydration
  - **Guidelines for Cholera Treatment with Antibiotics**
    - **Organization**
      - World Health Organization
      - Pan-American Health Organization
      - International Centre for Diarrhoeal Disease Research, Dhaka
      - Medicine Sans Frontières
    - **Recommendation**
      - Antibiotic treatment for cholera patients with severe dehydration only
      - Antibiotic treatment for cholera patients with moderate or severe dehydration
    - **First line drugs chosen**
      - Doxycycline
      - Ciprofloxacin
    - **Alternate drug chosen**
      - Tetracycline
      - Ciprofloxacin
    - **Drug chosen for children’s treatment**
      - Enrofloxacin is recommended for children

---

**Cholera Vaccine, Live, Oral (Vaxchora)**

- **Parameter**
  - Drug Information
    - **Drug Information**
      - **Parameter**
        - Pregnancy
          - • No available human data
          - • Only use if clearly needed
        - Pediatrics
          - • Not established
        - Dose
          - • Mild to moderate hepatic impairment reduce dose, avoid in severe
          - • Mild to moderate renal impairment no adjustment, no data severe
        - Drug-drug Interactions
          - • Ciprofloxacin, co-administration does not alter pharmacokinetics of ciprofloxacin or obiltoxaximab
Cholera Vaccine, Live, Oral

**Parameter** | **Drug Information**
---|---
Generic | Cholera Vaccine, Live, Oral
Brand | Vaxchora
Manufacturer | PaxVax Bermuda Ltd.
FDA Approval Date | June 10, 2016
FDA Indications | Active immunization against disease caused by *Vibrio cholerae* serogroup O1
Dosing | Administered orally a minimum of 10 days before potential exposure to cholera
Available preparations | Suspension for oral administration supplied as a single dose carton containing two packets. Reconstitute: 100 mL water

**Efficacy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PXVX0200 10 Day Challenge N=35, n (%)</th>
<th>PXVX0200 3 Month Challenge N=35, n (%)</th>
<th>Combined Placebo Challenges N=66, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine Efficacy (95% CI)</td>
<td>90.3 (62.7, 100.00)</td>
<td>79.5 (49.9, 100.00)</td>
<td>61 (92.4)</td>
</tr>
<tr>
<td>Overall Severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No qualifying diarrhea</td>
<td>30 (85.7)</td>
<td>18 (54.5)</td>
<td>5 (7.6)</td>
</tr>
<tr>
<td>Mild: &lt; 3 L – L of diarrhea</td>
<td>3 (8.6)</td>
<td>11 (33.3)</td>
<td>22 (33.3)</td>
</tr>
</tbody>
</table>

**Results**

- **Pharmacokinetics**
  - Protein binding (>99%) primarily to serum albumin and alpha1-acid glycoprotein
  - Metabolism: Hepatic, primarily by CYP3A4 and CYP2D6; major metabolite, DM-3411 (inactive)
- **Contraindications**: pre-existing hepatic disease or impairment, autoimmune diseases, and hypersensitivity
- **Warnings & Precautions**
  - Autoimmune hepatitis, bilirubin elevation, skin reactions, lymphadenopathy, colitis, hypersensitivity, infections, depression, and suicide
- **Adverse Reactions**
  - Nasopharyngitis, upper respiratory infections, rash, influenza, dermatitis, oropharyngeal pain, bronchitis, eczema, lymphadenopathy, tonsillitis, acne

**Drug Interactions**

- Avoid concomitant administration with systemic antibiotics since these agents may be active against the vaccine strain and prevent a sufficient degree of multiplication to occur in order to induce a protective immune response
  - Chloroquine, antimalarial
  - Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids

**Pregnancy Concerns**

- Not absorbed systemically following oral administration
  - Maternal use is not expected to result in fetal exposure to the drug
**Cholera Vaccine, Live, Oral**

- Effectiveness demonstrated based on human challenge data
- Serious adverse events were uncommon
- Ongoing studies required to evaluate efficacy in children ≥ 2 years to < 18 years
- First viable option for prevention of cholera

---

**Lifitegrast**

**Parameter**

<table>
<thead>
<tr>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic lifitegrast</td>
</tr>
<tr>
<td>Brand Xiidra</td>
</tr>
<tr>
<td>Manufacturer Shire</td>
</tr>
<tr>
<td>FDA Approval July 11, 2016</td>
</tr>
<tr>
<td>Approval Type New molecular entity</td>
</tr>
<tr>
<td>Type of drug LFA-1 antagonist</td>
</tr>
<tr>
<td>FDA Indications Treatment for the signs and symptoms of dry eye disease (DED)</td>
</tr>
<tr>
<td>Dosing 1 drop into each eye BID (~12 hours apart)</td>
</tr>
<tr>
<td>Available preparations Ophthalmic solution containing lifitegrast 5% (50mg/mL)</td>
</tr>
</tbody>
</table>

**Lifitegrast Efficacy**

- **Study Design**
  - Four studies, R, DB, MC, PA, PC,
  - Duration: 84 days, n = 1181

- **Patient characteristics**
  - >18 years of age (mean 59 yo)
  - Baseline CFS (mean 2.1) and STT (mean 4.8)
  - Baseline EDS (mean 58) and ODS (mean 1.9)

- **Treatment**
  - R (1:1)
  - Lifitegrast vs PBO

- **Efficacy Measures**
  - Primary
    - Avg Δ from baseline and tx difference in EDS (symptoms)
    - EDS scale
      - 0 = no discomfort
      - 100 = maximal discomfort

DB=double-blind; MC=multi-center; PA=parallel arm; PC=placebo-controlled; R=randomized; CFS= corneal fluorescein staining; STT=Schirmer tear test; EDS=eye dryness score; ODS=ocular discomfort score
### Lifitegrast Results

#### Phase 2

<table>
<thead>
<tr>
<th>Visit</th>
<th>Placebo (N=58)</th>
<th>Lifitegrast 5.0% (N=58)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>51.8</td>
<td>51.5</td>
<td>0.1 (-13.1, 13.0)</td>
</tr>
<tr>
<td>Day 14</td>
<td>-3.9</td>
<td>-6.9</td>
<td>-5.1 (-13.1, 3.0)</td>
</tr>
<tr>
<td>Day 42</td>
<td>-7.9</td>
<td>-17.3</td>
<td>-9.4 (-17.0, -5.9)</td>
</tr>
<tr>
<td>Day 84</td>
<td>-7.2</td>
<td>-14.4</td>
<td>-7.3 (-16.1, 1.4)</td>
</tr>
</tbody>
</table>

#### Phase 3: OPUS-1

<table>
<thead>
<tr>
<th>Visit</th>
<th>Placebo (N=205)</th>
<th>Lifitegrast 5.0% (N=203)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>41.6</td>
<td>40.2</td>
<td>0.1 (-13.1, 4.1)</td>
</tr>
<tr>
<td>Day 14</td>
<td>-7.5</td>
<td>-6.7</td>
<td>-0.8 (-13.1, 7.5)</td>
</tr>
<tr>
<td>Day 42</td>
<td>-9.1</td>
<td>-12.6</td>
<td>-3.5 (-13.0, 6.0)</td>
</tr>
<tr>
<td>Day 84</td>
<td>-11.2</td>
<td>-15.2</td>
<td>-4.0 (-9.9, 1.0)</td>
</tr>
</tbody>
</table>

#### Phase 3: OPUS-2

<table>
<thead>
<tr>
<th>Visit</th>
<th>Placebo (N=360)</th>
<th>Lifitegrast 5.0% (N=358)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>69.2</td>
<td>69.7</td>
<td>0.5 (-10.0, 11.0)</td>
</tr>
<tr>
<td>Day 14</td>
<td>-13.1</td>
<td>-19.7</td>
<td>-6.6 (-10.0, -3.2)</td>
</tr>
<tr>
<td>Day 42</td>
<td>-18.2</td>
<td>-28.3</td>
<td>-10.2 (-14.0, -6.4)</td>
</tr>
<tr>
<td>Day 84</td>
<td>-22.8</td>
<td>-35.3</td>
<td>-12.5 (-16.4, -8.6)</td>
</tr>
</tbody>
</table>

#### Phase 3: OPUS-3

<table>
<thead>
<tr>
<th>Visit</th>
<th>Placebo (N=295)</th>
<th>Lifitegrast 5.0% (N=293)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>41.6</td>
<td>40.2</td>
<td>0.1 (-10.0, 11.0)</td>
</tr>
<tr>
<td>Day 14</td>
<td>-7.5</td>
<td>-6.7</td>
<td>-0.8 (-13.1, 7.5)</td>
</tr>
<tr>
<td>Day 42</td>
<td>-9.1</td>
<td>-12.6</td>
<td>-3.5 (-13.0, 6.0)</td>
</tr>
<tr>
<td>Day 84</td>
<td>-11.2</td>
<td>-15.2</td>
<td>-4.0 (-9.9, 1.0)</td>
</tr>
</tbody>
</table>

### Lifitegrast vs Cyclosporine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cyclosporine (Restasis)</th>
<th>Lifitegrast (Xiidra)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of administration</td>
<td>Twice daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Dosage forms</td>
<td>Ophthalmic emulsion</td>
<td>Ophthalmic emulsion</td>
</tr>
<tr>
<td>Strengths</td>
<td>0.05%</td>
<td>5%</td>
</tr>
<tr>
<td>Package Sizes</td>
<td>30 vials, each 0.4 ml</td>
<td>60 vials, each 0.4 ml</td>
</tr>
<tr>
<td>Comments</td>
<td>Can be used concomitantly with artificial tears</td>
<td>Single use containers; Remove contacts before instillation</td>
</tr>
</tbody>
</table>

### Lifitegrast Summary

- Novel mechanism of action
- Only agent approved to treat the signs and symptoms of dry eye disease
- Adverse events were minor and limited in duration
- Closest comparator is cyclosporine 0.05% topical emulsion
- Possible faster onset of action than cyclosporine 0.05%

### Pulmonology

#### Glycopyrrolate/Formoterol fumarate (Bevespi Aerosphere)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic</td>
<td>Glycopyrrolate and formoterol fumarate</td>
</tr>
<tr>
<td>Brand</td>
<td>Bevespi Aerosphere</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>AstraZeneca (Pearl Therapeutics Inc.)</td>
</tr>
<tr>
<td>FDA Approval</td>
<td>April 25, 2016</td>
</tr>
<tr>
<td>Approval Type</td>
<td>NDA – 505(b)(2)</td>
</tr>
<tr>
<td>Type of drug</td>
<td>Inhaled LABA-LAMA combination</td>
</tr>
<tr>
<td>FDA Indications</td>
<td>Long-term, maintenance treatment of airflow obstruction in COPD</td>
</tr>
<tr>
<td>Dosing</td>
<td>2 inhalations BID</td>
</tr>
<tr>
<td>Available preparations</td>
<td>• Pressurized metered dose inhaler of 9 mcg glycopyrrolate/4.8 mcg formoterol as inhalation aerosol • 120 inhalations/canister</td>
</tr>
</tbody>
</table>

Glycopyrrolate/Formoterol

Parameter | Drug Information
--- | ---
**Background** | • First LAMA-LABA combination bronchodilator therapy for COPD formulated in a pressurized metered-dose inhaler (pMDI)
**Comments** | • Not indicated for use in asthma
**Adverse Reactions** | • UTI and cough
**Contraindications** | • Use in asthma without long-term asthma controller medication
**Black Box Warning Or Significant Adverse Effects** | • BBW: LABAs can increase risk of asthma-related death
• Paradoxical bronchospasm
• Hypokalemia or hyperglycemia
• Worsening of narrow-angle glaucoma or urinary retention

**Parameter Drug Information**

1. **Clinical Development Program**
   - 8 dose-ranging trials (n=822)
   - Glycopyrrolate: 6 doses, 14-day R, DB, PC, incomplete-block crossover trial
   - Formoterol: 3 doses, single-dose, R, DB, PC, crossover trial
2. **Baseline characteristics**
   - 2, R, DB, PC, PG lung function trials, 24-weeks

**Bevespi Aerosphere (glycopyrrolate/formoterol fumarate). Product labeling. AstraZeneca. April 2016.**

**Glycopyrrolate/Formoterol Efficacy**

**Parameter** | **Drug Information**
--- | ---
**Clinical Development Program** | 8 dose-ranging trials (n=822)
- Glycopyrrolate: 6 doses, 14-day R, DB, PC, incomplete-block crossover trial
- Formoterol: 3 doses, single-dose, R, DB, PC, crossover trial
**Baseline characteristics** | 2, R, DB, PC, PG lung function trials, 24-weeks

**Bevespi Aerosphere (glycopyrrolate/formoterol fumarate). Product labeling. AstraZeneca. April 2016.**

**Glycopyrrolate/Formoterol Summary**

- 4<sup>th</sup> LAMA/LABA combination
- 1<sup>st</sup> pMDI, others are breath actuated or Respimat
- COPD maintenance therapy
- BID drug vs 2 other once daily drugs
- Offers no compelling advantages

**Bevespi Aerosphere (glycopyrrolate/formoterol fumarate). Product labeling. AstraZeneca. April 2016.**

---

**Nuclear**

**Fluciclovine F 18 (Axumin)**
**Fluciclovine F 18**

### Generic Information
- **Drug Name:** Fluciclovine F 18
- **Brand Name:** Axumin
- **Manufacturer:** Blue Earth Diagnostics Ltd.
- **FDA Approval:** May 27, 2016
- **Approval Type:** NDA

### FDA Indications
- Positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment.

### Dosing
- 370 MBq (10 mCi) administered as an intravenous bolus injection.

### Available Preparations
- 30 mL multiple-dose glass vial containing approximately 26 mL solution.

### Background
- Amino acid transported across cell membranes by amino acid transporters which are upregulated in prostate cancer cells.

### Comments
- Not for female use.

### Adverse Reactions
- Injection site pain, erythema, and dysgeusia.

### Contraindications
- None.

### Special Instructions
- Patients should avoid significant exercise for at least a day before the PET scan.
- Patients should not eat or drink for at least 4 hours before the PET scan.

### Study Efficacy/Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Treatment</th>
<th>Efficacy Measures</th>
<th>Results</th>
</tr>
</thead>
</table>
| Study 1 | Patient characteristics: Men with suspected recurrence of prostate cancer (N = 99, open label, prospective, single center study) | Fluciclovine F18 + 111 Capromab pendetide | Positive predictive value (PPV) | PPV ≥ 1.78 11/15 (73.3%)  
PSA > 1.78 - ≤ 4.48 17/22 (77.3%)  
PSA > 4.48 - ≤ 9.25 20/27 (84%)  
PSA > 9.25 20/24 (83.3%) |
| Study 2 | Patient characteristics: Men with median PSA value of 1.44 ng/mL (N = 50, open label, prospective, single center study) | Fluciclovine F18 + C11 choline | Concordance between Axumin and C11 choline scans | Next Slide |

### Fluorine-18 Results

<table>
<thead>
<tr>
<th>Fluorine-18 ([-])</th>
<th>Fluorine-18 ([+])</th>
</tr>
</thead>
<tbody>
<tr>
<td>18O-Choline ([-])</td>
<td>33</td>
</tr>
<tr>
<td>18F-Fluciclovine ([-])</td>
<td>6</td>
</tr>
</tbody>
</table>

### Summary
- Primary and recurrent prostatic carcinoma is a major public health issue in the US.
- In men with recurrent prostate cancer, Fluocilovine F18 is useful for the detection of metastases as verified by histopathology and patient follow up.
- The standard imaging modalities have limitations.
- New diagnostic options are needed.
**Morphine Extended-Release**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic</td>
<td>Morphine Extended-Release</td>
</tr>
<tr>
<td>Brand</td>
<td>Morphabond</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Inspirion Delivery Technologies , LLC</td>
</tr>
<tr>
<td>Approval Date</td>
<td>October 2, 2015</td>
</tr>
<tr>
<td>FDA Indications</td>
<td>Management of severe pain that requires long-term treatment and for which other options are inadequate</td>
</tr>
<tr>
<td>Dosing</td>
<td>Administered orally every 12 hours</td>
</tr>
<tr>
<td>Available preparations</td>
<td>15, 30, 60, 100 mg tablets</td>
</tr>
</tbody>
</table>

**Oxycodone Extended-Release**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic</td>
<td>Oxycodone Extended-Release</td>
</tr>
<tr>
<td>Brand</td>
<td>Xtampza ER</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Collegium Pharmaceutical, Inc.</td>
</tr>
<tr>
<td>Approval Date</td>
<td>April 26, 2016</td>
</tr>
<tr>
<td>FDA Indications</td>
<td>Management of severe pain that requires long-term treatment and for which other options are inadequate</td>
</tr>
<tr>
<td>Dosing</td>
<td>Administered orally every 12 hours with food</td>
</tr>
<tr>
<td>Available preparations</td>
<td>9, 13.5, 18, 27, 36 mg capsules</td>
</tr>
</tbody>
</table>

**Nebivolol/Valsartan**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic</td>
<td>Nebivolol/valsartan</td>
</tr>
<tr>
<td>Brand</td>
<td>Byvalson</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Allergan, Inc</td>
</tr>
<tr>
<td>Approval Date</td>
<td>June 3, 2016</td>
</tr>
<tr>
<td>FDA Indications</td>
<td>Treatment of hypertension, to lower blood pressure</td>
</tr>
<tr>
<td>Dosing</td>
<td>Administered orally once daily</td>
</tr>
<tr>
<td>Available preparations</td>
<td>5 mg/80 mg tablets</td>
</tr>
</tbody>
</table>

**Calcifediol**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic</td>
<td>Calcifediol</td>
</tr>
<tr>
<td>Brand</td>
<td>Rayaldee</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Opko Ireland Global</td>
</tr>
<tr>
<td>FDA Approval Date</td>
<td>June 17, 2016</td>
</tr>
<tr>
<td>Approval Type</td>
<td>New Formulation, Standard Review Drug</td>
</tr>
<tr>
<td>FDA Indications</td>
<td>Treatment of secondary hyperparathyroidism in adults with stage 3 or 4 chronic kidney disease and serum total 25-hydroxyvitamin D levels less than 30 ng/mL</td>
</tr>
<tr>
<td>Dosing</td>
<td>Administered orally once daily at bedtime</td>
</tr>
<tr>
<td>Available preparations</td>
<td>30 mcg extended-release capsules</td>
</tr>
</tbody>
</table>

**Key Points**

- For further details regarding formulary decisions, see individual agency websites
  - [https://online.epocrates.com/TRICARE formulary](https://online.epocrates.com/TRICARE formulary)
- For more information on specific drugs, see the Drugs at FDA website and individual manufacturer websites

**Self-Assessment Question 1**

1. What is the mechanism of action of ixekizumab?

   a) IL-2 inhibitor  
   b) BCL-2 inhibitor  
   c) IL-17a receptor antagonist  
   d) Tyrosine kinase inhibitor
Self-Assessment Question 2

2. Tumor lysis syndrome is a concern with which drug?
   
   a) lifitegrast
   b) pimavanserin
   c) cabozantanib
   d) venetoclax

Self-Assessment Question 3

3. Which drug : indication pairing is correct?
   
   a) Elbasvir/grazoprevir: cholera
   b) Glycopyrrolate and formoterol fumarate: COPD
   c) Lifitegrast: erectile dysfunction
   d) Fluciclovine F18: breast cancer

New Drugs of 2016

Amy M. Lugo, PharmD, BCPS, BC-ADM, FAPhA
Clinical Pharmacy Specialist
Director, Managed Care Residency
Defense Health Agency
Pharmacy Operations Division
Formulary Management Branch
San Antonio, Texas

LCDR Kendra N. Jenkins, USPHS
PharmD, BCPS
Program Management Officer
Immigration and Customs Enforcement (ICE)
Enforcement and Removal Operations
ICE Health Service Corps
Washington, DC