New Drugs of 2015

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Learning Objectives

Pharmacist:
1. List new therapeutic agents that were approved by the Food and Drug Administration (FDA) in 2015 and added to the federal formularies.
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.

Technician:
1. List new therapeutic agents that were approved by the Food and Drug Administration (FDA) in 2015 and added to the federal formularies.
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 flibanserin?
   a) PDE-5 inhibitor like sildenafil
   b) Serotonergic activity
   c) Hedgehog pathway inhibitor
   d) Histone deacetylase (HDAC) inhibitor
Self-Assessment Question 2

2. Which of the following is a concern with regard to the PCSK9 inhibitors?

a) Effects of very low cholesterol
b) Effect on cardiovascular mortality
c) Cost
d) All of the above

Self-Assessment Question 3

3. Which drug : indication pairing is correct?

a) Edoxaban : prevention of VTE after hip and knee surgery
b) Secukinumab : treatment of Crohn’s disease
c) Daclatasvir : treatment of chronic hepatitis C virus (HCV) genotype 4
d) Ivabradine : chronic heart failure

New Drugs to be Reviewed

- Endocrinology (1)
- Dermatology (1)
- Hematology/Oncology (1 of 5)
- Infectious Disease (1 of 4)
- Cardiology (3 of 5)
- Gastrointestinal (1)
- Pulmonology
- Neurology/Psychiatry (2)

Parathyroid hormone (Natpara)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>NPS Pharma</td>
</tr>
<tr>
<td>FDA Approval Date</td>
<td>January 2015</td>
</tr>
<tr>
<td>FDA Approved Indication</td>
<td>Adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Exogenous parathyroid hormone (PTH); raises serum calcium concentrations by 1) increasing renal tubular calcium reabsorption, 2) increasing intestinal calcium absorption, and by 3) increasing bone turnover, which releases calcium into the circulation</td>
</tr>
<tr>
<td>Formulations</td>
<td>SubQ injection; 25mcg, 50mcg, 75mcg, or 100mcg</td>
</tr>
<tr>
<td>Dosing</td>
<td>50mcg once daily; Increase in increments of 25 mcg/day every 4 weeks; maximum daily dose: 100 mcg/day</td>
</tr>
</tbody>
</table>

Endocrinology

Parathyroid hormone

- Pharmacokinetics: Duration: 24 hours; Excretion: primarily renal
- Contraindications: none
- Warnings & Precautions: hypercalcemia, hypocalcemia, osteosarcoma
- Black Box Warning: risk of osteosarcoma due to observations in studies with rodents
  - Whether PTH causes osteosarcoma in humans is unknown
  - Only available through a restricted REMS program
  - Occurrence of osteosarcoma was dependent on dose and treatment duration
- Adverse Reactions
  - Most common ADRs occurring in ≥ 10% of individuals: paresthesia, hypocalcemia, HA, hypercalcemia, N/V/D, hypoesthesia, arthralgia, hypercalciuria, and pain in extremity
**Parathyroid hormone**

**Warnings & Precautions**
- Calcium supplementation: maintain the same dose at initiation of PTH therapy. May require titration during PTH therapy based on albumin-corrected serum calcium concentrations.
- Vitamin D: In patients receiving active forms of vitamin D, reduce the dose of vitamin D by 50% at initiation of PTH therapy if serum calcium is >7.5 mg/dL.

**Drug Interactions:** PTH may enhance the effects of digoxin.

**Pregnancy category:** C

**Monitoring Parameters**
- Total serum calcium (albumin-corrected) prior to initiation, within 3-7 days following initiation or dosage adjustments until maintenance dose has been achieved, and periodically.
- Urinary calcium excretion (after maintenance dose is achieved); signs and symptoms of hypo- and hypercalcemia.

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**Efficacy**

**Study Design**
- 24-week, R (2:1), DB, FC, trial (REPLACE trial) in patients with established hypoparathyroidism.

**Baseline characteristics:**
- Baseline serum Ca = 8.6 mg/dL
- Average dose of oral active vitamin D = 2000 mg/day
- Average dose of oral active vitamin D = 0.75 mcg daily of calcitriol
- Average age = 47 yo; Female (79%); Caucasian (96%)

**Treatment Arms**
- PTH 50mcg SubQ daily
- Placebo

**Endpoints**
- Proportion of pts achieving a ≥ 50% ↓ from baseline in daily dose of oral Ca and active vit D while maintaining a serum Ca level at or above their baseline value and at or below the ULN.

**Results**
- Forty-eight (53%) patients in the PTH group achieved the primary endpoint vs one (2%) patient in the placebo group.
- 42% of PTH-treated patients achieved normal Ca levels on reduced doses of Ca and active forms of vitamin D, compared to 3% in the placebo group.
- ADRs and serious ADRs were similar between groups.

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**Dermatology**

**Secukinumab (Cosentyx)**

**Parameter**
- Manufacturer: Novartis
- FDA Approval Date: January 2015
- Biologics License Application (BLA)
- FDA Approved Indication: Moderate to severe plaque psoriasis

**Mechanism of Action**
- First-in-class agent; selectively binds to the interleukin-17A (IL-17A) cytokine and inhibits its interaction with the IL-17 receptor

**Formulations**
- SubQ injection: 150mg/mL (1mL) Sensoready Pen and 150mg/mL (1mL) prefilled syringe

**Dosing**
- 300mg SubQ once weekly (given as two 150mg SubQ injections) at weeks 0, 1, 2, 3, and 4 followed by 300mg every 4 weeks
- 150mg may be beneficial for some patients

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**Pharmacokinetics:**
- Half-life = 22-31 days
- Secukinumab clearance and volume of distribution increase as body weight increases

**Contraindications:**
- Hypersensitivity

**Warnings & Precautions**
- May exacerbate infections and Crohn’s disease.
- Patients should be brought up to date with all immunizations before initiating therapy.
- Live vaccines should not be given concurrently.

**Adverse Reactions**
- Infection (29% to 48%); nasopharyngitis (11% to 12%)
- Diarrhea (3% to 4%); mucocutaneous candidiasis (1%); oral herpes (≤1%)
- Infection, URTI (3%); pharyngitis (1%); rhinitis (1%)

**Drug Interactions:** Numerous

**Pregnancy category:** B

**Monitoring Parameters:** Signs and symptoms of infection, active tuberculosis (during and after treatment), and exacerbations of Crohn’s disease.
**Secukinumab Efficacy**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Patients</th>
<th>Treatment Arms</th>
<th>Efficacy Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERASURE</td>
<td>Plaque psoriasis Age = 18 BSA = 10% (32.8 + 19.2) PASI 11-72 &gt; 12</td>
<td>ERASURE R (1:1:1), DB, PC, Phase 3 study</td>
<td>Secukinumab qweek injections at weeks 0, 1, 2, 3, 4; then q 4 weeks 150 mg (n=245) 300 mg (n=245) vs PBO (n=248) 12 weeks PASI 75, IGA/PGA</td>
</tr>
<tr>
<td>FIXTURE</td>
<td>Plaque psoriasis Age &gt; 18 BSA &gt; 10% (34.3 + 19.2) PASI 0-72 &gt; 12</td>
<td>FIXTURE R (1:1:1:1), DB, PC, AC, Phase 3 study</td>
<td>Secukinumab qweek injections at weeks 0, 1, 2, 3, 4; then q 4 weeks 150 mg (n=327) 300 mg (n=327) vs Etanercept BIW at baseline to week 12; then qweek 50 mg (n=326) PBO (n=326) 12 weeks PASI 75, IGA/PGA</td>
</tr>
</tbody>
</table>

- **Plaque psoriasis**
- **Age > 18**
- **BSA > 10%**
- **PASI 11-72 > 12**
- **Candidate for phototherapy or systemic therapy**
- **Secukinumab qweek injections at weeks 0, 1, 2, 3, 4; then q 4 weeks**
- **150 mg** (n=245)
- **300 mg** (n=245)
- **vs PBO** (n=248)
- **12 weeks PASI 75, IGA/PGA**
- **FIXTURE R (1:1:1:1), DB, PC, AC, Phase 3 study**
- **Duration:** 52 weeks (induction 12 weeks + maintenance 40 weeks)
- **Plaque psoriasis**
- **Age > 18**
- **BSA > 10%**
- **PASI 0-72 > 12**
- **Candidate for phototherapy or systemic therapy**
- **Secukinumab qweek injections at weeks 0, 1, 2, 3, 4; then q 4 weeks**
- **150 mg** (n=327)
- **300 mg** (n=327)
- **Etanercept BIW at baseline to week 12; then qweek 50 mg** (n=326)
- **PBO** (n=326)
- **12 weeks PASI 75 (PBO)**
- **IGA/PGA**

**Secukinumab Results**

- **Primary endpoint:** Psoriasis Area and Severity Index (PASI) 75
- **Secondary endpoints:** PASI 90, PSD

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dose</th>
<th>PASI 75 12 weeks</th>
<th>PASI 75 52 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERASURE</td>
<td>Secukinumab 300 mg</td>
<td>200/245 (81.6%)</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>Secukinumab 150 mg</td>
<td>174/243 (71.6%)</td>
<td>126/174 (72.4%)</td>
</tr>
<tr>
<td></td>
<td>PBO</td>
<td>11/246 (4.5%)</td>
<td>NE</td>
</tr>
<tr>
<td>FIXTURE</td>
<td>Secukinumab 300 mg</td>
<td>249/323 (77.1%)</td>
<td>210/249 (84.3%)</td>
</tr>
<tr>
<td></td>
<td>Secukinumab 150 mg</td>
<td>219/327 (67%)</td>
<td>180/219 (82.2%)</td>
</tr>
<tr>
<td></td>
<td>Etanercept 50 mg</td>
<td>142/323 (44%)</td>
<td>103/142 (72.5%)</td>
</tr>
<tr>
<td></td>
<td>PBO</td>
<td>16/324 (4.9%)</td>
<td>NE</td>
</tr>
</tbody>
</table>

- * p<0.001 for comparison with placebo
- ** p<0.001 for comparison with etanercept

**Systematic Review and Meta-Analysis of Treatments for Moderate – Severe Psoriasis**

- Limitations include low quality evidence and that a clear ranking is limited by lack of head-to-head trials
- Available evidence suggest infliximab, secukinumab, and ustekinumab are the most efficacious long-term therapies

<table>
<thead>
<tr>
<th>Drug (# of trials)</th>
<th>PASI 75 Pooled RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab (6)</td>
<td>13.07</td>
<td>8.60-19.87</td>
</tr>
<tr>
<td>Secukinumab (2)</td>
<td>11.97</td>
<td>8.83-16.23</td>
</tr>
<tr>
<td>Ustekinumab (6)</td>
<td>11.39</td>
<td>8.94-14.51</td>
</tr>
<tr>
<td>Adalimumab (3)</td>
<td>7.92</td>
<td>6.33-12.57</td>
</tr>
<tr>
<td>Etanercept (9)</td>
<td>6.39</td>
<td>6.74-10.45</td>
</tr>
<tr>
<td>Apremilast (1)</td>
<td>5.82</td>
<td>5.05-13.17</td>
</tr>
</tbody>
</table>

- **Systematic Review (25 RCTs, n=11,279 patients)**

**Hematology/Oncology Drugs**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Route</th>
<th>MFR</th>
<th>Indication</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panobinostat</td>
<td>Farydak</td>
<td>oral</td>
<td>Novartis</td>
<td>Multiple myeloma</td>
<td>Feb 2015</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>Brioverride</td>
<td>oral</td>
<td>Pfizer</td>
<td>Metastatic breast cancer</td>
<td>Feb 2015</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>Lenvima</td>
<td>oral</td>
<td>Eisai</td>
<td>Thyroid cancer</td>
<td>Feb 2015</td>
</tr>
<tr>
<td>Dinutuximab</td>
<td>Unituxin</td>
<td>IV</td>
<td>United Therapeutics</td>
<td>Highrisk neuroblastoma</td>
<td>March 2015</td>
</tr>
<tr>
<td>Sonidegib</td>
<td>Odomzo</td>
<td>oral</td>
<td>Novartis</td>
<td>Advanced basal cell carcinoma</td>
<td>July 2015</td>
</tr>
</tbody>
</table>

**Panobinostat (Farydak)**

- **Manufacturer:** Novartis
- **Approval Date:** February 2015
- **FDA Approved Indication:** Relapsed multiple myeloma (in combination with bortezomib and dexamethasone) in patients who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent
- **Mechanism of Action:** First-in-class; histone deacetylase (HDAC) inhibitor; inhibits enzymatic activity of HDACs which leads to ↑ histones and proteins that induce cell cycle arrest and/or apoptosis
- **Formulations:** 10mg, 15mg, 20mg oral capsules
- **Dosing:** 20mg every other day for 3 doses each week (on Days 1, 3, 5, 8, 10, and 12) during weeks 1 & 2 of a 21-day cycle, up to 8 cycles
- **Issues:** May repeat an additional 8 cycles (in combination with bortezomib & dexamethasone) in patients experiencing clinical benefit and acceptable toxicity
Panobinostat Efficacy

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Treatment Arms</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>R (1:1), DB, PC study (n=788) of patients with relapsed multiple myeloma who had received 1 to 3 prior therapies</td>
<td>Bortezomib + dexamethasone + panobinostat 20 mg vs Bortezomib + dexamethasone + PBO</td>
<td>Primary endpoint: progression free survival (PFS)</td>
</tr>
</tbody>
</table>

- Results
  - Median PFS was 12 months (10.3, 12.9) in the panobinostat arm vs 8.1 months (7.6, 9.2) in the placebo arm
  - Overall survival was not statistically different between groups in the interim analysis
  - Approval was based on a subgroup analysis of 193 pts who had received prior treatment
  - PFS was almost twice as long (10.6 mo vs. 5.8 mo) in the panobinostat-treated patients who had received more than two prior lines of therapy

Palbociclib (Ibrance)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Pfizer</td>
</tr>
<tr>
<td>FDA Approval Date</td>
<td>February 2015</td>
</tr>
<tr>
<td>FDA Approved Indication</td>
<td>Metastatic breast cancer: Treatment of estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer (in combination with letrozole) in postmenopausal women as initial endocrine-based therapy for metastatic disease</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>A reversible small molecule cyclin-dependent kinase (CDK) inhibitor selective for CDK 4 and 6. Prevents progression from the G1 to the S cell cycle phase</td>
</tr>
<tr>
<td>Formulations</td>
<td>75 mg, 100 mg, 125 mg oral capsules</td>
</tr>
<tr>
<td>Dosing</td>
<td>125 mg once daily for 21 days, followed by a 7-day rest period to complete a 28-day treatment cycle (in combination with continuous letrozole)</td>
</tr>
</tbody>
</table>

Palbociclib Issues

- Avoid CYP2D6 substrates and strong CYP3A inducers
  - The dose of palbociclib should be ↓ when given with strong CYP3A inhibitors
- No dose adjustment for renal impairment however concerns exist with hepatic impairment
- Pregnancy must be ruled out prior to treatment; women should use effective contraception
- BBW: severe and fatal cardiac ischemic events, severe arrhythmias, and electrocardiogram (ECG) changes
- Warnings: risk of fatal and serious GI and pulmonary hemorrhage, hepatotoxicity, and embryo-fetal toxicity

Lenvatinib (Lenvima)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Eisai</td>
</tr>
<tr>
<td>FDA Approval Date</td>
<td>February 2015</td>
</tr>
<tr>
<td>FDA Indication</td>
<td>Treatment of locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC)</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Multitargeted tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF) receptors (VEGFR1 (FLT1), VEGFR2 (KDR), VEGFR3 (FLT4)), fibroblast growth factor (FGF) receptors (FGFR1, 2, 3, and 4), platelet derived growth factor receptor alpha (PDGFR alpha), and other RTKs. Inhibition leads to ↓ tumor growth and slowing of cancer progression</td>
</tr>
<tr>
<td>Formulations</td>
<td>4 mg, 10 mg oral capsules</td>
</tr>
<tr>
<td>Dosing</td>
<td>24 mg once daily until disease progression or unacceptable toxicity. Do not take a missed dose within 12 hours of the next dose.</td>
</tr>
</tbody>
</table>
### Lenvatinib Efficacy

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Treatment Arms</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>R (2:1), DB, PC study of (n=392) patients with locally recurrent or metastatic thyroid cancer that was refractory to radioactive iodine</td>
<td>Lenvatinib 24mg once daily vs Placebo</td>
<td>Primary endpoint: progression free survival (PFS)</td>
</tr>
</tbody>
</table>

- **Results**
  - Statistically significant ↑ in PFS was seen in the lenvatinib treated arm (median PFS 18.3 months) compared to those receiving placebo (median PFS 3.6 months)

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### Lenvatinib Concerns

- **Warnings & Precautions**
  - Hypertension, cardiac failure, arterial thrombotic events, hepatotoxicity, and proteinuria
- **Pregnancy & Lactation**
  - May cause fetal harm; discontinue breast-feeding
- **Adverse Reactions**
  - (>30%) HTN, fatigue, N/V/D, arthralgia/myalgia, ↓ in appetite and wt, stomatitis, HA, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, and dysphonia

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### Sonidegib (Odomzo)

**Parameter** | **Drug Information**
---|---
Manufacturer | Novartis
FDA Approval Date | July 24, 2015
FDA Approved Indication | Locally advanced basal cell carcinoma that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation
Mechanism of Action | Hedgehog pathway inhibitor; binds to and inhibits smoothened (SMO), a transmembrane protein involved in Hh signal transduction
Formulations | 200mg oral capsule
Dosing | 200 mg once daily given on an empty stomach at least 1 hour before or 2 hours after a meal

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### Sonidegib Efficacy

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Treatment Arms</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOLT Trial, R (2:1), MC, DB, multiple cohort study of (n=230) patients with locally advanced basal cell carcinoma (laBCC) (n=194) or metastatic basal cell carcinoma (mBCC) (n=36)</td>
<td>Sonidegib 800mg daily (n=128) vs Placebo</td>
<td>Primary endpoint: Objective response rate (ORR)</td>
</tr>
<tr>
<td>Sonidegib 200mg daily (n=66)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Results**
  - ORR was 58% for those who received sonidegib 200mg (n=66)
  - 3 patients (5%) achieved a complete response
  - 35 patients (53%) achieved a partial response
  - Duration of response ranged from 1.9 to 18.6 months
  - Tumor shrinkage lasted at least 6 months in ~ ½ of patients

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### Sonidegib Concerns

- **Warnings & Precautions**
  - Do not donate blood for at least 20 months s/p treatment
  - Musculoskeletal ADRs: check CK and creatinine levels at baseline and periodically
- **Adverse Reactions**
  - (>10%): muscle spasms, alopecia, dysgeusia, fatigue, N/V/D, musculoskeletal pain, ↓ weight, ↓ appetite, myalgia, abd pain, HA, pain, pruritus
- **Pregnancy & Lactation Concerns**
  - May cause fetal harm; do not breastfeed

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### Infectious Disease
**Infectious Disease**

- Ceftazidime-avibactam (Avycaz)
- Isavuconazonium sulfate (Cresemba)
- Daclatasvir (Daklinza)
- Paritaprevir/Ritonavir/Ombitasvir (Technivie)

**QIDP Antibiotics**

- Qualified infectious disease product (QIDP)
- Generating Antibiotic Incentives Now (GAIN)
  - An act signed into law in July 2012 that encourages development of new antibiotics for neglected diseases
  - The designation provides an expedited review process and an additional 5 years of marketing exclusivity for antibacterial and antifungal drugs intended to treat serious or life-threatening infections
- Infectious Diseases Society of America’s challenge
  - To industry and policymakers
  - To develop and approve 10 new antibiotics by 2020

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### FDA Approved Qualified Infectious Disease Products

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Manufacturer</th>
<th>Class</th>
<th>Route</th>
<th>FDA Approval</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>dalbavancin</td>
<td>Dalvance</td>
<td>Durata</td>
<td>glycopeptide</td>
<td>IV</td>
<td>May 2014</td>
<td>ABSSSI</td>
</tr>
<tr>
<td>tedizolid phosphate</td>
<td>Sivextro</td>
<td>Cubist</td>
<td>oxazolidinone</td>
<td>IV, Oral</td>
<td>June 2014</td>
<td>ABSSSI</td>
</tr>
<tr>
<td>oritavancin</td>
<td>Zefose</td>
<td>Cubist</td>
<td>glycopeptide</td>
<td>IV</td>
<td>August 2014</td>
<td>ABSSSI</td>
</tr>
<tr>
<td>ceftolozane-tazobactam</td>
<td>Zerbaxa</td>
<td>Cubist</td>
<td>5th generation cephalosporin</td>
<td>IV</td>
<td>December 2014</td>
<td>cIaI, cUTI</td>
</tr>
<tr>
<td>ceftazidime-avibactam</td>
<td>Avycaz</td>
<td>Forest</td>
<td>3rd generation cephalosporin</td>
<td>IV</td>
<td>February 2015</td>
<td>cIaI, cUTI</td>
</tr>
</tbody>
</table>

**Isavuconazonium sulfate (Cresemba)**

- **Parameter**
  - Drug Information

  **Manufacturer**
  - Astellas

  **FDA Approval Date**
  - March 2015

  **FDA Approved Indication**
  - Treatment of invasive aspergillosis and mucormycosis in adults

  **Mechanism of Action**
  - Prodrug inhibits synthesis of ergosterol which leads to a weakened cell membrane

**Formulations**
- **IV:** 372 mg
- **Oral capsules:** 372 mg

**Dosing**
- **Loading Dose:** 372 mg (=200 mg) every 8 hours for 6 doses (48 hours) via oral (2 capsules) or IV (1 reconstituted vial)
- **Maintenance Dose:** 372 mg (= 200 mg) daily via oral (2 capsules) or IV (1 reconstituted vial) starting 12-24 hours after the last loading dose

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**Isavuconazonium sulfate**

- Isavuconazonium sulfate is a water soluble prodrug of isavuconazole
- There is a potential for development of resistance to isavuconazole
- Each capsule contains 186 mg isavuconazonium sulfate which is equivalent to 100 mg of isavuconazole
- IV and oral loading doses are given Q8H x 6 doses
- Isavuconazonium is not currently FDA approved for the treatment of candidiasis
- Serious hepatic reactions have been reported with isavuconazonium sulfate
  - Liver function should be evaluated prior to initiation of and periodically during therapy

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**Daclatasvir (Daklinza)**

- **Parameter**
  - Drug Information

  **Manufacturer**
  - Bristol-Myers Squibb

  **FDA Approval Date**
  - July 24, 2015

  **FDA Approved Indication**
  - Hepatitis C virus (HCV) NS5A inhibitor indicated for use with sofosbuvir for the treatment of chronic HCV genotype 3 infection

**MOA**
- Binds to the N-terminus within Domain 1 of HCV nonstructural protein 5A (NS5A) and inhibits viral RNA replication and virion assembly

**Formulations**
- **30mg and 60mg oral tablets**
- **60mg once daily with or without food in combination with sofosbuvir x 12 weeks**
- **Reduce dosage to 30mg once daily with strong CYP3A inhibitors and increase dosage to 60mg once daily with moderate CYP3A inducers**

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**Cresemba (isavuconazonium sulfate) Product labeling.** Astellas Pharmaceuticals Inc. March 2015.

**Direct Acting Hep C Agents**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Strengths &amp; Formulations</th>
<th>FDA Approval</th>
<th>Patent Expiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir</td>
<td>Victrelis (Merck)</td>
<td>200mg capsules</td>
<td>5/13/11</td>
<td>2022-2027</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>Incivek (Vertex)</td>
<td>375mg tablets</td>
<td>5/23/11</td>
<td>Voluntarily Withdrawn</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Olysio (Janssen)</td>
<td>150mg</td>
<td>11/22/2013</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Sovaldi (Gilead)</td>
<td>400mg</td>
<td>12/8/2013</td>
<td></td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>Harvoni (Gilead)</td>
<td>90mg/400mg</td>
<td>12/19/2014</td>
<td></td>
</tr>
<tr>
<td>Paritaprevir/Ritonavir/Ombitasvir &amp; Dasabuvir</td>
<td>Viekira Pak (Abbott/Entanta)</td>
<td>75mg/50mg/12.5mg &amp; 250mg</td>
<td>12/19/2014</td>
<td></td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Daklinza (BMS)</td>
<td>30mg, 60mg oral tablets</td>
<td>7/24/2015</td>
<td></td>
</tr>
<tr>
<td>Paritaprevir/Ritonavir/Ombitasvir</td>
<td>Technivie (Abbvie)</td>
<td>75mg/50mg/12.5mg oral tablet</td>
<td>7/24/2015</td>
<td></td>
</tr>
</tbody>
</table>

**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

**Daclatasvir**

- Pharmacokinetics: Steady state anticipated after ~4 days
- Contraindications: strong CYP3A inducers (CBZ, phenytoin, rifampin, and St Johns Wort)
- Warnings & Precautions
  - Bradycardia, drug interactions, not for monotherapy
- Adverse Reactions
  - Serious symptomatic bradycardia may occur in patients taking amiodarone with sofosbuvir in combination with another HCV direct-acting agent
  - Most common ADRs with sofosbuvir: HA and fatigue
- Drug Interactions: avoid concomitant use with: amiodarone, bosutinib, conivaptan, strong 3A4 inducers, fusidic acid, idelalisib, pazopanib, silodosin, SJW, topotecan, vincristine
- Pregnancy risk: Adverse events were not observed in animal reproduction studies
- Monitoring Parameters: liver enzymes and serum creatinine at baseline — and periodically; additional monitoring if used in combo with amiodarone

**Paritaprevir/Ritonavir/Ombitasvir (Technivie)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Abbvie</td>
</tr>
<tr>
<td>FDA Approved Date</td>
<td>July 24, 2015</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Ombitasvir: inhibits HCV NS5A and inhibits viral RNA replication and assembly</td>
</tr>
<tr>
<td></td>
<td>Paritaprevir: inhibits HCV NS3/4A protease and interferes with HCV-coded polypeptide cleavage necessary for viral replication</td>
</tr>
<tr>
<td></td>
<td>Ritonavir: potent CYP3A inhibitor that increases peak and trough plasma drug concentrations of paritaprevir and overall drug exposure (AUC)</td>
</tr>
<tr>
<td>Formulations</td>
<td>75mg/50mg/12.5mg oral tablet</td>
</tr>
<tr>
<td>Dosing</td>
<td>75mg/50mg/12.5mg tablet every morning with a meal in combination with ribavirin x 12 weeks</td>
</tr>
</tbody>
</table>

**Daclatasvir Efficacy**

- Efficacy
  - Phase 3, open-label ALLY-3 clinical trial
  - N=152 treatment-naïve and treatment-experienced patients received daclatasvir + sofosbuvir for 12 weeks
  - Patients had chronic HCV genotype 3 infection and compensated liver disease
  - Primary endpoint = SVR (sustained virologic response)
- Results
  - Treatment naive
    - SVR achieved in 98% with no cirrhosis and 58% with cirrhosis
  - Treatment experienced
    - SVR achieved in 92% with no cirrhosis and 69% with cirrhosis

**Paritaprevir/Ritonavir/Ombitasvir Efficacy**

- Efficacy
  - R (1:1), MC, OL, Phase 3, PEARL-I study
  - Patients had chronic HCV genotype 4 infection without cirrhosis in combination with ribavirin
  - n=135 treatment-naïve patients without cirrhosis received paritaprevir/ritonavir/ombitasvir + ribavirin for 12 weeks
  - Previous exposure to direct acting agents was prohibited
  - Primary endpoint = SVR (sustained virologic response)
- Results
  - SVR achieved in 100% of treatment naïve patients taking paritaprevir/ritonavir/ombitasvir + ribavirin compared with 91% of those who received the combo drug without ribavirin
AASLD/IDSA HCV Guidelines

Treatment Naïve

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>Treatment History</th>
<th>Cirrhosis Status</th>
<th>Treatment Regimen</th>
<th>Duration (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Naïve</td>
<td>Non-cirrhotic</td>
<td>SOF + RBV</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cirrhotic</td>
<td>SOF + RBV</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>Naïve</td>
<td>Non-cirrhotic &amp; Naïve</td>
<td>SOF + DAC</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Experienced</td>
<td>Cirrhotic</td>
<td>SOF + RBV</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>Naïve</td>
<td>Non-cirrhotic</td>
<td>Harvoni</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cirrhotic</td>
<td>Harvoni</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>Naïve</td>
<td>Non-cirrhotic</td>
<td>Viekira</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cirrhotic</td>
<td>Viekira</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>Naïve</td>
<td>Non-cirrhotic</td>
<td>TECH + RBV</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>Naïve</td>
<td>Non-cirrhotic</td>
<td>SOF + RBV</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>Naïve</td>
<td>SOF + RBV + IFN</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Naïve</td>
<td>Harvoni</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Cardiology

Edoxaban (Savaysa)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Daiichi Sankyo</td>
</tr>
<tr>
<td>FDA Approval Date</td>
<td>January 2015</td>
</tr>
<tr>
<td>FDA Approved Indication</td>
<td>Treatment of non-valvular atrial fibrillation (NVAF), DVT, and PE</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Selective factor Xa inhibitor that inhibits free factor Xa and prothrombinase activity and inhibits thrombin-induced platelet aggregation. Inhibitor of factor Xa in the coagulation cascade reduces thrombin generation and thrombus formation</td>
</tr>
<tr>
<td>Formulations</td>
<td>15 mg, 30 mg, 60 mg oral tablets</td>
</tr>
<tr>
<td>Dosing</td>
<td>DVT and PE: 60 mg once daily after 5-10 days of initial therapy with a parenteral anticoagulant; NVAF: 60 mg once daily; Weight ≤ 60kg: 30 mg once daily; Patients with drug interactions: 30 mg once daily</td>
</tr>
</tbody>
</table>

Anticoagulants and FDA Approved Indications

<table>
<thead>
<tr>
<th>Indication</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Enoxaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke prevention assoc with AFib</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Stroke prevention assoc with cardiac valve replacement</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE prophylaxis hip and knee</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>VTE treatment (DVT/PE)</td>
<td>X</td>
<td>X*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dec risk of recurrent PE/CVT</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dec death/recurrent MI/stroke or SE after MI</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Atrial Fibrillation Efficacy
- n = 21,105 patients with NVAF in the ENGAGE-AF TIMI 58 trial
- 60mg dose of edoxaban was similar to warfarin for the reduction in the risk of stroke, with significantly lower risk of major bleeding

DVT and PE Efficacy
- N = 8,292 patients with DVT and PE in the Hokusai VTE study
- Edoxaban was superior to warfarin in reducing the rate of symptomatic VTE

Edoxaban Efficacy

Edoxaban Issues
- Prior to initiation, assess renal function
- BBW: Do NOT use in patients with NVAF if CrCL is >95 mL/minute
- Contraindications: active bleeding
- Not recommended in patients with mechanical heart valves or with moderate to severe mitral stenosis
- Not recommended in moderate or severe hepatic impairment
- Adverse effects: most common ADRs (≥1%) seen in patients with DVT or PE include bleeding, rash, anemia, and abnormal LFTs
- No head to head studies with edoxaban and other novel oral anticoagulants
**Ivabradine (Corlanor)**

**Parameter** | **Drug Information**
---|---
Manufacturer | Amgen
FDA Approval Date | April 2015
FDA Approved Indication | • First-in-class agent: indicated for use in patients with chronic symptomatic heart failure with a left ventricular ejection fraction (LVEF) ≤ 35%, in sinus rhythm with a resting heart rate ≥ 70 bpm, and are maximized on beta blocker therapy or have a contraindication to beta-blocker use
Mechanism of Action | • If/If channel inhibitor: selective and specific inhibition of the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (I-If) within the sinoatrial (SA) node of cardiac tissue resulting in disruption of If ion current flow prolonging diastolic depolarization which slows firing in the SA node leading to reduction in heart rate

**Ivabradine Efficacy**

**Study Design**

<table>
<thead>
<tr>
<th>Treatment Arms</th>
<th>Primary Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivabradine vs Placebo</td>
<td>Composite of the 1st occurrence of either hospitalization for worsening heart failure or CV death</td>
</tr>
</tbody>
</table>

**Baseline characteristics**

- LVEF of <35%
- Initial heart rate of ≥70 bpm
- Admitted to the hospital for tx of HF within the previous year
- Clinically stable on maximally tolerated doses of beta-blockers, ACEIs or ARBs, spironolactone, and diuretics

**Results**

- 2% reduction over 2 years in all-cause hospitalization for worsening heart failure with ivabradine compared to placebo

**Sacubitril/Valsartan (Entresto)**

**Parameter** | **Drug Information**
---|---
Manufacturer | Novartis
FDA Approval Date | July 2015
FDA Approved Indication | • Reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure and reduced ejection fraction
Mechanism of Action | • Sacubitril: Prodrug that inhibits neprilysin (neutral endopeptidase [NEP]) through the active metabolite LBQ657, leading to ↑ levels of peptides, including natriuretic peptides • Valsartan: Angiotensin 2 receptor blocker (ARB)
Formulations | • Sacubitril 24mg/valsartan 26mg, sacubitril 49mg/valsartan 51mg, sacubitril 97mg/valsartan 103mg oral tablets
Dosing | • Starting dose: 49mg sacubitril & 51mg valsartan BID • After 2 to 4 weeks, double the dose to 97/103 mg sacubitril/valsartan BID

**Clinical trial results**

- Combination ↓ CV death and HF hospitalizations by 20% vs enalapril alone
- Greater ↑ in NT-proBNP levels with the combo compared to valsartan alone

**Study Design**

<table>
<thead>
<tr>
<th>Treatment Arms</th>
<th>Primary Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivabradine vs Placebo</td>
<td>Composite of the 1st occurrence of either hospitalization for worsening heart failure or CV death</td>
</tr>
</tbody>
</table>

**Baseline characteristics**

- LVEF of ≤ 35%
- Symptomatic HF with a resting HR <60 bpm prior to treatment
- Severe hepatic impairment
- Dependence on a pacemaker
- No significant effects on CV death or hospitalization due to either HF or AMI

**Results**

- 20% reduction in NT-proBNP levels with the combo compared to valsartan alone
**Sacubitril/Valsartan**

- **Pharmacokinetics**
  - Has an active metabolite LBQ657
  - Sacubitril is excreted primarily through urine; valsartan through feces
- **Contraindications**
  - May cause fetal toxicity; discontinue as soon as possible when pregnancy is detected
  - Concomitant use of an ACE inhibitor is contraindicated; allow a 36 hour washout period when switching from or to an ACE inhibitor
- **Warnings & Precautions:** same as other ARBs
- **Adverse Reactions:**
  - Most common ADRs: hypotension, hyperkalemia, cough, dizziness, and renal failure
  - Do not use in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy

**Alirocumab (Praluent)**

- **Pharmacokinetics**
  - Metabolism studies not conducted, because alirocumab is a protein
  - Expected to degrade to small peptides and individual amino acids
- **Contraindications:**
  - History of a serious hypersensitivity
- **Warnings & Precautions:**
  - Allergic reactions
- **Adverse Reactions**
  - Most common ADRs occurring in ≥5% of patients include nasopharyngitis, injection site reactions, and influenza
- **Drug Interactions:**
  - No clinically meaningful drug interactions
- **Pregnancy risk:**
  - No adverse effects in animal studies
- **Monitoring Parameters**
  - Measure LDL-C levels within 4 to 8 weeks of initiating or titrating therapy to assess response and adjust the dose PRN

**PCSK9 Inhibitors**

- **Mechanism of Action**
  - PCSK9
    - Protein that regulates LDL-C by regulating LDL receptor metabolism
    - Mutations causing PCSK9 loss of function result in LDL reductions
    - Degrades LDL receptors
    - Leading to ↑ LDL plasma concentrations
  - LDL receptors (LDL-R)
    - LDL receptors found on surface of hepatocytes
    - LDL circulating in the blood bind to LDL receptors
    - LDL taken up inside of cells
  - PCSK9 inhibitors
    - ↑ LDL receptors
    - ↓ plasma LDL ~65-70% even as add-on therapy to max dose of statin

**PCSK9 Inhibitors Current and Future**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand</th>
<th>Mfg</th>
<th>Anticipated Approval</th>
<th>Dosing Frequency</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Praluent</td>
<td>Sanofi/Regeneron</td>
<td>July 23, 2015</td>
<td>Human monoclonal AB</td>
<td>Q 2 weeks</td>
<td>SubQ</td>
</tr>
<tr>
<td>Repatha</td>
<td>Amgen</td>
<td>Aug 27, 2015</td>
<td>Human monoclonal AB</td>
<td>Q 2 or 4 weeks</td>
<td>SubQ</td>
</tr>
<tr>
<td>Pfizer</td>
<td>2016</td>
<td>Q 2 weeks</td>
<td>SubQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novartis</td>
<td>2018</td>
<td>Q 4 or 8 weeks</td>
<td>SubQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMS</td>
<td>7</td>
<td>100/35/100%</td>
<td>Q 2 or 4 weeks</td>
<td>SubQ</td>
<td></td>
</tr>
<tr>
<td>Amrylam</td>
<td>7</td>
<td>?</td>
<td>40ng/ml</td>
<td>SubQ</td>
<td></td>
</tr>
</tbody>
</table>

**PCSK9 Inhibitors Efficacy**

- **5 DB,PC trials with 3499 patients**
  - 36% HeFH, 54% ASCVD
  - All receiving maximally tolerated dose of statin (+ other lipid tx)

<table>
<thead>
<tr>
<th>Study</th>
<th>Tx vs PRD (n)</th>
<th>% HeFH &amp; ASCVD</th>
<th>LDL Baseline</th>
<th>Week 12 LDL Reduction</th>
<th>Week 24</th>
<th>Week 52</th>
<th>% requiring 150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>510 vs 378</td>
<td>36%/54%</td>
<td>122</td>
<td>68%</td>
<td>56%</td>
<td>52%</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>296 vs 17</td>
<td>100%</td>
<td>112</td>
<td>45%</td>
<td>44%</td>
<td>41%</td>
<td>17%</td>
</tr>
<tr>
<td>3-4</td>
<td>590 vs 245</td>
<td>100%/45%</td>
<td>141</td>
<td>43%</td>
<td>47%</td>
<td>46%</td>
<td>42%</td>
</tr>
<tr>
<td>5</td>
<td>77 vs 55</td>
<td>100%/50%</td>
<td>158</td>
<td>43%</td>
<td>43%</td>
<td>43%</td>
<td>100%</td>
</tr>
</tbody>
</table>

- **Safety**
  - Placebo controlled trials including 2,476 patients
  - 2,135 for 6 months, 1,999 for more than 1 year
  - Mean age: 59; 40% female, 90% Caucasians
  - 37% with HeFH, 66% with ASCVD
  - No data on pregnant women, pediatrics
### Evolocumab Efficacy

#### Study Design
- **Odyssey Long Term trial, R (2:1), PC, MC, MN (n=2,341)**

#### Treatment Arms
- **Evolocumab 150 mg (n=1,553) vs Placebo (n=778)**

#### Primary endpoint
- LDL change from baseline to 24 weeks

#### Baseline Characteristics
- **Age 60; White 52%; Male 63%**
- **High dose statin 46%; atorva 40-80 mg, rosuva 20-40 mg, simv: 80 mg**
- **HeFH 17%; CHD 68%; LDL 122**

#### Study Results
- Mean LDL change at week 24: 61% with evolocumab vs 0.8% placebo
- at week 24: LDL 48 mg/dL vs 119mg placebo
- at week 78: 52% decrease from baseline to 24 weeks
- at week 24: LDL 48 mg/dL vs 119mg placebo
- LSMD % for LDL change:
  - Diet Alone: 56%
  - Diet + 10mg Ezetimibe: 52%
  - Diet + 80mg Atorvastatin: 52%
  - Diet + 80mg Atorvastatin + 10mg Ezetimibe: 55%

### Evolocumab (Repatha)

#### Parameter
- **LDL change from baseline to 24 weeks**

#### Drug Information
- **Evolocumab 420mg SC Q 4 weeks x 48 weeks vs Placebo SC Q 4 weeks x 48 weeks**

#### Primary endpoint
- LDL % change from baseline to 52 wks

#### Baseline characteristics:
- **18-75 years old**
- **LDL ≥75mg/dL**
- **High dose statin 46%; atorva 40-80 mg, rosuva 20-40 mg, simv: 80 mg**
- **HeFH 17%; CHD 68%; LDL 122**

#### Study Results
- Mean LDL change at week 24: 61% with evolocumab vs 0.8% placebo
- at week 24: LDL 48 mg/dL vs 119mg placebo
- at week 78: 52% decrease from baseline to 24 weeks
- at week 24: LDL 48 mg/dL vs 119mg placebo
- LSMD % for LDL change:
  - Diet Alone: 56%
  - Diet + 10mg Ezetimibe: 52%
  - Diet + 80mg Atorvastatin: 52%
  - Diet + 80mg Atorvastatin + 10mg Ezetimibe: 55%

### PCSK9 Costs

#### Drug
- **Alirocumab 150mg**
- **Evolocumab 420mg**

#### Dosage
- **140mg monthly**
- **150mg every 2 weeks OR 420mg once monthly**
- **420mg monthly (given as 3 injections within 30 min)**

#### Cost Breakdown
- **$499.47**
- **$542.00**
- **$1,084.00**
- **$1,626.00**
- **$1,626.00**

#### Availability
- Both drugs available in prefilled syringes or prefilled pens at same cost
- Alirocumab available in packages of 1 or 2 pens/syringes
- Evolocumab available in 1 pack prefilled syringe or 1, 2, 3 packs of prefilled pens
### Ongoing PCSK9 Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Outcomes</th>
<th>Target Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODYSSEY OUTCOMES</td>
<td>Alirocumab</td>
<td>Time from randomization to 1st occurrence of one of the following clinical events: CHD death, any non-fatal MI, fatal and non-fatal ischemic stroke, USA requiring hospitalization</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>GLAGOV</td>
<td>Evolocumab</td>
<td>Nominal change in % atheroma volume (PAV) from baseline to week 78 post randomization, as determined by intravascular ultrasound (IVUS)</td>
<td>July 2016</td>
</tr>
<tr>
<td>FOURIER</td>
<td>Evolocumab</td>
<td>Time to CV death, MI, hospitalization for USA, stroke, or coronary revascularization</td>
<td>Oct 2017</td>
</tr>
</tbody>
</table>

https://clinicaltrials.gov/show/NCT01663402
https://clinicaltrials.gov/show/NCT01813422
https://clinicaltrials.gov/show/NCT01764633

### PCSK9 Inhibitors
#### Place in Therapy
- Statin intolerance
- Heterozygous FH
- Patients with high Lp(a)?
  - PCSK9 monoclonal antibodies significantly lower TC, LDL, Apo-B, and Lp(a)
- Immediately post-bypass surgery?
- Patients with severe renal insufficiency?

### Eluxadoline (Viberzi)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Forest/Actavis</td>
</tr>
<tr>
<td>FDA Approval Date</td>
<td>May 2015</td>
</tr>
<tr>
<td>FDA Approved Indication</td>
<td>Treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Mixed mu-opioid receptor agonist, delta opioid receptor antagonist, and kappa opioid receptor agonist which acts locally to reduce abdominal pain and diarrhea in patients with IBS-D without constipating side effects</td>
</tr>
<tr>
<td>Formulations</td>
<td>75mg, 100mg oral tablets</td>
</tr>
<tr>
<td>Dosing</td>
<td>100 mg BID with food</td>
</tr>
<tr>
<td>Patients with no gallbladder, are unable to tolerate the 100 mg dose, are receiving concomitant OATP 1B1 inhibitors, or have mild or moderate hepatic impairment: Dose of 75 mg BID</td>
<td></td>
</tr>
<tr>
<td>Schedule</td>
<td>Potential for abuse; pending controlled schedule by DEA</td>
</tr>
</tbody>
</table>

### Eluxadoline
#### Gastrointestinal

#### Contraindications
- Known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction
- History of pancreatitis or structural diseases of the pancreas, including known or suspected pancreatic duct obstruction
- Alcoholism, alcohol abuse, or alcohol addiction, or in patients who drink more than 3 alcoholic beverages per day
- Severe hepatic impairment (Child-Pugh class C)
- History of chronic or severe constipation or sequelae from constipation, or known or suspected mechanical GI obstruction

#### Warnings & Precautions
- May cause pancreatitis, may lead to Sphincter of Oddi spasm

#### Adverse Reactions
- Most common ADRs: constipation, nausea, abdominal pain

#### Pharmacokinetics
- Peak concentration in 1.5 - 2 h; linear PK with no accumulation upon repeated dosing; avg T ½ ranges from 3.7 - 6 hours; excreted primarily through feces

#### Pregnancy concerns
- ADRs were not observed in animal studies

#### Monitoring Parameters
- Monitor patients without a gallbladder for new or worsening abdominal pain, with or without N/V, or acute biliary pain with liver or pancreatic enzyme elevations
Eluxadoline Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Risk</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (Ethyl)</td>
<td>X</td>
<td>The adverse/toxic effect of eluxadoline may be enhanced. Specifically, alcohol use may increase the risk of pancreatitis.</td>
</tr>
<tr>
<td>Allergies (Opson)</td>
<td>X</td>
<td>May enhance the constipating effect of eluxadoline.</td>
</tr>
<tr>
<td>Antidepressive Agents</td>
<td>X</td>
<td>May enhance the constipating effect of eluxadoline.</td>
</tr>
<tr>
<td>Antihistamines, Trazodone</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine (Systemic)</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>D</td>
<td>May increase eluxadoline concentrations. Decrease the eluxadoline dose and monitor for toxicities.</td>
</tr>
<tr>
<td>Saquinavir, Atazanavir, Ritonavir</td>
<td>D</td>
<td>May increase eluxadoline concentrations. Decrease the eluxadoline dose and monitor for toxicities.</td>
</tr>
<tr>
<td>Eluxadoline may increase the serum concentration of rosuvastatin. Use the lowest effective dose of rosuvastatin.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk C: Monitor Therapy; Risk D: Consider therapy modification; Risk X: Avoid combination.

Eluxadoline Efficacy

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Treatment Arms</th>
<th>Primary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies 3001 &amp; 3002</td>
<td>Eluxadoline 75mg vs Placebo</td>
<td>↓ of ≥30% in WAP score AND ↓ in BSS score to &lt;5 on at least 50% of the days in week 1 - 12 week time interval</td>
</tr>
<tr>
<td>Two – 26 week, DB, PC trials (N=2,425)</td>
<td>Eluxadoline 100mg vs Placebo</td>
<td></td>
</tr>
</tbody>
</table>

Eluxadoline Efficacy

- 3001 & 3002 Trials (n=2425)

<table>
<thead>
<tr>
<th>75mg vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Endpoint @ 12 weeks</td>
</tr>
<tr>
<td>Composite Endpoint @ 26 weeks</td>
</tr>
<tr>
<td>Significant improvement in HrQoL and in the proportion of urgency-free days</td>
</tr>
</tbody>
</table>

Eluxadoline Study Limitations

- Definition of "adequate relief" not available
- Women in study limited to age >52 and postmenopausal
- FDA required 12 week data analysis
- EMA required 26 week data analysis
- No significant difference in abdominal pain relief at 12 weeks
- Significant placebo response


Lumacaftor/Ivacaftor (Orkambi)

- Parameter | Drug Information |
- Manufacturer | Vertex Pharmaceuticals |
- FDA Approval Date | July 2, 2015 |

Eluxadoline Efficacy

- 3001 & 3002 Trials (n=2425)

<table>
<thead>
<tr>
<th>75mg vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Endpoint @ 12 weeks</td>
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<tr>
<td>Composite Endpoint @ 26 weeks</td>
</tr>
<tr>
<td>Significant improvement in HrQoL and in the proportion of urgency-free days</td>
</tr>
</tbody>
</table>

Pulmonology
Lumacaftor/Ivacaftor

- Lumacaftor: CFTR corrector – helps CFTR proteins reach the cell surface
- Ivacaftor: CFTR potentiator – helps keep the CFTR protein channels on the cell surface open longer to increase the flow of NaCl into and out of the cell
- Only indicated in pts who can be genetically identified as having the F508del mutation
- Clinical trials
  - Two R, DB, PC trials (TRAFFIC & TRANSPORT trials) of 1,108 patients with CF
  - Primary end point = change in (FEV1) from baseline at week 24
  - Lumacaftor/ivacaftor improved FEV1 & pooled analyses showed the rate of pulmonary exacerbations was 30 to 39% lower in the lumacaftor/ivacaftor group

Neurology/Psychiatry

Brexpiprazole (Rexulti)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Otsuka</td>
</tr>
<tr>
<td>FDA Approval Date</td>
<td>July 10, 2015</td>
</tr>
<tr>
<td>FDA Approved Indication</td>
<td>Adjunctive treatment of major depressive disorder (MDD) and treatment of schizophrenia</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Mechanism unknown but efficacy may be mediated through a combination of partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors, and antagonist activity at serotonin 5-HT2A receptors</td>
</tr>
<tr>
<td>Formulations</td>
<td>0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg oral tablets</td>
</tr>
<tr>
<td>Dosing</td>
<td>MDD: Starting dose: 0.5mg – 1mg once daily; Recommended dose: 2mg/day; Max dose: 4mg/day; Schizophrenia: Starting dose: 1mg once daily on days 1 – 4; Recommended dose: 2mg – 4mg/day; Max dose: 4mg/day</td>
</tr>
</tbody>
</table>

Brexpiprazole MDD Efficacy

- **Drug Interactions:** numerous
- **Pregnancy Concerns:** ADEs were observed in some animal reproduction studies
- **Monitoring Parameters:** mental status, vitals, CBC, Chem-7, LFTs, lipids, glucose, and more

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Treatment Arms</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two 6-wk, DB, PC, fixed-dose trials of adult patients meeting DSM-IV-TR criteria for MDD, with or without symptoms of anxiety</td>
<td>Primary endpoint Depression: A 2 point difference from baseline to week 6 in Montgomery-Asberg Depression Rating Scale (MADRS) (0-60)</td>
<td></td>
</tr>
<tr>
<td>Baseline characteristics: Pts had prior antidepressant therapy (1 to 3 courses)</td>
<td>All patients maintained antidepressant therapy (ADT)</td>
<td></td>
</tr>
</tbody>
</table>

**Brexpiprazole MDD Efficacy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Group</th>
<th>N</th>
<th>Primary Efficacy Measure: MADRS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean Baseline Score (SD)</td>
</tr>
<tr>
<td>1</td>
<td>Brexpiprazole 2 mg + ADT</td>
<td>175</td>
<td>26.9 (5.7)</td>
</tr>
<tr>
<td></td>
<td>Placebo + ADT</td>
<td>178</td>
<td>27.3 (5.6)</td>
</tr>
<tr>
<td>2</td>
<td>Brexpiprazole 3 mg + ADT</td>
<td>211</td>
<td>26.5 (5.4)</td>
</tr>
<tr>
<td></td>
<td>Placebo + ADT</td>
<td>215</td>
<td>26.5 (5.3)</td>
</tr>
</tbody>
</table>

- **Results**
  - Brexpiprazole 2 mg & 3 mg daily + ADT were superior to placebo + ADT in reducing mean MADRS scores
  - Significant placebo response

**Brexpiprazole Schizophrenia Efficacy**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Value</th>
<th>Difference from Placebo</th>
<th>Statistical Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANSS Score</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Results**

- Study 3: Brexpiprazole 2 mg and 4 mg daily was superior to placebo in reducing PANSS total scores
- Study 4: Brexpiprazole 4 mg daily was superior to placebo in reducing PANSS total scores

**Flibanserin (Addyi)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Drug Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Sprout Pharmaceuticals, Inc</td>
</tr>
<tr>
<td>FDA Approval Date</td>
<td>August 18, 2015</td>
</tr>
</tbody>
</table>

**Mechanism of Action**

- Unknown in vitro, Flibanserin demonstrated agonist activity at 5-HT1/agonist and antagonist activity at 5-HT2A
- Flibanserin also has moderate antagonist activities at the 5-HT1B, 5-HT2C, and dopamine D4 receptors
- Mixed 5-HT1A agonist/5-HT2A antagonist

**Dosing**

- 100mg (oral tablet) once daily at bedtime
- Not recommended to take during waking hours due to risks of hypotension, syncope, accidental injury and CNS depression
- If dose is missed, do not take next dose until bedtime, do not double the dose

**Flibanserin**

- HSDD: characterized by low sexual desire that causes marked distress or interpersonal difficulty and is NOT due to:
  - A co-existing medical or psychiatric condition
  - Problems within the relationship
  - The effects of a medication or other drug substance

- Limitations of Use
  - Not for treatment of HSDD in POSTmenopausal women or in men
  - Not for sexual performance enhancement
Flibanserin

- **Mechanism of Action**
  - Corrects an imbalance of the levels of the neurotransmitters that affect sexual desire
  - **Flibanserin** $\uparrow$ dopamine and norepinephrine, both responsible for sexual excitement, and $\downarrow$ serotonin, responsible for sexual inhibition

- **Pregnancy & Lactation**
  - No human studies; animal studies showed adverse reproductive and developmental effects

- **Renal insufficiency**: no dosage adjustment

- **Hepatic insufficiency**
  - Contraindicated for use with any degree of impairment

- **Monitoring Parameters**
  - Increase monitoring for ADRs in poor metabolizers of CYP2C19

- **Contraindications**
  - Concomitant use of alcohol or moderate or strong CYP3A4 inhibitor
  - Hepatic impairment

- **Common ADRs**
  - Dizziness, somnolence, nausea, fatigue, insomnia, and dry mouth

- **Drug Interactions**
  - Alcohol: $\uparrow$ the risk of severe hypotension and syncope
  - Moderate or strong CYP3A4 inhibitors: $\uparrow$ flibanserin concentrations, which can cause severe hypotension and syncope

- **REMS**: due to $\uparrow$ risk of severe hypotension and syncope when used with alcohol

Miscellaneous New Drugs

- **Deoxycholic acid (Kybella)**
  - **Indication**: Excess subcutaneous fat of submental region
  - A cytolytic drug, injected repeatedly SubQ, that physically destroys the cell membrane causing lysis

- **Cholic acid (Cholbam)**
  - **Indication**: Bile acid synthesis disorders
  - Oral capsule enhances bile flow and provides the physiologic feedback inhibition of bile acid synthesis to maintain bile acid homeostasis

- **Cangrelor (Kengreal)**
  - **Indication**: Adjunct to percutaneous coronary intervention (PCI) for reducing the risk of periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis (ST)
  - IV direct P2Y$_{12}$ platelet receptor inhibitor that blocks adenosine diphosphate (ADP)-induced platelet activation and aggregation;

Key Points

- **For further details regarding formulary decisions, see individual agency websites**
  - www.health.mil/formulary
  - http://www.pbm.va.gov/
  - https://online.epocrates.com/ TRICARE formulary

- **For more information on specific drugs, see the Drugs at FDA website and individual manufacturer websites**

Answers To Self-Assessment Questions

1. What is the mechanism of action of flibanserin?
   - a) PDE-5 inhibitor like sildenafil
   - b) Serotonergic activity
   - c) Hedgehog pathway inhibitor
   - d) Histone deacetylase (HDAC) inhibitor

2. Which of the following is a concern with regard to the PCSK9 inhibitors?
   - a) Effects of very low cholesterol
   - b) Effect on cardiovascular mortality
   - c) Cost
   - d) All of the above
### Self-Assessment Question 3

3. Which drug : indication pairing is correct?

   a) **Edoxaban**: prevention of VTE after hip and knee surgery
   
   b) **Secukinumab**: treatment of Crohn’s disease
   
   c) **Daclatasvir**: treatment of chronic hepatitis C virus (HCV) genotype 4
   
   d) **Ivabradine**: chronic heart failure

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### New Drugs of 2015

Amy M. Lugo, PharmD, BCPS, BC-ADM, FAPhA  
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Pharmacy Operations Division  
Formulary Management Branch  
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