New Drugs Update: FDA Approvals for 2014-15

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Disclosure

☐ I will discuss off label use or investigational use in my presentation.

☐ I have no financial relationships to disclose.

Goals & Objectives

GOAL:
☐ To review selected new molecular entities approved by the Food & Drug Administration in 2014-15

OBJECTIVES:
☐ List the name, mechanism of action, pharmacological properties, route of administration, dosing schedule, and dosage forms for the new drugs reviewed

☐ Discuss cautions, side effects, potential drug interactions, and primary points of patient education for these medications

☐ Review the disease states where these medications are being used

☐ Compare and contrast their role in practice with existing medications prescribed for similar indications
New Application Approvals

<table>
<thead>
<tr>
<th>Number</th>
<th>Meaning</th>
<th>Letter</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>New molecular entity</td>
<td>P</td>
<td>Priority review drug</td>
</tr>
<tr>
<td>2</td>
<td>New active ingredient</td>
<td>S</td>
<td>Standard review drug</td>
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<tr>
<td>3</td>
<td>New dosage form</td>
<td>O</td>
<td>Orphan drug</td>
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<tr>
<td>4</td>
<td>New combination</td>
<td></td>
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<tr>
<td>5</td>
<td>New formulation or new manufacturer</td>
<td></td>
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<tr>
<td>6</td>
<td>New indication</td>
<td></td>
<td></td>
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<tr>
<td>7</td>
<td>Drug already marketed without an approved NDA</td>
<td></td>
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</tr>
<tr>
<td>8</td>
<td>OTC switch</td>
<td></td>
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<tr>
<td>10</td>
<td>New indication submitted as distinct NDA</td>
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</table>


2014 Statistics

- 41 NMEs (41 applications filed)
  - 41% first-in-class (Belsomra, Harvoni, Zydelig)
  - 41% orphan drugs (Cyramza, Keytruda, Sylvant)
- Fast track (N=17): Dalvance, Entyvio, Harvoni
- Breakthrough (N=9): Harvoni, Ofev, Opdivo
- Priority Review (N=25): Dalvance, Harvoni, Orbuscle
- Accelerated Approval (N=8): Blincyto, Keytruda, Opdivo
**FDA Drug Safety Communications**

- 9/10/15: canagliflozin and bone fracture risk and decreased bone mineral density
- 8/28/15: DPP-4 inhibitors and severe joint pain
- 5/15/15: SGLT-2 inhibitors and ketoacidosis
- 3/30/15: ferumoxytol and allergic reactions


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**2014/15 Notable Approvals**

- Dapagliflozin (Farxiga®)
- Certolizumab (Inflectra®)
- Vedolizumab (Entyvio®)
- Rotavirus (RotaTeq®)
- Flix移送シoule (Stadine®)
- Omalizumab (Xolair®)
- Omalizumab (Xolair®)
- Imeroptin (Imeroptin®)
- Ledipasvir/sofosbuvir (Harvoni®)
- Peramivir (Rapivab®)
- Cefotolozane/tazobactam (Zerbaxa®) and ceftazidime/avibactam (Avycaz®)

**Topics for Today’s Presentation**

- Biosimilars update
- Summary of newer mAbs and NIBs
- Edoxaban (Savaysa®)
- Peramivir (Rapivab®)
- Cefotolozane/tazobactam (Zerbaxa®) and ceftazidime/avibactam (Avycaz®)
- Ivabradine (Corlanor®)
- Sacubitril/valsartan (Entresto®)
- Brexipiprazole (Zaveel®)
- Rolapitant (Varubi®)
Biosimilar Resources

- FDA webpage on biosimilars
  - Biologics Price Competition and Innovation Act of 2009
  - Draft guidance for industry
  - Nonproprietary naming of biological products (August 2015)
  - Labeling, statistical approaches to evaluation of analytics similarity data, and considerations in demonstrating interchangeability to a referenced product
  - FDA Purple Book
- ASHP Resource Centers, Emerging Sciences, Biosimilars


Biosimilars

- FDA-approved biosimilars?
  - Enoxaparin (7/23/2010)
  - TBO-filgrastim (Granix®) by Teva: 8/29/2012
  - Insulin glargine (Basaglar®) by Eli Lilly and Co.: 8/18/2014 (tentative approval)
  - Filgrastim-SNDZ (Zarxio®) by Sandoz: 3/6/2015
- On the horizon
  - Epoetin alpha/beta, darbepoetin, somatropin
  - mAbs (rituximab, infliximab)

Monoclonal Antibodies: Elements of a Name

- Prefix (1-2 syllables)
- Infix (target/disease)
  - tu/t = tumors
  - li/i = immunomodulator
  - c/c = cardiovascular
- Infix (source)
  - zu = humanized
  - o = mouse
  - u = fully human
  - xi = chimeric
- Suffix “-mab” or “-pab”

Newer mAbs of 2014-15

- Ramucirumab (Cyramza®)
  - Eli Lilly, 4/21/2014
  - Advanced gastric cancer, or gastro-esophageal junction adenocarcinoma

- Siltuximab (Syveno®)
  - Janssen Biotech, 4/23/2014
  - Multicentric Castleman’s Disease who are HIV negative and human herpesvirus-8 negative

- Vedolizumab (Entyvio®)
  - Takeda Pharmaceuticals, 5/20/2014
  - Moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor blocker or immunomodulator, or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids

- Pembrolizumab (Keytruda®)
  - Merck, 9/4/2014
  - Unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor

- Blinatumomab (Blincyto®)
  - Amgen, 12/3/2014
  - Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia

- Nivolumab (Opdivo®)
  - Bristol-Myers Squibb, 12/22/2014
  - Unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor

- Secukinumab (Cosentyx®)
  - Novartis Pharmaceuticals, 1/21/2015
  - Moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

- Dinutuximab (Unituxin®)
  - United Therapeutics Corp, 3/10/2015
  - Pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodal therapy

- Alirocumab (Praluent®)
  - Sanofi Aventis, 7/24/2015
  - Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL cholesterol

- Evolocumab (Repatha®)
  - Amgen, 8/27/2015
  - Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL cholesterol
  - Other LDL-lowering therapies in patients with homozygous familial hypercholesterolemia who require additional lowering of LDL cholesterol
Kinase Inhibitors

- Inhibition of enzymes responsible for the activation of signal transduction cascades

- No standardized nomenclature, typically end with –inhib or –anib or –enib

- Multiple kinase inhibitors
  - BRAF inhibitor
  - Janus-Associated kinase inhibitor
  - Multikinase inhibitor
  - Tyrosine kinase inhibitor

Newer NIBs of 2014-15

- Ceritinib (Zykadia®)
  - Novartis Pharmaceuticals, 4/29/2014
  - Anaplastic lymphoma kinase-positive metastatic non-small cell lung cancer who have progressed on or are intolerant to crizotinib

- Idelalisib (Zydelig®)
  - Gilead Sciences Inc, 7/23/2014
  - Relapsed follicular B-cell non-Hodgkin lymphoma in patients who have received at least two prior systemic therapies and relapsed small lymphocytic lymphoma in patients who have received at least two prior systemic therapies

- Nintedanib (Ofev®)
  - Boehringer Ingelheim, 10/15/2014
  - Idiopathic pulmonary fibrosis

Newer NIBs of 2014-15

- Palbociclib (Ibrance®)
  - Pfizer Inc, 2/3/2015
  - Postmenopausal women with estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease

- Lenvatinib (Lenvima®)
  - Eisai Inc, 2/13/15
  - Locally recurrent or metastatic, progressive, radiorefractory differentiated thyroid cancer

- Sonidegib (Odomzo®)
  - Novartis Pharmaceuticals, 7/24/2015
  - Locally advanced basal cell carcinoma that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy
mAbs and NIBs: Issues

- NIOSH 2014 hazardous drug list?
- Initiation or continuation of outpatient therapy during inpatient stays
- Availability
  - REMS
  - Specialty pharmacies
  - Patient assistance programs

Edoxaban (Savaysa®)

- FDA approval: January 8, 2015
  - New Molecular Entity
  - Standard review drug
- Marketed by: Daiichi Sankyo
- Website information: [http://www.savaysa.com](http://www.savaysa.com)

Pipeline Factor Xa Inhibitors

- Betrixaban (Portola Pharma ended partnership with Merck, currently in phase III testing)
- Otamixaban (Sanofi ended development)
- Darexaban (Astellas Pharma ended development)
Edoxaban

- Mechanism of action: factor Xa inhibitor
- FDA-labeled indication:
  - Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
  - Treatment of deep vein thrombosis and pulmonary embolism following 5 to 10 days of initial therapy with a parenteral anticoagulant
- Dosage form/strength:
  - 15 mg, 30 mg, 60 mg tablets

Dosing and Administration

- Route: oral
- Dose: 60 mg once daily (Clcr 50-95 mL/min)
- Dose adjustment:
  - Clcr >95 mL/min: do not use
  - Clcr 15-50 mL/min: 30 mg once daily
  - Body weight ≤60 kg: 30 mg once daily
  - Concomitant use of certain P-gp inhibitors: 30 mg once daily
  - Transition to warfarin: 15 mg dose may be used if patient already taking 30 mg once daily

Factor Xa Inhibitor Comparison

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Approval</td>
<td>Xarelto®</td>
<td>Eliquis®</td>
<td>Savaysa®</td>
</tr>
<tr>
<td></td>
<td>July 2011</td>
<td>December 2012</td>
<td>January 2015</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>(20 mg once daily with evening meal)</td>
<td>(5 mg twice daily)</td>
<td>(60 mg once daily)</td>
</tr>
<tr>
<td>DVT/PE treatment</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>DVT prophylaxis (knee/hip replacement)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
## Factor Xa Inhibitor Comparison

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg (80-100%)</td>
<td></td>
<td>50%</td>
<td>62%</td>
</tr>
<tr>
<td>20 mg (66%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tmax</strong></td>
<td></td>
<td>3-4 hrs</td>
<td>1-2 hrs</td>
</tr>
<tr>
<td>2-4 hrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Protein Binding</strong></td>
<td></td>
<td>87%</td>
<td>55%</td>
</tr>
<tr>
<td>15 mg, 20 mg take with food</td>
<td>92-95%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg take with or without food</td>
<td>87%</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td><strong>Food effect</strong></td>
<td></td>
<td>Not significant</td>
<td>Not significant</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>CYP3A4/5,</td>
<td>CYP3A4</td>
<td>1A2, 2C8, 2C9, 2C19, 2J2</td>
</tr>
<tr>
<td></td>
<td>CYP2J2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Elimination half-life</strong></td>
<td>5-9 hrs</td>
<td>12 hrs</td>
<td>10-14 hrs</td>
</tr>
</tbody>
</table>

### Contraindications
- Active pathological bleeding
- Hypersensitivity to ingredients

### Warnings/Precautions
- Black Box Warning
  - Premature discontinuation
  - Hemorrhagic Firm
- Other Warnings/Precautions
  - Risk of bleeding
  - Prosthetic heart valves
  - Pregnancy related hemorrhage

### Drug Interactions
- CYP3A4 and P-glycoprotein
  - Inducers (i.e., carbamazepine, phenytoin, rifampin, St. John’s wort)
  - Inhibitors (i.e., ketoconazole, itraconazole, ritonavir, clarithromycin)
- Anticoagulants (i.e., enoxaparin, warfarin)
- NSAIDs/Aspirin/Platelet Aggregation Inhibitors

### Clinical Trial Data

<table>
<thead>
<tr>
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<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
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</thead>
<tbody>
<tr>
<td><strong>Primary Efficacy Outcome</strong></td>
<td></td>
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</tr>
<tr>
<td>HR 0.79; 95% CI, 0.66-0.96; p&lt;0.001</td>
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<tr>
<td>HR 0.79; 95% CI, 0.66-0.95; p&lt;0.001</td>
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</tr>
<tr>
<td>RR 0.66; 95% CI, 0.53-0.82; p&lt;0.001</td>
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</tbody>
</table>
Clinical Trial Data

![Graph showing primary safety outcomes](image)

Other Clinical Trials

- **Cancer-related VTE**
  - NCT02073682 (phase IV vs. dalteparin for acute VTE prevention)

- **Prevention of DVT/PE**
  - NCT01181167 (phase III vs. enoxaparin for prevention of thrombosis-related events following total hip arthroplasty)
  - NCT01181102 (phase III vs. enoxaparin for prevention of thrombosis-related events following total knee arthroplasty)
  - NCT01181141 (phase III vs. enoxaparin for prevention of thrombosis-related events following hip fracture surgery)

Comparative Pricing

- **Eliquis 60 count bottles**: $400 (SWP)
  - 2.5-5 mg twice daily

- **Savaysa 30 count bottles**: $332 (SWP)
  - 30-60 mg once daily

- **Xarelto 30 count bottles**: $400 (SWP)
  - 10-20 mg once daily
  - 15 mg twice daily for 21 days (VTE treatment)
Other Considerations

- Use in special populations
  - Do not use in patients with CrCl >95 mL/min (AF)
  - Recommended lower doses in patients with CrCl 15-50 mL/min, patients weighing <60 kg, or patients taking certain P-gp inhibitors (DVT treatment)
  - Avoid use in patients with CrCl <15 mL/min or dialysis
  - Avoid use in patients with moderate to severe hepatic impairment
- Discontinuation for surgery and other interventions
- Converting to or from apixaban/rivaroxaban/edoxaban
- Laboratory monitoring?
- Reversal agent?
  - Profilnine®, Bebulin VH® (available in US)
  - Cofact® (available in Europe)
  - Kcentra® (available in US)
  - Andexanet alfa (PRT4445): factor Xa inhibitor antidote
  - Designated as breakthrough therapy by FDA (pursuing Accelerated Approval pathway)

Patient Counseling

- Do not discontinue without talking to their physician first.
- May take longer than usual for bleeding to stop, may bruise/bleed more easily.
- Should tell physicians/dentists they are taking oral anticoagulant and/or any other product known to affect bleeding before procedures.
- Should tell physicians if they are pregnant or plan to become pregnant or are breastfeeding.
- Missed doses: dose should be taken as soon as possible on the same day and resume normal dosing schedule the following day. Do not double doses.

Dabigatran Reversal Agent

- Idarucizumab (proposed trade name is Praxbind®), developed by Boehringer Ingelheim
- RE-VERSE AD
  - NCT02104947 (phase III study) conducted among patients with serious bleeding or required urgent procedure
  - Two bolus infusions of 2.5 gm/50 mL no more than 15 minutes apart
  - 90 patients (51 in group A, 39 in group B)
    - 100% maximum percentage reversal among 58 patients with elevated dilute thrombin time and 30 patients with elevated ecarin clotting time
    - Normalized test results in 88-98% of patients
    - 35 patients undergoing surgery: 33 normal, 2 mildly abnormal, 1 moderately abnormal hemostasis observed
  - Anticipated availability: 5 gm vial: $??,???
Monoclonal Antibodies: Example

- Idarucizumab (Praxbind®)
  - idaru = “unique” syllable
  - ci = cardiovascular (DTI binding)
  - zu = humanized (source?)
  - mab = monoclonal antibody

Peramivir (Rapivab®)

- FDA approval: December 19, 2014
  - New Molecular Entity
  - Standard review drug

- Marketed by: Biocryst Pharmaceuticals, Inc.

- Website information:
  http://www.rapivab.com

Peramivir

- Neuraminidase inhibitor indicated for the treatment of acute uncomplicated influenza in patients 18 years of age and older who have been symptomatic for no more than two days

- Limitations of use:
  - Influenza type A
  - Influenza drug susceptibility
  - Efficacy could not be established in serious influenza requiring hospitalization
Peramivir

- 600 mg IV infusion for at least 15 minutes
- Renal impairment:
  - 30-49 mL/min: 200 mg
  - 10-29 mL/min: 100 mg
  - HD: administer after dialysis
- 200 mg/20 mL vial
  - Must be diluted prior to administration (saline, dextrose, LR)
  - Administer immediately or store under refrigerated conditions for up to 24 hours
- $1,140 per 3 vials (SWP)

Cephalosporins/Beta-Lactamase Inhibitor Combinations

- Ceftolozane/tazobactam (Zerbaxa®)
  - December 19, 2014
  - 4P, QIDP, Cubist Pharmaceuticals
  - Indicated for the treatment of:
    - Complicated intra-abdominal infections, used in combination with metronidazole
    - Complicated urinary tract infections, including pyelonephritis
- Ceftazidime/avibactam (Avycaz®)
  - February 25, 2015
  - 1P, QIDP, Cerexa Inc.
  - Indicated for the treatment of:
    - Complicated intra-abdominal infections, used in combination with metronidazole
    - Complicated urinary tract infections, including pyelonephritis

FDA Draft Guidance for Industry

- FDA Draft Guidance for Industry
  - Complicated IAIs: February 2015
  - Complicated UTIs: February 2015
- Qualified Infectious Disease Product (QIDP)
  - Generating Antibiotic Incentives Now (GAIN) Act, part of the 2012 FDA Safety and Innovation Act
  - QIDP designation provides incentives including priority review, eligibility for FDA’s fast track program, and 5 year extension of exclusivity under Hatch-Waxman Act
- IDSA Guidelines
  - Intra-abdominal 2010 (update in progress)
  - Uncomplicated cystitis and pyelonephritis 2011 (current)
Dosing/Administration

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>Usual Dosing</th>
<th>Usual Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9.9 mL/min: 250 mg every 8 hours</td>
<td>1.5 gm every 8 hours</td>
<td>2.5 gm every 8 hours</td>
</tr>
<tr>
<td>10-19 mL/min: 375 mg every 8 hours</td>
<td>30-50 mL/min: 750 mg every 8 hours</td>
<td>30-50 mL/min: 1.25 gm every 8 hours</td>
</tr>
<tr>
<td>20-29 mL/min: 750 mg every 8 hours</td>
<td>15-29 mL/min: 375 mg every 8 hours</td>
<td>15-29 mL/min: 0.94 gm every 12 hours</td>
</tr>
<tr>
<td>30-49 mL/min: 2 gm every 8 hours</td>
<td>6-15 mL/min: 375 mg every 8 hours</td>
<td>6-15 mL/min: 0.64 gm every 24 hours</td>
</tr>
</tbody>
</table>

Administration Notes

All doses are administered over 1 hour. Dilute reconstituted solution in 100 mL 0.9% NaCl or D5W.

Ivabradine (Corlanor®)

- FDA approval: April 15, 2015
  - New Molecular Entity
  - Priority review drug

- Marketed by: Amgen Inc.

- Website information:
  http://www.corlanor.com

Ivabradine

- Mechanism of action: hyperpolarization-activated cyclic nucleotide-gated channel responsible for the cardiac pacemaker If current, which regulates heart rate

- FDA-labeled indication: reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤35% who are in sinus rhythm with resting heart rate ≥70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use

- Dosage form/strength:
  - 5 mg and 7.5 mg film-coated tablets
Ivabradine Pharmacokinetics

- Bioavailability: 40% (first-pass metabolism)
- Food delays absorption by ~1 hour and increases plasma exposure by 20-40%
- Protein binding: 70%
- Extensively metabolized via CYP3A4-mediated oxidation
- Effective half-life: 6 hours

Dosing and Administration

- Dose: 5 mg tablet twice daily with food. After 2 weeks of treatment, adjust dose based on heart rate (max dose is 7.5 mg twice daily)
- Dose adjustment: in patients with conduction defects or in whom bradycardia could lead to hemodynamic compromise, initiate dosing at 2.5 mg twice daily

Contraindications/Warnings/Precautions

- Contraindications
  - Acute decompensated heart failure
  - Blood pressure less than 90/50 mmHg
  - Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present
  - Resting heart rate less than 60 bpm prior to treatment
  - Severe hepatic impairment
  - Pacemaker dependence
  - In combination with strong cytochrome P3A4 inhibitors

- Warnings, precautions
  - Fetal toxicity
  - Monitor patients for atrial fibrillation
  - Monitor heart rate decreases and bradycardia symptoms during treatment
  - No recommended in patients with 2nd degree AV block
Adverse Events

- Bradycardia
- Hypertension
- Atrial fibrillation
- Luminous phenomena (phosphenes)

Drug Interactions

- Strong CYP3A4 inhibitors (contraindicated)
  - Azole antifungals, macrolide antibiotics, HIV protease inhibitors, nefazodone
- Moderate CYP3A4 inhibitors
  - Diltiazem, verapamil, grapefruit juice
- CYP3A4 inducers
  - St. John’s wort, rifampicin, barbiturates, phenytoin
- Negative chronotropes
- Pacemakers

Patient Counseling

- Fetal toxicity
- Low heart rate
- Atrial fibrillation
- Phosphenes
- Drug interactions (grapefruit juice and St. John’s wort)
- Take with food
- Missed doses: dose should be taken as soon as possible on the same day and twice daily administration should be resumed. Do not double doses.
Cangrelor (Kengreal®)

- FDA approval: June 22, 2015
  - New Molecular Entity
  - Standard review drug

- Marketed by: The Medicines Co.

- Website information: [http://www.kengreal.com](http://www.kengreal.com)

Cangrelor

- Mechanism of action: P2Y12 platelet inhibitor

- FDA-labeled indication: adjunct to percutaneous coronary intervention for reducing the risk of periprocedural myocardial infarction, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a P2Y12 platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor

- Dosage form/strength:
  - 50 mg lyophilized powder vial
  - Reconstitute each vial with SWI 5 mL
  - Dilute with D5W or 0.9% NaCl 250 mL (stable for 12-24 hours)
  - Patients 100 kg and over will require a minimum of 2 bags

Dosing and Administration

- Dose: 30 mcg/kg IV bolus followed by a 4 mcg/kg/min IV infusion through a dedicated IV line

- Duration: for at least 2 hours or for the duration of PCI, whichever is longer

- Transition patients to oral P2Y12 therapy:
  - Ticagrelor: 180 mg at any time during cangrelor infusion or immediately after discontinuation
  - Prasugrel: 60 mg immediately after discontinuation of cangrelor
  - Clopidogrel: 600 mg immediately after discontinuation of cangrelor
Contraindications/Warnings/Precautions

- Contraindications
  - Significant active bleeding
  - Known hypersensitivity

- Warnings, precautions
  - Bleeding

- Adverse Reactions
  - Bleeding
  - Hypersensitivity reactions

- Drug-drug interactions
  - Thienopyridines (clopidogrel/prasugrel will have no antiplatelet effect until next dose administered)

Familial Hypercholesterolemia

- Heterozygous
  - 1 in 200-500 in North America and Europe
  - Single abnormal copy of LDLR gene
  - High-dose statin therapy

- Homozygous
  - 1 in 1,000,000 births
  - Two abnormal copies of LDLR gene
  - High-dose statin therapy and LDL apheresis with adjunctive therapy (e.g., torin2 and/or mipomersen, ezetimibe)

- Defects in selected genes
  - LDL receptor
  - Apolipoprotein B
  - PCSK9

PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>Generic</th>
<th>Alirocumab</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade</td>
<td>Praluent®</td>
<td>Repath®</td>
</tr>
<tr>
<td>Manufacturer/FDA Approval</td>
<td>Sanofi Aventis, July 24, 2015; BLA</td>
<td>Amgen, August 27, 2015; BLA</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Human monoclonal IgG2 directed against human proprotein convertase subtilisin kexin 9 (PCSK9).</td>
<td>[null]</td>
</tr>
<tr>
<td>Indication*</td>
<td>Alirocumab/Evolocumab: Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of LDL-cholesterol.</td>
<td>Evolocumab: Other LDL-lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH), who require additional lowering of LDL-cholesterol.</td>
</tr>
<tr>
<td>Availability/Dosing</td>
<td>75 mg/mL or 150 mg/mL single dose per/syringe</td>
<td>140 mg/mL single dose syringe/autosyringe</td>
</tr>
<tr>
<td></td>
<td>75 mg SQ every 2 weeks (max of 150 mg every 2 weeks)</td>
<td>140 mg, single dose syringe/autosyringe</td>
</tr>
<tr>
<td></td>
<td>140 mg SQ every 2 weeks (max of 420 mg every 4 weeks)</td>
<td>[null]</td>
</tr>
<tr>
<td></td>
<td>210 mg SQ every 4 weeks</td>
<td>420 mg SQ every 4 weeks</td>
</tr>
</tbody>
</table>

*To administer 420 mg, give 1 injection consecutively within 30 minutes.
PCSK9 Inhibitor Comparison

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>85%</td>
<td>72%</td>
</tr>
<tr>
<td>Tmax</td>
<td>3-7 days</td>
<td>3-4 days</td>
</tr>
</tbody>
</table>
| Metabolism           | • Saturable binding to target  
                      | • Non-saturable proteolytic pathway |
| Elimination half-life| 17-20 days | 11 to 17 days |

Contraindications
- History of serious hypersensitivity reaction

Warnings/Precautions
- Hypersensitivity reactions (pruritis, rash, urticaria), including some serious events (hypersensitivity vasculitis, and hypersensitivity reactions requiring hospitalization)

Adverse Reactions
- Nasopharyngitis, injection site reactions, influenza

Drug Interactions
- No significant DDIs

Questions?