New Drug Review
Fall 2015

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UAMS College of Pharmacy
Disclosure

• I do not have any conflict of interest or relevant financial relationship to report.
Objectives

• Define the STEPS mnemonic used to help assess new drug approvals.

• Describe the indications, pharmacological categories, dosage forms, contraindications/ warnings, and most common side effects of some of the newest drugs and biologics approved for use in the United States.

• Describe in greater detail the pharmacology of recently approved drugs and biologics that possess a novel mechanism of action.

• Introduce important new formulations and/or indications for previously approved drugs and biologics.
A mnemonic to provide an analytic framework for making better decisions about a new drug’s appropriate place in therapy.

- New drugs are often less tested and have very little published safety & efficacy data

S = Safety
T = Tolerability
E = Efficacy
P = Price
S = Simplicity
Avycaz® (ceftazidime/avibactam)

• Category
  • Cephalosporin/beta-lactamase inhibitor combination

• Indications
  • Complicated intra-abdominal infections (cIAI)
    • Use with metronidazole
  • Complicated urinary tract infections (cUTI)
    • Includes pyelonephritis
Mechanism of Action

• Ceftazidime
  • 3rd generation cephalosporin
  • Inhibits bacterial cell-wall synthesis by binding to penicillin-binding proteins (PBPs) located in the cell wall
  • Bactericidal - Time-dependent killing

• Avibactam
  • Inhibits bacterial beta-lactamases
  • Non-beta-lactam
  • Protects against TEM, SHV, CTX-M, Klebsiella pneumoniae carbapenemase (KPC), and certain oxacilllinases
Spectrum of Activity

cfIAI coverage
- *Escherichia coli*
- *Enterobacter cloacae*
- *Klebsiella pneumoniae*
- *Klebsiella oxytoca*
- *Proteus mirabilis*
- *Providencia stuartii*
- *Pseudomonas aeruginosa*

cUTI coverage
- *Escherichia coli*
- *Enterobacter aerogenes*
- *Enterobacter cloacae*
- *Klebsiella pneumoniae*
- *Proteus spp.*
- *Pseudomonas aeruginosa*
- *Citrobacter freundii*
- *Citrobacter koseri*
Safety

- Hypersensitivity
  - anaphylaxis, serious skin reactions

- Reduced efficacy in patients with CrCl 30-50 ml/min

- *Clostridium difficile*-associated diarrhea

- CNS Reactions (including seizures)
  - Higher risk in renal impairment
Tolerability

Most Common ADRs
• Nausea/vomiting
• Constipation
• Abdominal pain
• Anxiety

Drug Interactions
• Probenecid
  • Inhibits avibactam elimination

Lab interference
• May cause false-positive urine glucose result
Efficacy

Phase II, randomized, double blind trial for treatment of cIAI

203 adult patients randomized to receive 5-14 days therapy with

- Ceftazidime-avibactam 2.5 gm IV q8h + metronidazole 500 mg IV q8h (n=101)
- Meropenem 1000 mg IV q8hr (n=102)

Primary endpoint

- Clinical response in microbiologically evaluable (ME) patients at the test-of-closure (TOC) visit 2 weeks after last dose
- Clinical response defined as complete resolution or significant improvement of signs/symptoms of infection with no need for additional antibiotics or surgery
Efficacy


• **Primary outcome (ME)**
  - 91.2% (62/68) ceftazidime-avibactam
  - 93.4% (71/76) meropenem

• **Clinically Evaluable (CE)**
  - 92.0% vs. 94.4%

• **mMITT**
  - 82.4% vs. 88.8%

• **All patients**
  - 83.2% vs. 89.2%
Efficacy


• Phase II, multicenter, randomized, double blinded, patient-blinded study

• 135 patients with cUTI randomized to receive
  • Ceftazidime-avibactam 625 mg (500/125) IV q8h (n=68)
  • Imipenem-cilastatin 500 mg IV q6h (n=67)
  • Could be switched to PO ciprofloxacin after 4 days
  • Duration = 7-14 days

• Primary outcome measure
  • Favorable microbiological response at the TOC visit 5-9 days post therapy in ME patients (n=62)
Efficacy


- Only 62 included in the primary endpoint ME population
  - Ceftazidime-avibactam response - 70.4% (n=27)
  - Imipenem-cilastatin response - 71.4% (n=35)

<table>
<thead>
<tr>
<th>Table 4. Favorable microbiological response rate at test-of-cure visit according to primary diagnosis and baseline uropathogens (microbiologically evaluable population).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary diagnosis, n (%):</strong></td>
</tr>
<tr>
<td>Acute pyelonephritis</td>
</tr>
<tr>
<td>Other cUTI</td>
</tr>
<tr>
<td><strong>Baseline uropathogen, n (%)</strong></td>
</tr>
<tr>
<td><em>E. coli</em></td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
</tr>
<tr>
<td><em>C. koseri</em></td>
</tr>
<tr>
<td><em>E. cloacae</em></td>
</tr>
<tr>
<td><em>P. mirabilis</em></td>
</tr>
<tr>
<td><strong>Ceftazidime-resistant pathogens, n (%)</strong></td>
</tr>
<tr>
<td><em>E. coli</em></td>
</tr>
<tr>
<td><em>E. cloacae</em></td>
</tr>
</tbody>
</table>

n, number of patients; CI, confidence interval; cUTI, complicated urinary tract infection.
Price

• How supplied
  • 2.5 g vials (powder for reconstitution)
  • Consists of 2 g ceftazidime / 0.5 g avibactam

• Price (AWP)
  • $342 per vial / $1,026 per day

Comparators (AWP)
• Meropenem (1 gm IV q8h)
  • $10-70/1-gm vial or $30-210 per day
• imipenem-cilastatin (500 mg IV q6h)
  • $10-20/500-mg vial or $40-80 per day

Simplicity

• Normal dosing
  • 2.5 g (2 g ceftazidime-0.5 g avibactam) IV every 8 hours
  • Infuse over 2 hours

• Length of therapy
  • cIAI = 5 to 14 days
  • cUTI = 7 to 14 days

• Preparation & Stability
  • Mix gently after reconstitution
  • Dilute in 50 to 250 ml of NS, D₅W, or LR
  • Stable for 12 hrs at room temp or 24 hrs refrigerated

• Renal Dosing

<table>
<thead>
<tr>
<th>Estimated CrCl (ml/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>No adjustment</td>
</tr>
<tr>
<td>31 to 50</td>
<td>1.25 g IV every 8 hrs</td>
</tr>
<tr>
<td>16 to 30</td>
<td>0.94 g IV every 12 hrs</td>
</tr>
<tr>
<td>6 to 15</td>
<td>0.94 g IV every 24 hrs</td>
</tr>
<tr>
<td>≤ 5</td>
<td>0.94 g IV every 48 hrs</td>
</tr>
</tbody>
</table>

ceftazidime/avibactam
Zerbaxa® (ceftolozane/tazobactam)

Category
- Cephalosporin/beta-lactamase inhibitor combination

Indication
- Complicated intra-abdominal infections (cIAI)
  - Use with metronidazole
- Complicated urinary tract infections (cUTI)
  - Includes pyelonephritis
Mechanism of Action

• Ceftolozane
  • Cephalosporin - undetermined generation
  • Inhibits bacterial cell-wall synthesis by binding to penicillin-binding proteins (PBPs) located in the cell wall
  • Bactericidal - Time-dependent killing

• Tazobactam
  • Inhibits bacterial beta-lactamases
  • Protects against TEM, SHV, CTX-M, OXA

ceftolozane/tazobactam
Spectrum of Activity

**cIAI coverage**

Gram-negative bacteria:
- *Enterobacter cloacae*
- *Escherichia coli*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*

Gram-positive bacteria:
- *Streptococcus anginosus / constellatus / salivarius*

**Anaerobic bacteria:**
- *Bacteroides fragilis*

**cUTI coverage**

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*

ceftolozane/tazobactam
Safety

• Hypersensitivity
  • anaphylaxis

• Reduced efficacy in patients with CrCl 30-50 ml/min
  • monitor renal function daily

• *Clostridium difficile*-associated diarrhea
Tolerability

Most Common ADRs
- Nausea
- Diarrhea
- Headache
- Pyrexia

Drug Interactions
- None in PI
Efficacy - ASPECT-cIAI

CID 2015:60(10):1462-71

• Phase III, multicenter, randomized, double-blind, non-inferiority trial
• 993 adult patients with cIAI randomized to receive 4 to 14 days of
  • Ceftolozane-tazobactam 1.5 g IV q8h + metronidazole 500 mg IV q8h (n=487)
  • Meropenem 1 gm IV q8h (n=505)
• Primary outcome
  • Clinical cure rates at TOC (24-32 days from start of therapy) in the microbiological intent to treat population
• Secondary outcome
  • Same outcome measure for Microbiologically evaluable (ME) population
• Noninferiority margin of 10%
Efficacy - ASPECT-cIAI

CID 2015:60(10):1462-71

Ceftolozane/tazobactam
Efficacy - ASPECT-cUTI

- Phase III, multicenter, randomized, double-blind, non-inferiority trial
- 1,083 adult patients with cUTI, including pyelonephritis, randomized to receive 7 days of:
  - Ceftolozane-tazobactam 1.5 g IV q8h (n=543)
  - Levofloxacine 750 mg IV once daily (n=540)
- Primary outcome
  - Composite of microbiological eradication and clinical cure 5-9 days after treatment in the MITT population
- Non-inferiority margin of 10%
## Efficacy - ASPECT-cUTI

*Lancet* 2015; 385: 1949-56

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### Figure 2: Primary and secondary endpoints at the test-of-cure visit

**mMITT** = microbiological modified intention-to-treat population. **NI** = non-inferiority.

### Table: Composite cure

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>NI margin</th>
<th>95% CI</th>
<th>Ceftolozane-tazobactam</th>
<th>Levofloxacin</th>
<th>Percentage difference (95% CI)</th>
<th>Percentage difference (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite cure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint mMITT population</td>
<td>306/398 (76.9%)</td>
<td>306/398 (76.9%)</td>
<td>275/402 (68.4%)</td>
<td>8.5 (2.3 to 14.6)</td>
<td>8.5 (0.4 to 16.5)</td>
<td></td>
</tr>
<tr>
<td>Secondary endpoint per-protocol population</td>
<td>284/341 (83.3%)</td>
<td>284/341 (83.3%)</td>
<td>266/353 (75.4%)</td>
<td>8.0 (2.0 to 14.0)</td>
<td>8.0 (0.01 to 15.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Microbiological eradication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mMITT population</td>
<td>320/398 (80.4%)</td>
<td>320/398 (80.4%)</td>
<td>290/402 (72.1%)</td>
<td>8.3 (2.4 to 14.1)</td>
<td>8.3 (2.4 to 14.1)</td>
<td></td>
</tr>
<tr>
<td>Per-protocol population</td>
<td>294/341 (86.2%)</td>
<td>294/341 (86.2%)</td>
<td>274/353 (77.6%)</td>
<td>8.6 (2.9 to 14.3)</td>
<td>8.6 (2.9 to 14.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical cure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mMITT population</td>
<td>366/398 (92.0%)</td>
<td>366/398 (92.0%)</td>
<td>356/402 (88.6%)</td>
<td>3.4 (0.7 to 7.6)</td>
<td>3.4 (0.7 to 7.6)</td>
<td></td>
</tr>
<tr>
<td>Per-protocol population</td>
<td>327/341 (95.9%)</td>
<td>327/341 (95.9%)</td>
<td>329/353 (93.2%)</td>
<td>2.7 (0.8 to 6.2)</td>
<td>2.7 (0.8 to 6.2)</td>
<td></td>
</tr>
</tbody>
</table>
Price

• How supplied
  • 1.5 g vials (powder for reconstitution)

• AWP
  • $99.60 per vial / $298.80 per day

• Comparators (AWP)
  • Meropenem (1 gm IV q8h)
    • $10-70/1-gm vial
    • $30-210 per day
Simplicity

• Normal dosing
  • 1.5 g (1 g ceftolozane-0.5 g tazobactam) IV every 8 hours
  • Infuse over 1 hour
• Length of therapy
  • cIAI = 4 to 14 days
  • cUTI = 7 days
• Preparation & Stability
  • Mix gently after reconstitution
  • Dilute in 100 ml of NS or D$_5$W
  • Stable for 24 hrs at room temp or 7 days refrigerated

• Renal Dosing

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<tr>
<td>&gt; 50</td>
<td>No adjustment</td>
</tr>
<tr>
<td>30 to 50</td>
<td>750 mg IV every 8 hrs</td>
</tr>
<tr>
<td>15 to 29</td>
<td>375 mg IV every 12 hrs</td>
</tr>
<tr>
<td>ESRD on HD</td>
<td>750 mg x1; followed by 150 mg IV every 8 hrs</td>
</tr>
</tbody>
</table>
Cresemba® (isavuconazonium)

• Category
  • Azole antifungal

• Indication
  • Invasive aspergillosis
  • Invasive mucormycosis
Mechanism of Action

- Prodrug - rapidly converted to isavuconazole by esterases
- Inhibits ergosterol synthesis and thus disrupting fungal cell wall
- 98% oral bioavailability
- $t_{1/2} = 130$ hrs
- $V_d = 450$ L
Safety

• Contraindications
  • Hypersensitivity to isavuconazole
  • Strong CYP3A4 inhibitors/inducers
  • Familial short QT syndrome

• Hepatic adverse effects
  • Elevated ALT/AST, Alk. Phos., T.bili. seen in trials
  • Generally reversible
  • Check LFTs prior to and during therapy
Safety

- Infusion related reactions
  - Hypotension, dyspnea, chills, dizziness, paresthesia, hypoesthesis

- Hypersensitivity reactions
  - Same potential as other azole antifungals

- Pregnancy
  - May cause fetal harm
  - Use only if potential benefit outweighs risk

- Drug particulates
  - IV formulation may precipitate
**Tolerability**

**Most common ADRs**
- Nausea/vomiting (26/25%)
- Diarrhea (22%)
- Headache (17%)
- Elevated LFTs (16%)
- Hypokalemia (14%)
- Constipation (13%)
- Dyspnea (12%)
- Cough (12%)
- Peripheral edema (11%)
- Back pain (10%)

**Drug interaction**
- CYP3A4 inhibitors/inducers
- Isavuconazole is a moderate inhibitor of CYP3A4 and mild inhibitor of P-gp and OCT2
Efficacy

• Phase III, randomized, double-blind, non-inferiority, multicenter, active-controlled study

• 516 adults with invasive fungal disease (IFD) caused by *Aspergillus* species or other filamentous fungi

• Randomized 1:1 to receive either of the following
  • Isavuconazonium 200 mg IV TID x 2 days; then 200 mg IV/PO once daily (n=258)
  • Voriconazole 6 mg/kg IV BID x 2 days; then 4 mg/kg IV or 200 mg PO BID (n=258)

• Primary endpoint
  • All cause mortality through day 42 (ITT population)

• 10% non-inferiority margin
# Efficacy

<table>
<thead>
<tr>
<th>Comparison</th>
<th>isavuconazonium</th>
<th>voriconazole</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All cause mortality (ITT)</strong></td>
<td>N=258</td>
<td>48 (18.6%)</td>
<td>N=258</td>
</tr>
<tr>
<td><strong>All cause mortality</strong> (proven or probably aspergillosis)</td>
<td>N=123</td>
<td>23 (18.7%)</td>
<td>N=108</td>
</tr>
<tr>
<td><strong>Overall response success at end of treatment</strong> (proven or probable aspergillosis)</td>
<td>N=123</td>
<td>43 (35.0%)</td>
<td>N=108</td>
</tr>
</tbody>
</table>
Efficacy

• Open-label, non-comparative trial evaluated safety and efficacy of isavuconazonium in 37 patients with invasive mucormycosis

| Table 10. All-Cause Mortality and Overall Response Success in Mucorales Patients |
|-------------------------------------------------|----------------|----------------|----------------|----------------|
| Primary N=21                                    | Refractory N=11| Intolerant N=5 | Total N=37     |
| All-cause Mortality Through Day 42              | 7 (33%)        | 5 (46%)        | 2 (40%)        | 14 (38%)       |
| Overall Response Success Rate at End-of-Treatment | 6/19\(^{a}\) (32%) | 4/11 (36%)     | 1/5 (20%)      | 11/35\(^{a}\) (31%) |

\(^{a}\) Two primary mucormycosis patients were not assessed at End-of-Treatment due to ongoing treatment.
Price

• How Supplied
  • 186 mg capsules (equivalent to 100 mg isavuconazole)
  • 372 mg single-dose vials (equivalent to 200 mg isavuconazole)

• Cost (AWP)
  • PO - $84 per cap or $168 per dose
  • IV - $286.20 per vial
  • Loading dose (first 2 days) = $1,008 (PO) or $1,717.20 (IV)

• Comparators (AWP per unit & for 100 kg patient)
  • Voriconazole 200 mg vials = $152.58
  • Day 1=$915.49 then $610.32 per day
  • Voriconazole 200 mg tab = $46.91
  • $187.64 per day
Simplicity

• Loading dose
  • 372 mg IV or PO every 8 hrs for 6 doses (48 hrs)

• Maintenance dose
  • 372 mg IV or PO once daily
  • Start 12-24 hrs after last loading dose

• May switch from IV to PO formulations at any time as they are bioequivalent

• Swallow capsule whole

• Infuse IV over 1 hour
Simplicity

- Gently shake vial after reconstituting to avoid foaming
- Dilute in 250 ml of NS or D$_5$W
- Diluted solution may show visible particles of drug
- Avoid unnecessary vibrations/shaking of solution
  - DO NOT TUBE
- Infuse with in-line 0.2-1.2 micron filter
- Stable for 6 hrs at room temp; 24 hrs refrigerated
Rapivab® (peramivir)

• **Category**
  • Neuraminidase inhibitor

• **Indication**
  • Treatment of acute uncomplicated influenza in patients ≥ 18 year who have been symptomatic for no more than 2 days

• Efficacy could not be established in patients with serious influenza requiring hospitalization
Mechanism of Action

- Peramivir inhibits neuraminidase which is responsible for viral entry and release from plasma membranes of infected cells
- Cross-resistance has been observed
- Half-life = 20 hrs
- Renally eliminated
Safety

• Serious skin/hypersensitivity reactions (rare)
  • Erythema multiforme
  • Stevens-Johnson syndrome

• Neuropsychiatric events
  • Case reports of delirium and abnormal behavior with use of neuraminidase inhibitors
Tolerability

**Most common ADRs**
- Diarrhea (8%)
- Constipation (4%)
- Insomnia (3%)
- AST increase (3%)
- Hypertension (2%)

**Influenza vaccine interaction**
- Inactivated vaccine can be administered any time
- Live attenuated vaccine (LAIV) nasal - avoid use 2 weeks before and 48 hours after administration
Efficacy
Antimicrobial Agents and Chemotherapy, Nov. 2011, p. 5267–5276

• Phase III, multicenter, randomized, double-blind, non-inferiority study
• 1,091 patients with seasonal influenza virus infection presenting < 48 hrs of symptom onset were randomized to receive
  • Peramivir 300 mg IV x1
  • Peramivir 600 mg IV x1
  • Oseltamivir 75 mg PO BID x 5 days
• Primary endpoint
  • Time to alleviation of influenza symptoms
• Non-inferiority margin set at 0.170 for hazard model analysis
Efficacy

Placebo-controlled, randomized, doubled-blinded trial referenced in PI shows peramivir

- alleviates symptoms a median of 21 hours sooner than placebo
- Recovery of normal body temp was approximately 12 hours sooner
Price

• How supplied
  • 200 mg/20 ml single-use vial

• Price (AWP)
  • $380 per vial
  • $1,140 per dose

• Comparators (AWP)
  • Tamiflu (oseltamivir) - $16.43 each / $164.30 for 5-day treatment
  • Relenza (zanamivir) - $3.69 each / $73.80 for 5-day treatment

http://rapivab.com
Simplicity

- Administer within 2 days of symptom onset
- Normal dose - 600 mg IV X1 infused over 15-30 min.
- Renal adjustment (CrCl)
  - 39-49 = 200 mg
  - 10-29 = 100 mg
- Dilute with up to 100 ml NS, ½NS, D5W, or LR
- Stable up to 24 hours refrigerated
Corlanor® (ivabradine)

• Category
  • Hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocker

• Indication
  • To reduce the risk of hospitalization for worsening heart failure (HF) in patients with all of the following criteria:
    • Stable, symptomatic HF
    • Left-ventricular ejection fraction (LVEF) ≤ 35%
    • Sinus rhythm
    • Resting heart rate (HR) ≥ 70 beats per minute (BPM)
    • On maximum tolerated doses of beta-blocker or have contraindication to beta-blocker use
MOA

• Blocks the HCN channel responsible for the cardiac pacemaker $I_f$ current in the sinoatrial (SA) node

• Results in a dose-dependent reduction in HR

• No effect on myocardial contractility

ivabradine

Safety - Contraindications

• Acute decompensated HF
• Blood pressure < 90/50
• Sick sinus syndrome, SA block, 3\textsuperscript{rd} degree AV block; unless functioning demand pacemaker is present
• Resting HR < 60 bpm
• Severe hepatic impairment
• Pacemaker dependence
• Use of strong CYP3A4 inhibitors
Safety

• Pregnancy/Lactation
  • Cardiac teratogenic effects observed in animal studies
  • Avoid use

• Atrial Fibrillation
  • 5.0% vs. 3.9% vs. placebo (per patient-year)

• Bradycardia
  • 6.0% vs. 1.3% vs. placebo (per patient-year)
Tolerability

Most common ADRs
• Bradycardia (10%)
• Hypertension (8.9%)
• Atrial fibrillation (8.3%)
• Luminous phenomena (phosphenes) (2.8%)

Drug Interactions
• CYP3A4 inhibitors/inducers
• Negative chronotropes
• Pacemakers
  • Not recommended with demands set to rates ≥ 60 bpm
Efficacy - SHIFT trial
*Lancet* 2010; 376: 875-85

- Randomized, double-blind, placebo-controlled trial
- 6,505 patients at least 18 years old with symptomatic HF and
  - LVEF ≤ 35%
  - In normal sinus rhythm with HR ≥ 70 bpm
  - Hospitalized for HF within the previous year
  - On stable background treatment including a beta-blocker for ≥ 4 weeks
- Randomized to ivabradine 5 mg PO BID or matching placebo
- Dose adjusted to target HR of 50-60 bpm
- Primary endpoint
  - Composite of CV death or hospitalization for worsening HF
# Efficacy - SHIFT trial

*Lancet* 2010; 376: 875-85

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Ivabradine group (n=3241)</th>
<th>Placebo group (n=3264)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death or hospital admission for worsening heart failure</td>
<td>793 (24%)</td>
<td>937 (29%)</td>
<td>0.82 (0.75-0.90)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mortality endpoints</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>503 (16%)</td>
<td>552 (17%)</td>
<td>0.90 (0.80-1.02)</td>
<td>0.092</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>449 (14%)</td>
<td>491 (15%)</td>
<td>0.91 (0.80-1.03)</td>
<td>0.128</td>
</tr>
<tr>
<td>Death from heart failure</td>
<td>113 (3%)</td>
<td>151 (5%)</td>
<td>0.74 (0.58-0.94)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other endpoints</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause hospital admission</td>
<td>1231 (38%)</td>
<td>1556 (42%)</td>
<td>0.89 (0.82-0.96)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hospital admission for worsening heart failure</td>
<td>514 (16%)</td>
<td>672 (21%)</td>
<td>0.74 (0.66-0.83)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any cardiovascular hospital admission</td>
<td>977 (30%)</td>
<td>1122 (34%)</td>
<td>0.85 (0.78-0.92)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Cardiovascular death, or hospital admission for non-fatal myocardial infarction</td>
<td>825 (25%)</td>
<td>979 (30%)</td>
<td>0.82 (0.74-0.89)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

| Data are number of first events (%), hazard ratio (HR; 95% CI), and p values.  |
|-----------------------------------------------------------------------------|------------------------|------------------|----------|

*Table 3: Effects on primary and major secondary endpoints*
# Efficacy - effect of baseline HR

*Clin Res Cardiol* (2013) 102:11-22

## Table 2

Effect of ivabradine on outcomes in patients with heart rate $\geq$75 bpm ($n = 4,150$) and $<75$ bpm ($n = 2,351$)

<table>
<thead>
<tr>
<th></th>
<th>Heart rate at baseline $\geq$75 bpm</th>
<th>Heart rate at baseline $&lt;75$ bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ivabradine ($N = 2,052$) Placebo ($N = 2,098$)</td>
<td>Hazard ratio (95% CI) $P$ value</td>
</tr>
<tr>
<td><strong>Primary composite endpoint</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death or hospital admission for worsening heart failure</td>
<td>545 (27%) 688 (33%)</td>
<td>0.76 (0.68–0.85) $&lt; 0.0001$</td>
</tr>
<tr>
<td><strong>Mortality endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>340 (17%) 407 (19%)</td>
<td>0.83 (0.72–0.96) 0.0109</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>304 (15%) 364 (17%)</td>
<td>0.83 (0.71–0.97) 0.0166</td>
</tr>
<tr>
<td>Death from heart failure</td>
<td>78 (4%) 126 (6%)</td>
<td>0.61 (0.46–0.81) 0.0006</td>
</tr>
<tr>
<td><strong>Other endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital admission for worsening heart failure</td>
<td>363 (18%) 503 (24%)</td>
<td>0.70 (0.61–0.80) $&lt; 0.0001$</td>
</tr>
<tr>
<td><strong>Failure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause hospital admission</td>
<td>796 (39%) 932 (44%)</td>
<td>0.82 (0.75–0.90) $&lt; 0.0001$</td>
</tr>
<tr>
<td>Any cardiovascular hospital admission</td>
<td>640 (31%) 779 (37%)</td>
<td>0.79 (0.71–0.88) $&lt; 0.0001$</td>
</tr>
</tbody>
</table>

Hazard ratios between-treatment groups (ivabradine/placebo) based on an adjusted Cox’s proportional hazards model with baseline beta-blocker intake as covariate. $P$ value from the same model (Wald test). Data are number of first events (%), hazard ratio (HR 95% CI), and $p$ values.
Price

• How Supplied
  • 5 mg & 7.5 mg film-coated tablets

• AWP
  • $7.50 per tab / $450 per 30-day supply

http://www.multivu.com/players/English/7414051-amgen-corlanor-fda-approval/
Simplicity

• Starting dose - 5 mg BID with meals

• Lower starting dose to 2.5 mg BID in patients with increased sensitivity to bradycardia

• Adjust at 2 weeks to achieve a target resting HR of 50-60 bpm

• Maximum dose - 7.5 mg BID
Entresto® (sacubitril-valsartan)

• Category
  • Neprilysin inhibitor - angiotensin II receptor blocker (ARB)
  • Synonym = LCZ696

• Indication
  • To reduce the risk of cardiovascular (CV) death and hospitalization for HF in patients with chronic HF (NYHA II-IV) and reduced ejection fraction
  • In combination with other HF therapies
  • In place of ACE inhibitor or ARB
Mechanism of Action

**Sacubitril**
- Neprilysin inhibitor
  - Neutral endopeptidase (NEP)
- Prodrug
  - LBQ657 - active metabolite
- Increases levels of natriuretic peptides (i.e. ANP/BNP)

**Valsartan**
- Blocks angiotensin II type-1 receptors
- Improved bioavailability of valsartan
  - 103 mg = 160 mg of other marketed tablets

[Diagram of the mechanism of action of LCZ696: A First-in-Class Angiotensin Receptor Neprilysin Inhibitor]

Safety

• Contraindications
  • Hypersensitivity
  • History of angioedema to previous ACE-I or ARB therapy
  • Use with an ACE-I
  • Use with aliskiren in patients with diabetes

• Pregnancy
  • Fetal harm possible (similar warning as ARB)

• Angioedema
  • 0.5% vs. 0.2% (vs. enalapril)
Safety

• Hypotension
  • 18% vs. 12% (vs. enalapril)

• Impaired renal function
  • 5% in both groups

• Hyperkalemia
  • 14% vs. 12% (vs. enalapril)
Tolerability

Most Common ADRs
- Hypotension
- Hyperkalemia
- Cough
- Dizziness
- Renal failure

Drug Interactions
- Potassium-sparing diuretics
- NSAIDs
- Lithium
  - ↑ lithium concentrations
Efficacy – PARADIGM-HF trial


- A multicenter, randomized, double-blind, parallel group, active-controlled, two-arm, event-driven trial
- 8,399 patients with class II-IV HF and reduced LVEF ≤ 40% (later changed to ≤ 35%) on stable ACE-I/ARB + beta-blocker were randomized according to the schema below

![Figure 1 PARADIGM-HF study schema.](image-url)
## Efficacy - PARADIGM-HF trial


### Table 2. Primary and Secondary Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LCZ696 (N = 4187)</th>
<th>Enalapril (N = 4212)</th>
<th>Hazard Ratio or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary composite outcome — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes or first hospitalization for worsening heart failure</td>
<td>914 (21.8)</td>
<td>1117 (26.5)</td>
<td>0.80 (0.73–0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>558 (13.3)</td>
<td>693 (16.5)</td>
<td>0.80 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First hospitalization for worsening heart failure</td>
<td>537 (12.8)</td>
<td>658 (15.6)</td>
<td>0.79 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Secondary outcomes — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>711 (17.0)</td>
<td>835 (19.8)</td>
<td>0.84 (0.76–0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in KCCQ clinical summary score at 8 mo†</td>
<td>-2.99±0.36</td>
<td>-4.63±0.36</td>
<td>1.64 (0.63–2.65)</td>
<td>0.001</td>
</tr>
<tr>
<td>New-onset atrial fibrillation‡</td>
<td>84 (3.1)</td>
<td>83 (3.1)</td>
<td>0.97 (0.72–1.31)</td>
<td>0.83</td>
</tr>
<tr>
<td>Decline in renal function§</td>
<td>94 (2.2)</td>
<td>108 (2.6)</td>
<td>0.86 (0.65–1.13)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

* Hazard ratios were calculated with the use of stratified Cox proportional-hazard models. P values are two-sided and were calculated by means of a stratified log-rank test without adjustment for multiple comparisons.

† Scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. The treatment effect is shown as the least-squares mean (±SE) of the between-group difference.

‡ A total of 2670 patients in the LCZ696 group and 2638 patients in the enalapril group who did not have atrial fibrillation at the randomization visit were evaluated for new-onset atrial fibrillation during the study.

§ A decline in renal function was defined as end-stage renal disease or a decrease of 50% or more in the estimated glomerular filtration rate (eGFR) from the value at randomization or a decrease in the eGFR of more than 30 ml per minute per 1.73 m², to less than 60 ml per minute per 1.73 m².
Price

• How Supplied
  • 24/26 mg, 49/51 mg, 97/103 mg film-coated tablets

• AWP - $7.50 per tab / $450 per 30-days

• Comparators
  • Generic ACE-inhibitors = typically on $4 lists
  • Valsartan 160 mg BID = $5 per tab or $300 per 30 days


sacubitril-valsartan
Simplicity

• Normal Starting Dose - 49/51 mg BID

• Increase at 2 to 4 weeks to target dose of 97/103 mg BID

• Lower starting dose to 24/26 mg in following patients:
  • Not previously on ACE-I/ARB or previously taking low doses
  • Severe renal impairment
  • Moderate hepatic impairment (Child-Pugh B)

• Allow 36 hour washout period if switching from an ACE-I
Kengreal® (cangrelor)

• Category
  • P2Y\textsubscript{12} platelet inhibitor

• Indication
  • Adjunct to percutaneous coronary intervention (PCI) for reducing the risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis
  • NOT being treated with P2Y\textsubscript{12} platelet inhibitor
  • NOT being given a glycoprotein IIb/IIIa inhibitor
Mechanism of Action

• Direct, reversible P2Y$_{12}$ platelet inhibitor
• Blocks ADP-induced platelet activation and aggregation
• Onset = 2 minutes
• Platelet function returns to normal within 1 hour of d/c
• Half-life = 3-6 min.

http://www.nature.com/nrcardio/journal/v7/n9/fig_tab/nrcardio.2010.101_F1.html
Safety

• Contraindications
  • Active bleeding
  • Hypersensitivity

• Bleeding is the primary ADR concern

• Other less common ADRs
  • Hypersensitivity
  • Worsening renal function
  • Dyspnea
### Tolerability

Safety data from CHAMPION PHOENIX trial

<table>
<thead>
<tr>
<th>End Point</th>
<th>Cangrelor (n=5529)</th>
<th>Clopidogrel (n=5527)</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GUSTO-defined bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe/life-threatening</td>
<td>9 (0.2%)</td>
<td>6 (0.1%)</td>
<td>1.50 (0.53-4.22)</td>
<td>0.44</td>
</tr>
<tr>
<td>Moderate</td>
<td>22 (0.4%)</td>
<td>13 (0.2%)</td>
<td>1.69 (0.85-3.37)</td>
<td>0.13</td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>31 (0.6%)</td>
<td>19 (0.3%)</td>
<td>1.63 (0.92-2.90)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>TIMI-defined bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>5 (0.1%)</td>
<td>5 (0.1%)</td>
<td>1.00 (0.29-3.45)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Minor</td>
<td>9 (0.2%)</td>
<td>3 (0.1%)</td>
<td>3.00 (0.81-11.10)</td>
<td>0.08</td>
</tr>
<tr>
<td>Major or minor</td>
<td>14 (0.3%)</td>
<td>8 (0.1%)</td>
<td>1.75 (0.73-4.18)</td>
<td>0.20</td>
</tr>
<tr>
<td>Blood transfusions</td>
<td>25 (0.5%)</td>
<td>16 (0.3%)</td>
<td>1.56 (0.83-2.93)</td>
<td>0.16</td>
</tr>
</tbody>
</table>
Efficacy – CHAMPION PHOENIX trial

• Phase III, randomized, double-blind, active-controlled, superiority study
• 11,145 patients with stable angina, STEMI, or NSTE-ACS who require PCI and have not previously received a P2Y$_{12}$ inhibitor

• Treatment groups
  • Cangrelor 30 mcg/kg IV bolus followed by 4 mcg/kg/min infusion for at least 2 hrs; followed by clopidogrel 600 mg (n=5472)
  • Clopidogrel loading dose (either 300 mg or 600 mg PO) administered at the time of PCI (n=5470)
  • Both groups then received ASA 75-325 mg + clopidogrel 75 mg daily for maintenance afterward

• Primary endpoint
  • Composite rate of death from any cause, MI, ischemia-driven revascularization, or stent thrombosis in the 48 hours after randomization in the mITT population
Efficacy - CHAMPION PHOENIX trial


**Figure 1.** Kaplan–Meier Curves for the Primary Efficacy End Point.

**Table 2.** Efficacy and Safety End Points at 48 Hours after Randomization.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Cangrelor</th>
<th>Clopidogrel</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients in modified intention-to-treat population</td>
<td>5472</td>
<td>5470</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary end point: death from any cause, myocardial infarction, ischemia-driven revascularization, or stent thrombosis†</td>
<td>257/5470 (4.7)</td>
<td>322/5469 (5.9)</td>
<td>0.78 (0.66–0.93)</td>
<td>0.005</td>
</tr>
<tr>
<td>Key secondary end point: stent thrombosis</td>
<td>46/5470 (0.8)</td>
<td>74/5469 (1.4)</td>
<td>0.62 (0.43–0.90)</td>
<td>0.01</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>207/5470 (3.8)</td>
<td>255/5469 (4.7)</td>
<td>0.80 (0.67–0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>Q-wave myocardial infarction</td>
<td>11/5470 (0.2)</td>
<td>18/5469 (0.3)</td>
<td>0.61 (0.29–1.29)</td>
<td>0.19</td>
</tr>
<tr>
<td>Ischemia-driven revascularization</td>
<td>28/5470 (0.5)</td>
<td>38/5469 (0.7)</td>
<td>0.74 (0.45–1.20)</td>
<td>0.22</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>18/5470 (0.3)</td>
<td>18/5469 (0.3)</td>
<td>1.00 (0.52–1.92)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>18/5470 (0.3)</td>
<td>18/5469 (0.3)</td>
<td>1.00 (0.52–1.92)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Death or stent thrombosis</td>
<td>59/5470 (1.1)</td>
<td>87/5469 (1.6)</td>
<td>0.67 (0.48–0.94)</td>
<td>0.02</td>
</tr>
<tr>
<td>Death, Q-wave myocardial infarction, or ischemia-driven revascularization</td>
<td>49/5470 (0.9)</td>
<td>64/5469 (1.2)</td>
<td>0.76 (0.53–1.11)</td>
<td>0.16</td>
</tr>
</tbody>
</table>
# Efficacy

## Table 4: Summary of the CHAMPION Trials

<table>
<thead>
<tr>
<th></th>
<th>PCI</th>
<th>PLATFORM</th>
<th>PHOENIX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects Randomized (% of planned enrollment)</td>
<td>8,846 (99%)</td>
<td>5,346 (84%)</td>
<td>11,145 (100%)</td>
</tr>
<tr>
<td>Primary Endpoint at 48 hours</td>
<td>Death, MI, or IDR</td>
<td>Death, MI, or IDR</td>
<td>Death, MI, IDR, or ST</td>
</tr>
<tr>
<td>Outcome of primary analysis, OR (95% CI)</td>
<td>1.05 (0.88, 1.24)</td>
<td>0.87 (0.71, 1.07)</td>
<td>0.78 (0.66, 0.93)</td>
</tr>
<tr>
<td>Clopidogrel dose and time in clopidogrel arm</td>
<td>600 mg immediately before PCI</td>
<td>600 mg immediately after PCI</td>
<td>300 or 600 mg shortly before or shortly after PCI</td>
</tr>
<tr>
<td>Population enrolled (%)</td>
<td>Stable angina: 15%</td>
<td>5%</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td>UA/NSTEMI: 74%</td>
<td>95%</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>STEMI: 11%</td>
<td>Excluded</td>
<td>16%</td>
</tr>
</tbody>
</table>
Price

• How Supplied
  • 50 mg single-use vials (lyophilized powder)
  • Can store at room temp

• AWP - $898 per vial

Simplicity

- **Bolus:** 30 mcg/kg IV
  - Give over <1 min; from the diluted bag
  - Give prior to start of PCI
- **Infusion:** 4 mcg/kg/min IV
  - Continue for at least 2 hours or for the duration of PCI
- **Transition to an oral therapy**
  - Clopidogrel 600 mg immediately after discontinuation
  - Prasugrel 60 mg immediately after discontinuation
  - Ticagrelor 180 mg during infusion or immediately after discontinuation
Simplicity

- Reconstitute 50 mg vial with 5 ml sterile water
- Avoid vigorous mixing
- Dilute in 250 ml of NS or D$_5$W
  - Results in 200 mcg/ml concentration
- Patients > 100 kg will require more than 1 bag
- Stability (room temp)
  - 12 hrs in D$_5$W
  - 24 hrs in NS
Praluent® (alirocumab)

- **Category**
  - Proprotein convertase subtilisin kexin Type 9 (PCSK9) inhibitor

- **Indication**
  - Adjunct to diet and maximally tolerated statin therapy in adults with (1) heterozygous familial hypercholesterolemia or (2) clinical atherosclerotic cardiovascular disease; who require additional lowering of LDL-cholesterol
Mechanism of Action

- Human monoclonal antibody that binds PCSK9
- Reduces LDL-receptor degradation
- End result is an increase in number of LDL-receptors and decrease in LDL-C levels
- Max concentration after SQ administration seen at 3 to 7 days
- Median half-life = 17 to 20 days
Mechanism of Action

alirocumab

http://www.nature.com/nrcardio/journal/v11/n11/fig_tab/nrcardio.2014.137_F6.html
Safety

- Hypersensitivity - allergic reactions
  - Pruritus, rash, urticarial
  - Some serious - hypersensitivity vasculitis, nummular eczema
Tolerability

**Most Common ADRs**
- Nasopharyngitis
- Injection site reactions
  - Erythema/redness; itching, swelling; pain/tenderness
- influenza

**Less Common ADRs**
- Confusion/memory impairment (0.2% vs. 0.1%)
- Abnormal LFTs (2.5% vs. 1.8%)
- Low LDL-C
  - 796 had levels < 25 mg/dl
  - 288 had levels < 15 mg/dl
- Immunogenicity
  - Anti-drug antibodies (ADA)
# Efficacy

**FDA Advisory Committee Briefing Document**

**Figure 1: Percent Change from Baseline in Calculated LDL-C at Week 24 in Phase 3 Studies**

<table>
<thead>
<tr>
<th>Comparison Study</th>
<th>% change from baseline LS means (SE)</th>
<th>Difference in % change from baseline LS mean difference (95% CI)</th>
<th>P-value</th>
<th>N Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Alirocumab</td>
<td>Alirocumab - Control</td>
<td></td>
</tr>
<tr>
<td><strong>Alirocumab 150 vs Placebo (with statins)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LONG TERM</td>
<td>0.8 (1.0)</td>
<td>-61.0 (0.7)</td>
<td>H</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HIGH FH</td>
<td>-6.6 (4.9)</td>
<td>-45.7 (3.5)</td>
<td>H</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Alirocumab 75/150 vs Placebo (with statins)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMBO I</td>
<td>-2.3 (2.7)</td>
<td>-48.2 (1.9)</td>
<td>H</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FH I</td>
<td>9.1 (2.2)</td>
<td>-48.8 (1.6)</td>
<td>H</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FH II</td>
<td>2.8 (2.8)</td>
<td>-48.7 (1.9)</td>
<td>H</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Alirocumab 75/150 vs Ezetimibe 10 (with statins)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMBO II</td>
<td>-20.7 (1.9)</td>
<td>-50.6 (1.4)</td>
<td>H</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OPTIONS I</td>
<td>-21.4 (3.3)</td>
<td>-48.5 (3.2)</td>
<td>H</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OPTIONS II</td>
<td>-11.6 (4.4)</td>
<td>-42.7 (4.3)</td>
<td>H</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Alirocumab 75/150 vs Ezetimibe 10 (without statin)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALTERNATIVE</td>
<td>-14.6 (2.2)</td>
<td>-45.0 (2.2)</td>
<td>H</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MONO</td>
<td>-15.6 (3.1)</td>
<td>-47.2 (3.0)</td>
<td>H</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Efficacy-ODYSSEY LONG TERM


- Phase III, multicenter, double-blind, placebo-controlled trial
- 2341 patients at high-risk for CV events with LDL-C ≥ 70 mg/dl and were receiving statins at maximum tolerated dose
Efficacy-ODYSSEY LONG TERM

Post hoc analysis for major adverse CV events
- Alirocumab 27 of 1550 (1.7%)
- Placebo 26 of 788 (3.3%)
- HR 0.52 (95% CI 0.31-0.890; p=0.02)

ODYSSEY OUTCOMES trial currently being conducted to evaluate CV outcomes
- estimated completion - 12/2017

Figure 2. Calculated LDL Cholesterol Levels over Time (Intention-to-Treat Analysis).
Price

- **How Supplied**
  - 75 & 150 mg prefilled pen
  - 75 & 150 mg prefilled syringe
  - Store refrigerated

- **AWP**
  - $672 each
  - $1,344 for 4-week supply
  - $17,472 per year
Simplicity

- Starting dose - 75 mg SQ every 2 weeks
- Check LDL-C within 4 to 8 weeks of initiating or titrating therapy
- May increase dose to 150 mg if LDL-C response is inadequate
- Injection sites - abdomen, thigh, upper arm
- May take pen up to 20 seconds to inject dose
Repatha® (evolocumab)

- Category
  - PCSK9 inhibitor

- Indication
  - Adjunct to diet and maximally tolerated statin therapy in adults with (1) heterozygous familial hypercholesterolemia or (2) clinical atherosclerotic cardiovascular disease; who require additional lowering of LDL-cholesterol
  - Adjunct therapy for homozygous familial hypercholesterolemia (HoFH)
Mechanism of Action

• Human monoclonal antibody that binds PCSK9

• Reduces LDL-receptor degradation

• End result is an increase in number of LDL-receptors and decrease in LDL-C levels

• Max concentration seen at 3 to 4 days

• Median half-life = 11 to 17 days
Safety

• Hypersensitivity - allergic reactions
  • Rash, eczema, urticaria
Tolerability

Most Common ADRs

• Nasopharyngitis
• Injection site reactions
  • Erythema; pain; bruising
• Influenza
• Upper respiratory tract infection
• Back pain

Less Common ADRs

• Neurocognitive events
  • 0.2% vs. 0.2%
• Abnormal LFTs
  • 2.5% vs. 1.8%
• Low LDL-C
  • 1609 had levels < 25 mg/dl
• Immunogenicity
  • Anti-drug antibodies (ADA)
### Efficacy

#### FDA Advisory Committee Briefing Document

**Table 39: Summary of Evolocumab Efficacy Results from the Four Individual Phase 3 Trials in Primary Hyperlipidemia and Mixed Dyslipidemia**

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>LDL-C percent change from baseline to week 12 (relative to placebo and ezetimibe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20110114</td>
<td>Monotherapy (12 weeks): 140 mg SC Q2W + placebo PO QD</td>
<td>+140 mg SC Q2W: Reflexive: +57 vs placebo; -39 vs ezetimibe</td>
</tr>
<tr>
<td>(N = 615)</td>
<td>EvoMab 420 mg SC QM + placebo PO QD</td>
<td>Calculated: +57 vs placebo; +40 vs ezetimibe</td>
</tr>
<tr>
<td></td>
<td>Placebo SC Q2W + placebo PO QD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo SC QM + Placebo PO QD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo SC Q2W + 10 mg ezetimibe PO QD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo SC QM + 10 mg ezetimibe PO QD</td>
<td></td>
</tr>
<tr>
<td>20110115</td>
<td>Combination with atorvastatin, rosuvastatin, or simvastatin (12 weeks):</td>
<td></td>
</tr>
<tr>
<td>(N = 1899)</td>
<td>EvoMab 140 mg SC Q2W</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EvoMab 420 mg SC QM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo SC Q2W</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo SC QM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For atorvastatin arms, added ezetimibe 10 mg or placebo PO QD</td>
<td></td>
</tr>
<tr>
<td>20110117</td>
<td>In HFH subjects (12 weeks):</td>
<td></td>
</tr>
<tr>
<td>(N = 331)</td>
<td>EvoMab 140 mg SC Q2W</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EvoMab 420 mg SC QM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo SC Q2W</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo SC QM</td>
<td></td>
</tr>
</tbody>
</table>

**Table 40: Summary of Evolocumab Efficacy Results from Individual Trials in HoFH**

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>UC and calculated LDL-C percent change from baseline to week 12 (relative to placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20110223</td>
<td>Phase 2/3 HoFH trial (12 weeks):</td>
<td><strong>Bold font</strong> indicates p &lt; 0.001</td>
</tr>
<tr>
<td>Part B</td>
<td>Placebo (n=50)</td>
<td>Placebo (n=16)</td>
</tr>
<tr>
<td>(N = 49)</td>
<td>Phase 3, randomized, double-blind, placebo-controlled</td>
<td>Evolocumab (n=33)</td>
</tr>
<tr>
<td></td>
<td>EvoMab 420 mg SC QM</td>
<td>Treatment difference (n=49)</td>
</tr>
<tr>
<td></td>
<td>Placebo QM</td>
<td>UC LDL-C: 7.9</td>
</tr>
<tr>
<td></td>
<td>Atorv 10 mg vs placebo</td>
<td>-23.1</td>
</tr>
<tr>
<td>Atorv 10 mg (vs eze)</td>
<td>-71</td>
<td>-74</td>
</tr>
<tr>
<td>Atorv 80 mg (vs eze)</td>
<td>-47</td>
<td>-50</td>
</tr>
<tr>
<td>Rosu 5 mg (vs pbo)</td>
<td>-68</td>
<td>-71</td>
</tr>
<tr>
<td>Rosu 40 mg (vs pbo)</td>
<td>-68</td>
<td>-71</td>
</tr>
<tr>
<td>20110271</td>
<td>Phase 2/3 HoFH open label, long-term study (5 years):</td>
<td><strong>Bold font</strong> indicates p &lt; 0.001</td>
</tr>
<tr>
<td>(N = 96)</td>
<td>Ongoing; interim analysis based on 01 April 2014</td>
<td>Placebo (n=46)</td>
</tr>
<tr>
<td></td>
<td>EvoMab 420 mg SC Q2W</td>
<td>Evolocumab (n=13)</td>
</tr>
<tr>
<td></td>
<td>Evolocumab 420 mg SC QM</td>
<td>Non-apheresis (n=33)</td>
</tr>
<tr>
<td></td>
<td>Placebo QM</td>
<td>Evolocumab 420 mg SC Q2W</td>
</tr>
<tr>
<td>UC LDL-C:C</td>
<td>-23</td>
<td>-20</td>
</tr>
<tr>
<td>UC LDL-C :</td>
<td>-23</td>
<td>-20</td>
</tr>
</tbody>
</table>

---
Efficacy - OSLER 1 & 2 trials

*evolocumab*

Efficacy - OSLER 1 & 2 trials


**LDL Cholesterol**

- **Standard of care alone**
  - 61% reduction (95%CI 59-63%), *P* < 0.0001
  - Absolute reduction: 73 mg/dL (95%CI 71-76%)

- **Evolocumab plus standard of care**

<table>
<thead>
<tr>
<th>Time</th>
<th>N</th>
<th>Baseline</th>
<th>4 weeks</th>
<th>12 weeks</th>
<th>24 weeks</th>
<th>36 weeks</th>
<th>48 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td></td>
<td></td>
<td>(Parent)</td>
<td>(OSLER)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td></td>
<td>4465</td>
<td>1258</td>
<td>4259</td>
<td>4204</td>
<td>1243</td>
<td>3727</td>
</tr>
</tbody>
</table>

**LDL Cholesterol Goals**

- Standard of care alone
- Evolocumab plus standard of care

- **Proportion Achieving Goal (%)**
  - LDL-C Goal (mg/dL) at 12 weeks
  - <100: 26.0 vs 90.2, P < 0.001
  - <70: 3.8 vs 73.6, P < 0.001
Efficacy – OSLER 1 & 2 trials

*Pre-specified exploratory outcome*

*Events were adjudicated by central clinical-events committee that was blinded from treatment group*

*FOURIER trial currently being conducted to evaluate CV outcomes*
  *Estimated completion - 2/2018*
Price

• How Supplied
  • 140 mg prefilled pen
  • 140 mg prefilled syringe
  • Store refrigerated
  • Use within 30 days if stored at room temp

• AWP
  • $650.77 each
  • $1,301.54 to $1,952.31 for 4-week supply
  • $16,920.02 to $25,380.03 per year
Simplicity

• Starting dose
  • 140 mg SQ every 2 weeks OR
  • 420 mg SQ every 4 weeks (recommended dose for HoFH)

• Must give 3 injections within 30 min for 420 mg dose

• Injection sites - abdomen, thigh, upper arm

• May take pen about 15 seconds to inject dose
Savaysa® (edoxaban)

- **Category**
  - Factor Xa inhibitor

- **Indication**
  - Stroke and systemic embolism prophylaxis in patients with non-valvular atrial fibrillation (NVAF)
  - Treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE)
    - Following an initial 5 to 10 day treatment with a parenteral anticoagulant
Mechanism of Action

- Selective, direct factor-Xa inhibitor
- Peak effect seen in 1-2 hrs
- Steady state reached in 3 days
- $t_{1/2} = 10-14$ hours

http://www.medscape.org/viewarticle/757521_2
Safety - Black Box Warning edoxaban

• Reduced efficacy in NVAF patients with CrCl > 95 ml/min
  • Do not use in these patients
  • Increased risk of ischemic stroke compared to warfarin

• Premature discontinuation increases risk of ischemic events
  • Consider coverage with another anticoagulant if discontinuation is necessary

• Spinal/epidural Hematoma
  • Can occur in patients receiving neuraxial anesthesia or spinal puncture
Safety

• Contraindicated in active bleeding

• No antidote to reverse anticoagulant effects

• Use not recommended in patients with mechanical heart valves or moderate to severe mitral stenosis (no data)
Tolerability

Most Common ADRs

• Bleeding
• Anemia
• Rash
• Abnormal LFTs

EDOXBAN

ENGAGE AF-TIMI 48

B Major Bleeding

Hazard ratio and 95% confidence intervals
High-dose edoxaban vs. warfarin, 0.80 (0.71–0.91); P<0.001
Low-dose edoxaban vs. warfarin, 0.47 (0.41–0.55); P<0.001

<table>
<thead>
<tr>
<th>Years</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
<th>2.5</th>
<th>3.0</th>
<th>3.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Event (%)</td>
<td>0</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Warfarin</th>
<th>High-dose edoxaban</th>
<th>Low-dose edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7012</td>
<td>7012</td>
<td>7002</td>
</tr>
<tr>
<td></td>
<td>6116</td>
<td>6039</td>
<td>6218</td>
</tr>
<tr>
<td></td>
<td>5630</td>
<td>5594</td>
<td>5791</td>
</tr>
<tr>
<td></td>
<td>5278</td>
<td>5232</td>
<td>5437</td>
</tr>
<tr>
<td></td>
<td>4941</td>
<td>4910</td>
<td>5110</td>
</tr>
<tr>
<td></td>
<td>3446</td>
<td>3471</td>
<td>3635</td>
</tr>
<tr>
<td></td>
<td>1687</td>
<td>1706</td>
<td>1793</td>
</tr>
<tr>
<td></td>
<td>370</td>
<td>345</td>
<td>386</td>
</tr>
</tbody>
</table>
Efficacy - ENGAGE AF-TIMI 48


- Phase III, three-group, randomized, double-blind, double dummy, non-inferiority trial
- 21,2015 patients with moderate-to-high risk atrial fibrillation (CHADS$_2$ = 2 or higher) randomized to
  - Edoxaban 60 mg once daily (high-dose) [n=7035]
  - Edoxaban 30 mg once daily (low-dose) [n=7034]
  - Warfarin (dose adjusted to achieve INR of 2-3 [n=7036]
- Primary endpoint
  - Incidence of stroke (ischemic or hemorrhagic) or systemic embolic event
# Efficacy - ENGAGE AF-TIMI 48


## Table 2. Efficacy End Points.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Warfarin (N=7036)</th>
<th>High-Dose Edoxaban (N=7035)</th>
<th>High-Dose Edoxaban vs. Warfarin</th>
<th>Low-Dose Edoxaban (N=7034)</th>
<th>Low-Dose Edoxaban vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients with event</td>
<td>% of patients/yr</td>
<td>no. of patients with event</td>
<td>% of patients/yr</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td><strong>Primary end point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified intention-to-treat population in the treatment period†</td>
<td>232</td>
<td>1.50</td>
<td>182</td>
<td>1.18</td>
<td>0.79 (0.63-0.99)</td>
</tr>
<tr>
<td>Intention-to-treat population in the overall study period§</td>
<td>337</td>
<td>1.80</td>
<td>296</td>
<td>1.57</td>
<td>0.87 (0.73-1.04)</td>
</tr>
<tr>
<td>Event during the 30-day transition¶</td>
<td>7</td>
<td>—</td>
<td>7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>317</td>
<td>1.69</td>
<td>281</td>
<td>1.49</td>
<td>0.88 (0.75-1.03)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>90</td>
<td>0.47</td>
<td>49</td>
<td>0.26</td>
<td>0.54 (0.38-0.77)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>235</td>
<td>1.25</td>
<td>236</td>
<td>1.25</td>
<td>1.00 (0.83-1.19)</td>
</tr>
<tr>
<td>Nondisabling and nonfatal§</td>
<td>190</td>
<td>1.01</td>
<td>154</td>
<td>0.81</td>
<td>0.80 (0.65-0.99)</td>
</tr>
<tr>
<td>Disabling or fatal¶</td>
<td>135</td>
<td>0.71</td>
<td>132</td>
<td>0.69</td>
<td>0.97 (0.76-1.23)</td>
</tr>
<tr>
<td>Fatal</td>
<td>86</td>
<td>0.45</td>
<td>80</td>
<td>0.42</td>
<td>0.92 (0.68-1.25)</td>
</tr>
<tr>
<td>Systemic embolic event</td>
<td>23</td>
<td>0.12</td>
<td>15</td>
<td>0.08</td>
<td>0.65 (0.34-1.24)</td>
</tr>
<tr>
<td><strong>Key secondary end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke, systemic embolic event, or death from cardiovascular causes</td>
<td>831</td>
<td>4.43</td>
<td>728</td>
<td>3.85</td>
<td>0.87 (0.78-0.96)</td>
</tr>
<tr>
<td>Major adverse cardiac event††</td>
<td>926</td>
<td>4.98</td>
<td>827</td>
<td>4.41</td>
<td>0.88 (0.81-0.97)</td>
</tr>
<tr>
<td>Stroke, systemic embolic event, or death</td>
<td>1046</td>
<td>5.57</td>
<td>949</td>
<td>5.01</td>
<td>0.90 (0.82-0.98)</td>
</tr>
</tbody>
</table>
Efficacy - Hokusai-VTE


- Phase III, randomized, double-blind, non-inferiority trial
- 4921 patients with DVT & 3319 with PE who had initially received heparin were randomized to
  - Edoxaban 60 mg (adjusted to 30 mg if needed) once daily \[n=4118\]
  - Warfarin (dose adjusted to maintain INR between 2-3 \[n=4122\]
- Primary endpoint
  - Incidence of symptomatic recurrent venous thromboembolism (composite of DVT or nonfatal or fatal PE)
Efficacy – Hokusai-VTE


**edoxaban**

HR 0.89 (95% CI 0.70-1.13)  
*p*<0.001 (noninferiority)

HR 0.81 (95% CI 0.71-0.94)  
*p*<0.004 (superiority)

---

**Figure 2.** Kaplan–Meier Cumulative Event Rates for the Primary Efficacy Outcome.

**Figure 3.** Kaplan–Meier Cumulative Event Rates for the Principal Safety Outcome.
Price

• How Supplied - 15, 30, & 60 mg tablets

• AWP - $11.08 each or $332.40 per 30-day supply

• Comparators
  • Generic warfarin tablets = $4 plans
  • Eliquis - $6.67 each - $400.20 per 30-days
  • Xarelto - $13.33 each - $399.90 per 30-days
  • Pradaxa - $6.29 each - $377.40 per 30-days
Simplicity

• NVAF Dosing
  • Assess CrCl prior to initiating therapy
  • CrCl >50 to ≤ 95 ml/min - 60 mg PO once daily
  • CrCl 15 to 50 ml/min - 30 mg PO once daily

• DVT/PE Dosing
  • 60 mg PO once daily (no upper limit on CrCl)
  • CrCl 15 to 50 ml/min - 30 mg PO once daily

• Can be given with or without food

• Discontinue at least 24 hours before invasive surgery/procedure
## Simplicity - Transitioning

<table>
<thead>
<tr>
<th>From</th>
<th>To</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>warfarin</td>
<td>edoxaban</td>
<td>d/c warfarin and start edoxaban when INR ≤ 2.5</td>
</tr>
<tr>
<td>Other oral anticoagulants</td>
<td>edoxaban</td>
<td>d/c current therapy and start edoxaban at the time of next scheduled dose</td>
</tr>
<tr>
<td>LMWH</td>
<td>edoxaban</td>
<td>d/c LMWH and start edoxaban at the time of next scheduled dose</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>edoxaban</td>
<td>d/c heparin infusion and start edoxaban 4 hours later</td>
</tr>
<tr>
<td>edoxaban</td>
<td>warfarin</td>
<td><strong>Oral option</strong>: half the edoxaban dose and start warfarin concomitantly; measure INR at least weekly; d/c edoxaban once INR ≥ 2.0&lt;br&gt;<strong>Parenteral option</strong>: d/c edoxaban; start parenteral anticoagulant + warfarin at next scheduled dose; d/c parenteral anticoagulant once INR ≥ 2.0</td>
</tr>
<tr>
<td>edoxaban</td>
<td>Other oral anticoagulant</td>
<td>d/c edoxaban and start new agent at next scheduled dose</td>
</tr>
<tr>
<td>edoxaban</td>
<td>Parenteral anticoagulant</td>
<td>d/c edoxaban and start new agent at next scheduled dose</td>
</tr>
</tbody>
</table>
New Dosage Forms
New Extended-Release products

• Aptensio XR® (methylphenidate) capsules
  • Once daily - for ≥ 6 y/o - 40/60% IR/XR - caps can be opened
  • AWP = $7.80 per cap

• Elepsia XR® (levetiracetam) tablets
  • 1,000 to 3,000 mg once daily - do not crush/chew/cut
  • Not yet marketed - launch plans pending

• Envarsus XR® (tacrolimus) tablets
  • Once daily on empty stomach - conversion = 80% of total daily IR dose
  • Available Fall 2015

• Tuzistra XR® (codeine polistirex-chlorpheniramine polistirex)
  • Extended-release oral suspension (14.7-2.8 mg per 5 ml)
  • Dose = 10 ml every 12 hours - AWP=$1.27 per ml; supplied as 473 ml bottle
Duopa®

- Carbidopa/levodopa enteral suspension
- Administered over 16 hours through a PEG-J tube using CADD-Legacy 1400 portable infusion pump
- 4.63-20 mg per ml
- Supplied as 7-100 ml cartridges
  - Store in freezer
  - Thaw in frig prior to dispensing
- AWP=$242.21 per cartridge

http://www.nature.com/nrneurol/journal/v5/n7/full/nrneurol.2009.84.html
http://www.empr.com/duopa/drug/34394/
Rytary®

- Extended-release carbidopa-levodopa capsules dosed TID
- Contains mixture of IR/ER beads
- 1:4 carbidopa:levodopa ratio
  - 23.75/95; 36.25/145; 48.75/195; 61.25/245 mg capsules
- May be opened and sprinkled on food
- 70% relative bioavailability compared to IR tabs
- AWP=$2.76-$3.47 each

http://rytaryhcp.com/dosing
Glyxambi®

• New diabetes SGLT-2 inhibitor / DPP-4 inhibitor combination
  • Empagliflozin 10 mg / linagliptin 5 mg tablet
  • Empagliflozin 25 mg / linagliptin 5 mg tablet

• Dosed once daily in the morning with or without food for Type 2 DM

• AWP=$19.20 each or $576 for 30-days
Invega Trinza®

• Paliperidone palmitate 3-month IM injection
  • Supplied in 273, 410, 546, & 819 mg strengths
• Must already be treated with Invega Sustena® (1-month) product for at least 4 months
• May give injection ± 2 weeks from scheduled dose
• If dose is missed and interval is > 4 months; patient must reinitiate with Invega Sustena®
• Must be administered by a healthcare professional
• AWP=$2,342.50 to $7,234.27 per dose
Jadenu®

- New oral tablet formulation of deferasirox
- Iron chelator for chronic iron overload
- Improved bioavailability vs. Exjade
- Reduce Exjade dose by 30%, then round to nearest tablet strength
- AWP=$34.00 to $135.98

Prestalia®

- Perindopril/amlodipine combination tablets for treatment of hypertension
- Given once daily
- How supplied: 3.5/2.5 mg, 7/5 mg, and 14/10 mg
- AWP=$5.87 each or $176.10 for 30-days
Stiolto Respimat®

• Tiotropium/olodaterol combination inhaler for COPD
• Combines a long-acting muscarinic antagonist (LAMA) and long acting beta-2 agonist (LABA)
• 2 inhalations once daily
• AWP=$378.82

Toujeo®

- 300 unit/ml insulin glargine
- Forms a smaller insulin depot that leads to slower absorption and longer duration
- PI recommends a unit per unit conversion from 100 units/ml insulin glargine; some references indicate up to 10% increase may be needed
- Supplied in a 1.5 ml prefilled pen
- Once daily at any time of day
Triferic®

- Ferric pyrophosphate citrate - 27.2 mg of iron (III) per 5 ml ampule
- Indicated for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease
- First iron preparation delivered via dialysate
- Add 1 ampule to 2.5 gallons of bicarbonate concentrate to achieve final concentration of 2µM (110 mcg/ml)
- Hypersensitivity, including anaphylaxis, is possible
Zarxio®

- Filgrastim-sndz
- First biosimilar to receive FDA-approval
- Shares same indications as Neupogen® (filgrastim)
- Approved in Europe in 2009; current volume leader now
- AWP = $330.79 for 300 mcg; $526.78 for 480 mcg
Questions?

Arkansas Drug Information Center
Monday-Friday 8:30 AM to 5 PM

Local: 686-5072
Statewide Tollfree: (888) 228-1233