New Drug Review
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Disclosure

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

Objectives

• List the indications, pharmacological categories, dosage forms, drug interactions 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.

• Recognize 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

### Farxiga® (dapagliflozin)

- **Category**
  - Sodium-glucose cotransporter-2 (SGLT2) inhibitor

- **Indication**
  - Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (DM)
  - NOT indicated for type 1 DM

### Mechanism of Action

[Diagram of dapagliflozin's mechanism of action](http://www.nature.com/nrd/journal/v9/n7/fig_tab/nrd3180_F3.html)
Safety

- Contraindicated in severe renal impairment, end-stage renal disease, or dialysis
  - Do not use if eGFR is below 60 ml/min/1.73 m²
  - Increases serum creatinine & decreases eGFR
- Hypotension
  - Due to intravascular volume contraction (osmotic diuresis)
  - Assess volume status before use and correct hypovolemia
  - Patient at increased risk
    - Elderly
    - Renal dysfunction
    - Use of loop diuretics

Safety

- Hypoglycemia
  - when combined with insulin or insulin secretagogue
- Genital mycotic infections
- Increases LDL-C
- Bladder cancer
  - 10 cases (0.17%) vs. 1 case (0.03%) - insufficient data
  - Do not use in patients with bladder cancer

Tolerability

**Most common adverse reactions**
- Female genital mycotic infections
- Nasopharyngitis
- Urinary tract infections

**Other adverse reactions**
- Increased urination
- Male genital mycotic infections
- Dyslipidemia
- Constipation
- Discomfort with urination
- Nausea
- Volume depletion
**Efficacy** Diabetes Metab Res Rev 2014; 30: 204–221.

- Meta-analysis of 10 randomized controlled trials (RCTs) to assess efficacy and safety of dapagliflozin treatment
- 3,464 treated with dapagliflozin; 1,331 in control groups
- 308 trials initially identified
  - Exclusion reasons included not RCTs, did not describe dapagliflozin treatment, and durations < 12 weeks

<table>
<thead>
<tr>
<th></th>
<th>Weighted mean difference</th>
<th>95% confidence interval (CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>-0.53%</td>
<td>-0.58% to -0.47%</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>-1.06 mmol/L (19 mg/dl)</td>
<td>-1.20 to -0.92 mmol/L</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Body weight</td>
<td>-1.63 kg</td>
<td>-1.83 to -1.43 kg</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

**Efficacy** Diabetes, Obesity and Metabolism 2014. Published online July 2014. DOI: 10.1111/dom.12327

- 52 week, randomized, double blind study with 52-week double-blind extension period
- Dapagliflozin (n=406) vs. glipizide (n=408)
- All patients were on metformin ≥ 1500 mg/d
- Baseline HbA1c 6.5-10%
- Patients with inadequate response at max dose were discontinued from the study
- Primary endpoint - HbA1c non-inferiority
- Secondary endpoints - change in body weight
- Only ½ of the study participants completed 104 weeks
### Price

- **How Supplied** – 5 and 10 mg tablets
- **AWP**
  - $12.48 each
  - $374.40 per 30-day supply
- **Comparators**
  - Invokana® (canagliflozin) – $12.48 ea. ($374.40 per 30-d)
  - Jardiance® (empagliflozin) - $12.04 ea. ($361.20 per 30-d)

![Image of price](http://www.webmd.com/drugs/2/drug-165641/farxiga-oral/details#images)

### Simplicity

- **Starting Dose** – 5 mg once daily
  - Take in the morning
  - With or without food
- Dose can be increased to 10 mg once daily in patients tolerating the drug who need additional glycemic control
- Assess renal function prior to starting
- No dose adjustments needed in the elderly

![Image of simplicity](http://www.webmd.com/drugs/2/drug-165641/farxiga-oral/details#images)

### Jardiance® (empagliflozin)

- **Category**
  - Sodium-glucose cotransporter-2 (SGLT2) inhibitor
- **Indication**
  - Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (DM)
  - NOT indicated for type 1 DM

![Image of Jardiance](http://www.webmd.com/drugs/2/drug-165641/farxiga-oral/details#images)
Safety

- Contraindicated in severe renal impairment, end-stage renal disease, or dialysis
  - Do not use if eGFR is below 45 ml/min/1.73 m²
  - Increases serum creatinine & decreases eGFR
- Hypotension
  - Due to intravascular volume contraction (osmotic diuresis)
  - Assess volume status before use and correct hypovolemia
  - Patient at increased risk
    - Elderly
    - Renal dysfunction
    - Use of diuretics

Hypoglycemia
- when combined with insulin or insulin secretagogue

Genital mycotic infections

Urinary tract infections

Increases LDL-C

Tolerability

Most common adverse reactions
- Female genital mycotic infections
- Urinary tract infections

Drug Interactions
- Diuretics
- Insulin or insulin secretagogues

Other adverse reactions
- Upper respiratory tract infection
- Increased urination
- Male genital mycotic infections
- Dyslipidemia
- Nausea
- Volume depletion
Efficacy - The Lancet Diabetes & Endocrinology 2014; 2(9):691-700, September 2014

- 104-wk, randomized, active-control, double-blind, phase 3 trial
- 1549 patients with Type 2 DM and HbA1c of 7-10% despite metformin treatment
- Randomized 1:1 to either
  - Empagliflozin 25 mg once daily (n=765)
  - Glimepiride 1-4 mg once daily (n=780)
- Primary endpoint - change in HbA1c at 52 and 104 weeks

At week 104, adjusted mean difference in change from baseline in HbA1c with empagliflozin vs glimepiride was -0.11% (95% CI -0.15 to -0.07; p=0.003 for superiority).

Price

- How supplied - 10 & 25 mg tablets
- AWP
  - $12.04 each
  - $361.20 per 30-day supply
- Comparators
  - Invokana® (canagliflozin) - $12.48 ea. ($374.40 per 30-d)
  - Farxiga® (dapagliflozin) - $12.48 ea. ($374.40 per 30-d)
Simplicity

- Starting Dose - 10 mg once daily
  - Take in the morning
  - With or without food
- Dose can be increased to 25 mg once daily in patients tolerating the drug who need additional glycemic control
- Assess renal function prior to starting
- No dose adjustments needed in the elderly

Tanzeum® (albiglutide)

- Category
  - Glucagon-like peptide-1 (GLP-1) receptor agonist
- Indication
  - An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- Limitations
  - Not recommended as first-line therapy
  - Not for Type 1 DM or patients with severe GI disease
  - Has not been studied in patients with pancreatitis
  - Has not been studied in combination with prandial insulin

Mechanism of Action

- Recombinant fusion protein comprised of 2 tandem copies of modified human GLP-1 genetically fused in tandem to human albumin
- The GLP-1 fragment sequence 7 - 36 has been modified (glycine for alanine) at position 8 to confer resistance to DPP-IV
- The human albumin moiety together with the DPP-IV resistance, extends the half-life (5 days) allowing once-weekly dosing
Safety

**BLACK BOX WARNING**

- Risk of thyroid C-cell tumors (Medullary Thyroid Carcinoma)
- Contraindicated in patients with a personal or family history of MTC or multiple endocrine neoplasia syndrome type 2 (MEN 2)
- Based on rodent studies of clinically relevant doses of GLP-1 agonists
- Dose-dependent and treatment-duration-dependent
- Not known if increased risk in humans exist

Acute Pancreatitis

- 6 cases (0.3%) in clinical trials vs. 0 (placebo) / 2 (0.1%) active comparator
- Observe for s/s, discontinue if symptomatic
- Do not use in patients with h/o pancreatitis

Hypoglycemia

- Primarily when used with insulin or sulfonylurea
- Consider empirically lowering doses

Hypersensitivity

- Renal impairment
  - More common if suffering from n/v, diarrhea, dehydration

Tolerability

**Most common ADRs (≥10%)**

- Upper respiratory tract infection
- Diarrhea
- Nausea
- Injection site reaction
  - Hematoma, erythema, rash, pruritus, hypersensitivity

**Rare ADR**

- Pneumonia, atrial fibrillation, appendicitis, anti-albiglutide antibodies, LFT abnormalities

**Drug Interactions**

- Decreases absorption of oral medications due to delayed gastric emptying
Price

- How Supplied
  - 30 & 50 mg lyophilized powder in a single dose pen
  - AWP - $97.79 each ($391.16 per month)
- Comparators (AWP monthly cost)
  - Byetta® (exenatide BID) - $512-534
  - Bydureon® (exenatide once weekly) - $528.06
  - Victoza® (liraglutide once daily) - $470.88 or $706.32

Simplicity

- Starting dose - 30 mg SQ once weekly
- May increase to 50 mg dose if needed
- Injection sites - abdomen, thigh, upper arm
- Administer at any time of day without regard to meals
- No renal adjustment necessary
- Store refrigerated
  - Room temp for up to 4 weeks
- Use within 8 hours after reconstitution
Afrezza® (inhaled human insulin)

- Category
  - Rapid acting inhaled insulin
- Indication
  - To improve glycemic control in adult patients (≥18 y/o) with diabetes mellitus
- Limitations
  - Must use with long-acting insulin in Type 1 DM
  - Not recommended for treatment of DKA
  - Not recommended in patients who smoke

Mechanism of Action

- Insulin lowers blood glucose levels by
  - stimulating peripheral glucose uptake by skeletal muscle and fat
  - inhibiting hepatic glucose production
  - inhibits lipolysis in adipocytes
  - inhibits proteolysis, and enhances protein synthesis.

- Technosphere insulin (TI)
  - Insulin is adsorbed onto carrier particles consisting of fumaryl diketopiperazine (FDKP) and polysorbate 80 forming microspheres.

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Inhaled human insulin

Baseline-Corrected Glucose Infusion Rate (A) and Baseline-Corrected Serum Insulin Concentrations (B) after Administration of Afrezza or Subcutaneous Insulin Lispro in Type 1 Diabetes Patients

http://www.drugs.com/pro/afrezza.html
Safety

**BLACK BOX WARNING**
- Risk of acute bronchospasm in patients with chronic lung disease
- Contraindicated in asthma or COPD
- Baseline FEV₁ required for all patients

**Other contraindications**
- During an episode of hypoglycemia
- Hypersensitivity to regular human insulin
  - Severe, life-threatening allergic reactions to insulin products are possible

Safety

- Hypoglycemia
- Decline in pulmonary function
  - small (40 mL, 95% CI: -80, -1) but greater FEV₁ decline vs comparator
  - Reassess FEV₁ at 6-months, and then annually
  - Consider discontinuing in patients with decline of ≥ 20% in FEV₁
  - Effects of using > 2 years has not been established
- Lung cancer (data insufficient)
- DKA more common (0.43%; n=13 vs 0.14%; n=3)
- Hypokalemia
- Fluid retention/Heart failure when used with thiazolidinedione

Tolerability

**Most common ADRs (≥2%)**
- Hypoglycemia
- Cough (most common reason for d/c)
- Throat pain/irritation
- Others - headache, fatigue, diarrhea, nausea, weight gain
- Drug Interactions - same as other insulin products
Efficacy (Lancet 2010; 375: 2244–53)

• 52-week, randomized, open-label study
• 677 adult patients with Type 2 DM with poor glycemic control on insulin therapy
• Baseline HbA1c 7-11%
• Randomized 1:1 to
  • Prandial inhaled insulin + bedtime insulin glargine (n=334)
  • BID insulin aspart 70/30 mix (n=343)
• Primary Endpoint
  • Change in HbA1c from baseline
  • Non-inferiority margin - 0.4% (per protocol analysis)

Price

• How supplied
  • 4 unit and 8 unit single-use cartridges for oral inhalation
  • Inhaler can be used for up to 15-days, then discard
  • 2 inhalers come in each box of 60, 90, or 180 cartridges
• Price TBD
  • MannKind Corporation finalizing partnership agreement to help market the product
  • Anticipated availability - 1st quarter 2015
  • Expected to be par-priced with rapid-acting insulin pens
Simplicity

- Insulin Naïve Individuals
  - Start on 4 units at each meal
  - Titrate dose to desired effect
- Reduces # of injections/day
- Storage
  - Not in use - refrigerated
  - In use may be kept at room temp
  - 10 days unopened
  - 3 days opened

Mealtime dose conversion table

QUESTION #1

The new diabetes medication, canagliflozin, inhibits sodium-glucose co-transporter 2 (SGLT2) resulting in

A. increased pancreatic insulin secretion.
B. increased urinary glucose excretion.
C. decreased gastrointestinal glucose absorption.
D. improved insulin sensitivity.
QUESTION #1
The new diabetes medication, canagliflozin, inhibits sodium-glucose co-transporter 2 (SGLT2) resulting in
A. increased pancreatic insulin secretion.

B. increased urinary glucose excretion.
C. decreased gastrointestinal glucose absorption.
D. improved insulin sensitivity.

QUESTION #2
Patients with this condition should not use the new inhaled insulin product, Afrezza®?
A. COPD
B. Myocardial Infarction
C. Obesity
D. Pancreatitis
Sivextro® (tedizolid)

**Category**
- Oxazolidinone antibacterial agent

**Indication**
- Treatment of acute bacterial skin and skin structure infections (ABSSSI) in adult patients caused by designated susceptible bacteria including MRSA

**Mechanism of Action**
- Inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit
- Bacteriostatic
- Spectrum of Activity
  - Primarily Gram + organisms such as staphylococcus (including MRSA), streptococcus, enterococcus
- Prodrug (tedizolid phosphate)
  - Phosphatases convert to tedizolid

**Safety**
- Patients with neutropenia
  - Safety and efficacy not established
  - Animal studies showed activity was reduced in the absence of granulocytes
- *Clostridium difficile*-Associated Diarrhea (CDAD)
- Development of drug-resistant bacteria
  - Follow good antibiotic stewardship
Tolerability

**Most Common ADRs (≥2%)**
- Nausea
- Headache
- Diarrhea
- Vomiting
- Dizziness

**Rare**
- Myelosuppression
- Appears to be less than linezolid
- Peripheral & optic neuropathy

**Drug Interaction**
- MAO inhibitors
- Adrenergic agents
- Serotonergic agents
- Due to weak MAO inhibition
  - Initial data show minimal effects when tedizolid is combined with these drugs
  - No tyramine food restriction needed

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**Efficacy - Establish-1 study**

**JAMA. 2013;309(6):559-569**

- Randomized, double-blind, double-dummy, multicenter, phase 3 noninferiority trial
- 667 adult patients with ABSSSI (Gram + organism suspected or documented)
- Randomized 1:1 to receive oral treatment of
  - Tedizolid 200 mg once daily x 6 days (n=332)
  - Linezolid 600 mg BID x 10 days (n=335)
- Primary efficacy endpoint
  - Early clinical response at the 48-72 hour assessment
  - 10% noninferiority margin was predefined
Efficacy – Establish-2 study

**Lancet Infect Dis 2014; 14: 696–705**

- Randomized, double-blind, double-dummy, multicenter, phase 3 noninferiority trial
- 666 patients (age ≥ 12 yrs.) with ABSSSI (Gram + organism suspected or documented)
- Randomized 1:1 to receive IV treatment of
  - Tedizolid 200 mg once daily x 6 days (n=332)
  - Linezolid 600 mg BID x 10 days (n=334)
- Optional oral step-down allowed after 2 IV doses
- Primary efficacy endpoint
  - Early clinical response at the 48-72 hour assessment
  - 10% noninferiority margin was predefined

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**Price**

- How Supplied
  - 200 mg tablets
  - 200 mg lyophilized powder for injection in single-use vials

- AWP
  - PO - $354 each; $2,124 per 6-day regimen
  - IV - $282 each; $1,692 per 6-day regimen

- Comparator
  - Zyvox (linezolid) PO - $169.47 each; $3,389-4,745 per 10-14 days
  - IV - $174.33 each; $3,487-4,881 per 10-14 days
Simplicity

- 200 mg IV/PO once daily for 6 days
- PO dose can be given with or without food
- IV dose is diluted in 250 ml NS and administered over 1 hour
  - Do not shake vial during reconstitution due to foaming
  - Use within 24 hours
- No dosing adjustment needed in elderly or renal/hepatic impairment

**Vs. linezolid**
- 6 day vs. 10-14 day course
- Once daily vs. BID dosing
- Less potential for drug interactions / ADR
- Single indication currently
- Less familiarity

Dalvance® (dalbavancin)

- Category
  - Lipoglycopeptide antibiotic

- Indication
  - treatment of adult patients with ABSSSI caused by:
    - *Staphylococcus aureas* (including MRSA)
    - *Streptococcus pyogenes / agalactiae*
    - *Streptococcus anginosis* group

Mechanism of Action

- Interferes with cell wall synthesis
- Binds to D-alanyl-D-alanine terminus and prevents cross-linking
- Bactericidal
- Half-life = 2 weeks
Safety

- Hypersensitivity reactions
  - Both anaphylactic and skin reactions have been reported
  - Cross-sensitivity with other glycopeptides is possible
- Infusion related reactions - "Red-Man Syndrome"
- Hepatic effects – ALT elevation (≥3X ULN)
  - 12 (0.8%) vs. 2 (0.2%) for comparators
- CDAD
- Development of drug-resistant bacteria

Tolerability

<table>
<thead>
<tr>
<th>Table 1. Selected Adverse Reactions in Phase 2/3 Trials</th>
<th>Dalbavancin</th>
<th>Comparator*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 178)</td>
<td>(N = 1224)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>98 (5.5) 78 (6.4)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>50 (2.8) 37 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>79 (4.4) 72 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>83 (4.7) 59 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>48 (2.7) 30 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>28 (2.1) 43 (3.3)</td>
<td></td>
</tr>
</tbody>
</table>

* Comparators included linezolid, cefazolin, cephalixin, and vancomycin.

Efficacy - DISCOVER trials

- DISCOVER 1 & DISCOVER 2 - Identical double-blind, double-dummy, multicenter, randomized trials
- 1,312 adult patients with ABSSSI
- Randomized 1:1 to either
  - dalbavancin 1g IV on day 1, followed by 500 mg IV on day 8 (n=288/371)
  - vancomycin 1g (or 15 mg/kg) IV q12h for 10-14 days (n=285/368)
  - Allowed for pharmacist dose adjustment
  - After 3 days, a switch to PO linezolid 600 mg q12h was permitted
- Endpoints (10% noninferiority margin)
  - Primary - early clinical response (48 to 72 hr.)
  - Secondary - clinical status & investigator’s assessment of outcomes
**Efficacy - DISCOVER trials**

**Table 2. Primary and Secondary Efficacy End Points.**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Dalbavancin</th>
<th>Comparator</th>
<th>Absolute difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISCOVER 1</td>
<td>242/248 (98.3)</td>
<td>233/235 (99.6)</td>
<td>1.5 (0.4 to 7.0)</td>
</tr>
<tr>
<td>DISCOVER 2</td>
<td>283/297 (95.4)</td>
<td>268/284 (96.5)</td>
<td>1.5 (0.4 to 7.6)</td>
</tr>
<tr>
<td>Both trials</td>
<td>525/545 (97.7)</td>
<td>521/529 (97.8)</td>
<td>0.1 (0.1 to 0.4)</td>
</tr>
</tbody>
</table>

**Simplicity**

- Recommended 2-dose regimen
  - 1000 mg followed one week later by 500 mg
  - Renal dose adjustment for CrCl < 30 ml/min, not on HD
  - 750 mg followed one week later by 375 mg
  - Administer as IVPB over 30 minutes
  - Reconstitute with 25 ml sterile water; do not shake
  - Dilute only with D5W to final concentration 1 to 5 mg/ml
  - Saline-based IV solutions may cause precipitation
  - Expiration - 48 hours

**Price**

- **How Supplied**
  - 500 mg single-use vials containing sterile powder
  - Store at room temp

- **AWP** - $1,788 each or $5,364 per treatment

- **Comparator**
  - Vancocin® (vancomycin) - 6-7 per 1g vial ($168-196 per 14-days)
  - Vibativ® (telavancin) - $371.36 per 750 mg vial ($5,199 per 14 days)
  - Orbiactin® (oritavancin) - $1,160 per 400 mg vial ($3,480 per treatment)

**Efficacy - DISCOVER trials**

Simplicity

Efficacy – DISCOVER trials

[http://www.nature.com/nm/journal/v20/n7/full/nm0714-690.html]
Orbactiv® (oritavancin)

- Category
  - Lipoglycopeptide antibiotic

- Indication
  - Treatment of adult patients with ABSSSI caused by:
    - *Staphylococcus aureus* (including MRSA)
    - *Streptococcus pyogenes/*agalactiae*/dysgalactiae*
    - *Streptococcus anginosus* group
    - *Enterococcus faecalis* (vanc-susceptible isolates only)

Mechanism of Action

- Inhibits cell wall synthesis by:
  - Inhibition of transglycosylation (polymerization) step
  - Inhibition of transpeptidation (crosslinking)
- Disruption of bacterial membrane integrity leading to depolarization
- Bactericidal
- Half-life = 10 days

Safety

- IV Heparin use contraindicated for 48 hours after administration
  - Falsely elevates aPTT test results for 48 hours
  - Could use Factor Xa assay if therapy necessary
- Increased risk of bleeding when given with warfarin
  - Monitor for s/s of bleeding
  - PT/INR artificially prolonged for 24 hours
  - Use only when benefits outweigh risk of bleeding
Safety

• Hypersensitivity reactions
  • Cross-sensitivity with other glycopeptides possible
• Infusion related reactions - “Red Man’s Syndrome”
• Osteomyelitis
  • More cases reported with oritavancin than for vancomycin
  • Monitor patient for signs & symptoms
• CDAD
  • Development of drug resistant bacteria

Tolerability

**Most Common ADRs (≥3%)**

- Headache
- Nausea
- Vomiting
- Limb & subcutaneous abscess
- Diarrhea
- ALT increase (2.8%)
- Tachycardia (2.5%)

**Drug Interaction**

- Weak inhibitor of CYP2C9 & CYP2C19
- Weak inducer of CYP3A4 & CYP2D6
- May be of concern in drugs with narrow therapeutic index

Efficacy - SOLO 1 trial


• Randomized, double-blind, international, phase 3 trial
• 954 adult patient diagnosed with ABSSSI
• Randomized 1:1 to receive
  • oritavancin 1200 mg - single IV dose (n=475)
  • vancomycin 1 g (or 15 mg/kg) q12h x 7-10 days (n=479)
• Endpoints (10% noninferiority margin)
  • Primary - cessation of spreading or reduction in lesion size, absence of fever, and no need for a rescue antibiotic at 48 to 72 hours
  • Secondary - clinical cure at 7-14 days, reduction in lesion size of 20% or more at 48-72 hours
Efficacy – SOLO 1 trial

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Oritavancin</th>
<th>Vancomycin</th>
<th>Percentage Point Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate Haemodynamic instability</td>
<td>184 (48.6%)</td>
<td>180 (48.5%)</td>
<td>0.0 (0.0-0.1)</td>
</tr>
<tr>
<td>Severe Haemodynamic instability</td>
<td>179 (47.4%)</td>
<td>176 (47.1%)</td>
<td>0.0 (0.0-0.1)</td>
</tr>
<tr>
<td>Primary efficacy outcome (SOLO-1)</td>
<td>144 (42.8%)</td>
<td>141 (40.7%)</td>
<td>2.1 (0.2-4.0)</td>
</tr>
<tr>
<td>Lower vancomycin levels at 48 h</td>
<td>122 (35.6%)</td>
<td>120 (33.3%)</td>
<td>2.3 (0.4-4.2)</td>
</tr>
<tr>
<td>Primary efficacy outcome (SOLO-1)</td>
<td>142 (42.5%)</td>
<td>139 (40.5%)</td>
<td>2.0 (0.1-3.9)</td>
</tr>
<tr>
<td>Lower vancomycin levels at 48 h</td>
<td>120 (35.3%)</td>
<td>118 (34.0%)</td>
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<td>Primary efficacy outcome (SOLO-1)</td>
<td>141 (42.4%)</td>
<td>138 (40.5%)</td>
<td>1.9 (0.1-3.7)</td>
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<td>119 (35.0%)</td>
<td>117 (34.0%)</td>
<td>2.0 (0.2-3.9)</td>
</tr>
</tbody>
</table>

Figure 1. Primary and Secondary Efficacy End Points According to Analysis Populations and VAMCA Subgroups.

Price

- How Supplied
  - 400 mg single-use vials (lyophilized powder)
  - Stored at room temp

- AWP - $1,160 per vial or $3,480 per treatment

- Comparator (AWP)
  - Vancocin® (vancomycin) - $6-7 per 1g vial ($168-196 per 14-days)
  - Vibativ® (telavancin) - $371.36 per 750 mg vial ($5,199 per 14 days)
  - Dalvance® (dalbavancin) - $1,788 each ($5,364 per treatment)

Simplicity

- Recommended dose - 1,200 mg IVPB as single dose
- Administer over 3 hours
- Reconstitute each vial with 40 ml sterile water
- Gently swirl to avoid foaming
- Dilute in 1L of D5W (product is incompatible in saline)
- Withdraw 120 ml from liter bag prior to adding drug
- Expiration - 6 hrs room temp / 12 hrs refrigerated
QUESTION #3
When compared to linezolid, which is NOT a potential advantage of tedizolid?

A. Once daily dosing
B. Shorter course of therapy for treatment of skin infections
C. Less potential to cause drug-drug interactions
D. Higher number of FDA-approved indications

QUESTION #4
Which new antibiotic is approved to treat acute bacterial skin and skin structure infections (ABSSSI) with a single IV dose?

A. Dalvance® (dalbavancin)
B. Orbiactiv® (oritavancin)
C. Sivextro® (tedizolid)
D. Vibativ® (telavancin)
QUESTION #4
Which new antibiotic is approved to treat acute bacterial skin and skin structure infections (ABSSSI) with a single IV dose?

A. Dalvance® (dalbavancin)
B. Orbactiv® (oritavancin)
C. Sivextro® (tedizolid)
D. Vibativ® (telavancin)

Striverdi Respimat® (olodaterol)

• Category
  • Long-acting beta₂-adrenergic agonist (LABA)

• Indication
  • long-term, maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema
  • NOT indicated for acute symptom or asthma treatment

Mechanism of Action

• Activation of beta₂-receptors results in stimulation of intracellular adenyl cyclase, which synthesizes cAMP

• cAMP elevation results in relaxation of airway smooth muscles – leading to bronchodilation
**Safety**

**BLACK BOX WARNING - Asthma-Related Death**
- LABAs increase risk of asthma-related deaths
- Class effect - data is with salmeterol
- Contraindicated in asthma without use of a long-term control medication
- Do not use in patients with acutely deteriorating COPD
- Paradoxical bronchospasm may occur
- Use with caution in patients with convulsive disorders, thyrotoxicosis, QT-prolongation, or increased sensitivity to sympathomimetics
- Hypersensitivity reactions may occur

---

**Tolerability**

**Most Common ADRs (≥2%)**
- Nasopharyngitis
- Upper respiratory tract infection
- Bronchitis
- Urinary tract infection
- Cough
- Dizziness
- Rash
- Diarrhea
- Back pain
- Arthralgia

**Drug Interactions**
- Other adrenergic drugs
- May potentiate effects
- Xanthine derivatives, steroids, diuretics
- May potentiate hypokalemia
- MAO-I’s, TCAs, QT-prolonging drugs
- May potentiate CV effects
- Beta-blockers
- May decrease effectiveness

---

**Efficacy**

- Two replicate, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, Phase III studies
- 1,838 patients with COPD; age ≥40
- Randomized to receive
  - Olodaterol 5 mg once daily (n=227 / 232)
  - Olodaterol 10 mg once daily (n=225 / 234)
  - Formoterol 12 mcg BID (n=227 / 233)
  - Placebo (n=225 / 235)
- Primary Outcomes
  - FEV1 area under the curve from 0-3 hours (AUC0–3) response
  - Trough FEV1 response after 24 weeks of treatment

---
Efficacy

International Journal of COPD 2014:9 697–714

FEV₁ AUCₐ₀₋₃ Trough FEV₁ AUC

Price

• How Supplied
  - Respimat inhaler and cartridge
  - Each actuation delivers 2.5 mcg of olodaterol

• AWP - $186.84

• Comparators
  - Serevent Diskus® (salmeterol) - $277.20
  - Arcapta Neohaler® (indacaterol) - $220.04
  - Foradil Aerolizer® (formoterol) - $276.34

Simplicity

• 2 inhalations once daily at the same time of day
• Do not exceed 2 inhalations/day
• Unit must be primed
• No dose adjustments necessary for elderly or renal/hepatic impairment
Incruse Ellipta® (umeclidinium)

• Category
  - Inhaled anticholinergic
  - Long-acting muscarinic antagonist (LAMA)

• Indication
  - Long-term, maintenance treatment of airflow obstruction in patients with COPD

Mechanism of Action

• Long-acting, antimuscarinic agent
• Similar affinity for muscarinic receptors M1 to M5
• Bronchodilation effects are due to inhibition of M3 receptors in smooth muscles of the airway
• Half-life = 11 hours

Safety

• Contraindicated in patients with severe hypersensitivity to milk protein
• Do not initiate in acutely deteriorating COPD
• Paradoxical bronchoconstriction
• Narrow-angle glaucoma
• Worsening of urinary retention
  - Use with caution in patients with BPH
Tolerability

**Most Common ADRs (≥2%)**
- Nasopharyngitis
- Upper respiratory tract infection
- Cough
- Arthralgia

**Drug Interactions**
- Other anticholinergic drugs
  - Additive effects

**Efficacy**  
*Eur Respir J* 2014; 43: 72-81

- 12-week, randomized, double-blind, placebo-controlled, parallel-group study
- 206 patients ≥40 years old with COPD
- Randomized 1:1:1 to receive
  -umeclidinium 62.5 mg once daily (n=69)
  -umeclidinium 125 mg once daily (n=69)
  -or placebo once daily (n=68)
- Primary efficacy endpoints
  -Trough FEV₁ on day 85

![Graph showing changes in FEV₁ levels](image)
Price

- How Supplied
  - Disposable dry-powder inhaler
  - Double-foil blister strip with 30 blisters
  - Delivers 62.5 mcg of umeclidinium per inhalation
  - Discard 6 weeks after opening or when counter reads “0”

- Not yet marketed - anticipated launch is 4th quarter of 2014

- Expected to have similar price as competitors (AWP)
  - Spiriva HandiHaler (tiotropium) - $351.18
  - Tudorza Pressair (aclidinium) - $307.26

Simplicity

- 1 inhalation once daily
- No dosage adjustment needed for geriatric patients or for renal/hepatic impairment
- Combined with vilanterol (LABA) in product Anoro Ellipta®
  - Approved in Dec 2013
  - Once daily using same DPI technology

Zontivity® (vorapaxar)

- Category
  - Protease-activated receptor-1 (PAR-1) antagonist

- Indication
  - Reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD)
  - Reduces rate of combined endpoint of CV death, MI, stroke, and urgent coronary revascularization

http://www.sec.gov/Archives/edgar/data/1080014/000110465913068858/a13-20084_1ex99d2.htm
Mechanism of Action

- Reversible antagonist of the protease-activated receptor-1 (PAR-1) expressed on platelets
- Long half-life (3-4 days) makes it effectively irreversible
- Inhibits thrombin-induced and thrombin receptor agonist peptide (TRAP)-induced platelet aggregation

Safety

BLACK BOX WARNING - Bleeding Risk

- Do not use in patients with a history of stroke, TIA, or intracranial hemorrhage (ICH) or active bleeding
- Increases risk of bleeding, including ICH and fatal bleeds
- Avoid use with strong CYP3A inhibitors or inducers

Tolerability - TRA 2P-TIMI 50 study

<table>
<thead>
<tr>
<th>Bleeding</th>
<th>Vorapaxar</th>
<th>Placebo</th>
<th>Hazard Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI moderate or severe</td>
<td>13.08</td>
<td>13.08</td>
<td>1.00 (1.00-1.00)</td>
<td>-0.01</td>
</tr>
<tr>
<td>TIMI clinically significant</td>
<td>179 (13.8)</td>
<td>124 (13.2)</td>
<td>1.44 (1.06-1.97)</td>
<td>-0.08</td>
</tr>
<tr>
<td>Non-CABG-related major</td>
<td>267 (5.9)</td>
<td>186 (5.0)</td>
<td>1.44 (1.05-1.97)</td>
<td>-0.08</td>
</tr>
<tr>
<td>CABG-related major</td>
<td>11 (6.0)</td>
<td>10 (6.0)</td>
<td>1.13 (0.46-2.86)</td>
<td>0.79</td>
</tr>
<tr>
<td>Fatal</td>
<td>20 (3.3)</td>
<td>20 (3.3)</td>
<td>1.00 (0.42-2.50)</td>
<td>0.98</td>
</tr>
<tr>
<td>Intracranial</td>
<td>162 (4.0)</td>
<td>55 (0.9)</td>
<td>2.94 (1.39-6.20)</td>
<td>-0.01</td>
</tr>
<tr>
<td>Intracerebral</td>
<td>110 (3.6)</td>
<td>42 (0.4)</td>
<td>2.59 (1.31-5.17)</td>
<td>-0.01</td>
</tr>
<tr>
<td>Subdural or epidural</td>
<td>72 (3.0)</td>
<td>10 (0.1)</td>
<td>12.0 (3.52-7.29)</td>
<td>0.07</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.1)</td>
<td>2 (0.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Because older patients are generally at a higher risk of bleeding, consider patient age before initiating vorapaxar
Efficacy - TRA 2P-TIMI 50 trial


• Multinational, double-blind, placebo-controlled trial
• 26,449 patients with history of MI, ischemic stroke, or peripheral arterial disease - 94% on ASA, majority of MI dx on thienopyridine
• Randomly assigned in a 1:1 ratio to receive vorapaxar 2.5 mg once daily or matched placebo
• Primary efficacy end-point
  • Composite of CV death, MI, or stroke
• Secondary end-point
  • Composite of CV death, MI, stroke, or recurrent ischemia leading to urgent coronary revascularization
• Stopped early after 2 years in patients with h/o of stroke

<table>
<thead>
<tr>
<th>End Point</th>
<th>Vorapaxar</th>
<th>Placebo</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI, or stroke</td>
<td>1422 (5.5)</td>
<td>1224 (4.7)</td>
<td>1.17 (95% CI 1.04-1.32)</td>
<td>0.008</td>
</tr>
<tr>
<td>Cardiovascular death, MI, or stroke</td>
<td>1457 (5.4)</td>
<td>1259 (4.7)</td>
<td>1.17 (95% CI 1.04-1.32)</td>
<td>0.008</td>
</tr>
<tr>
<td>Cardiovascular death, MI, stroke, or recurrent ischemia leading to urgent coronary revascularization</td>
<td>799 (3.0)</td>
<td>691 (2.8)</td>
<td>0.86 (95% CI 0.78-0.96)</td>
<td>0.002</td>
</tr>
<tr>
<td>Stroke</td>
<td>286 (1.0%)</td>
<td>200 (0.7%)</td>
<td>1.42 (95% CI 1.07-1.88)</td>
<td>0.03</td>
</tr>
<tr>
<td>Non-CV death</td>
<td>415 (1.5%)</td>
<td>344 (1.2%)</td>
<td>1.21 (95% CI 1.03-1.43)</td>
<td>0.03</td>
</tr>
<tr>
<td>MI</td>
<td>128 (0.5%)</td>
<td>105 (0.4%)</td>
<td>1.23 (95% CI 1.01-1.51)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Price

• How Supplied
  • 2.08 mg tablets
  • Store in original package

• AWP - $10.69 each - $320 per month
Simplicity

- Dosing - 1 tablet (2.08 mg) PO once daily
  - with or without food
- Take with aspirin and/or clopidogrel
- No dose adjustment for renal or hepatic function
- No antidote to reverse antiplatelet effect

Northera® (droxidopa)

- Category
  - Vasopressor
  - Synthetic amino acid precursor of norepinephrine
- Indication
  - Treatment of symptomatic neurogenic orthostatic hypotension (NOH)
    - Primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure)
    - Dopamine beta-hydroxylase deficiency
    - Non-diabetic autonomic neuropathy
  - Effectiveness beyond 2 weeks of treatment has not been demonstrated.

Mechanism of Action

- Metabolized to norepinephrine by dopa-decarboxylase
- Norepinephrine increases blood pressure by inducing peripheral arterial and venous vasoconstriction
Safety

BLACK BOX WARNING - SUPINE HYPERTENSION
- Monitor supine blood pressure prior to and during treatment
- Elevating head of the bed lessens risk
- Reduce dose or discontinue if supine hypertension continues

- Hyperpyrexia and Confusion
  - Symptom complex resembling neurologic malignant syndrome (NMS)
  - Post-marketing reports in Japan
  - Observe closely during dosage changes or if concomitant levodopa dose is reduced or discontinued

Safety

- Ischemic heart disease, Arrhythmias, and CHF
  - May be exacerbated by droxidopa
  - Carefully consider potential risks prior to initiating therapy

- Allergic Reactions
  - 300 mg capsule contains FD&C Yellow #5 (tartrazine)
  - Causes allergic-type reactions in some patients (bronchial asthma)
  - Aspirin-hypersensitivity frequently seen in same patients

Tolerability

Most common ADRs (>5%)
- Headache
- Dizziness
- Nausea
- Hypertension
- Fatigue

Drug Interactions
- Drugs that increase blood pressure
  - Norepinephrine, ephedrine, midodrine, and triptans
- Parkinson’s Medications
  - Dopa-decarboxylase inhibitors may require dose adjustments
Efficacy

- Randomized, placebo-controlled, parallel-group trial
- 162 patients with Parkinson disease, multiple system atrophy, pure autonomic failure, or non-diabetic autonomic neuropathy
- Open-label droxidopa dose optimization (100-600 mg TID), followed, in responders, by 7-day washout and then a 7-day double-blind trial of droxidopa vs placebo
- Primary efficacy endpoint
  - change in overall composite score on the orthostatic hypotension questionnaire (OHQ) from randomization to end of study

Price

- How Supplied - 100, 200, and 300 mg capsules
- Specialty pharmacy drug

- AWP
  - 100 mg - $18.79 each - $1,690.80 per month
  - 200 mg - $37.57 each - $3,381.60 per month
  - 300 mg - $56.36 each - $5,072.40 per month
  - 600 mg (max dose) - $10,144.80 per month

- Comparators
  - midodrine (10 mg TID) - $4.84 each - $435.60 per month
  - fludrocortisone - (0.1-0.2 mg daily) - $0.80 each - $24-48 per month
Simplicity

- Starting dose - 100 mg TID during the day
  - Upon arising in AM, midday, late afternoon
- Titrate up by 100 mg/dose every 24-48 hours
- Maximum dose - 600 mg TID
- Take consistently with or without food
- Give last dose at least 3 hours prior to bedtime
- Take capsules whole
- Must monitor blood pressure
- No dose available for GFR < 30 ml/min

QUESTION #5

Which is CORRECT regarding vorapaxar?

A. It should not be used with other antiplatelet agents.
B. Vitamin K can be given as an antidote if serious bleeding develops.
C. It should not be used in patients with a history of stroke.
D. It is dosed twice daily.
Other New Dosage Forms

Evzio®
- New auto-injector formulation for emergency treatment of opioid overdose.
- Visual and voice instructions for guidance
- Inject into thigh
- Will go through clothing
- Seek emergency medical care immediately after use
- AWP - $862.50 for 2

Hemangeol®
- Propranolol HCl 4.28 mg/ml oral solution
- Indication - treatment of proliferating infantile hemangioma (≥ 5 weeks old)
- 0.15-0.4 ml/kg (0.6-1.7 mg/kg) BID
- Alcohol-free, paraben-free, sugar-free
- Propranolol 20 mg/5 ml oral solution also available - contains alcohol (0.6%) and paraben
- AWP cost comparison
  - Hemangeol - $450 per 120-ml bottle
  - Propranolol 20/5 - $12.83 for 120-ml ($53.47/500ml)

http://www.hemangeol.com/hcp/
**Invokamet®**

- New combination of canagliflozin + metformin for Type 2 DM
- Taken twice daily with meals
- Same warnings/precautions for each drug applies
- Available strengths
  - 50/500 mg
  - 50/1000 mg
  - 150/500 mg
  - 150/1000 mg
- AWP - $374 per month supply

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**Purixan®**

- First FDA-approved mercaptopurine oral suspension
- Indication - treatment of patients with acute lymphoblastic leukemia (ALL)
- 20 mg/ml - 100 ml bottle
- Previously only available as 50 mg tablets
  - Extemporaneously compounded into suspension in the past
- AWP
  - Purixan - $1,260 per bottle
  - Oral tablets (40) - $163.60

---

**Qudexy XR®**

- New extended-release topiramate capsules for seizure indications
- Available strengths
  - 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg
- Taken once daily; dose titrated to seizure control
- Capsules may be opened and contents sprinkled on soft food
- AWP ranges from $5.63 to $19.97 each
Targiniq ER®

- Combination of oxycodone-naloxone for severe pain
- Abuse-deterrent dosage form designed to interfere with IV or nasal inhalation abuse of these products.
- Naloxone is released and better absorbed if the dosage form is crushed
- Dosed every 12 hours
- Available as 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg tabs
- Swallow whole
- Not yet available - launch date pending

Xartemis XR®

- New extended-release combination product containing oxycodone/acetaminophen for acute, severe pain.
- 2 tablets every 12 hours with or without food
- Swallow whole
- Available as 7.5/325 mg extended-release tablets
- AWP = $2.76 each - $11.04 per day

New testosterone products

<table>
<thead>
<tr>
<th>Name</th>
<th>Dosage form</th>
<th>Dosing</th>
<th>AWP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aveed®</td>
<td>Testosterone undecanoate 250 mg/ml in oil for IM injection</td>
<td>750 mg; repeat in 4 weeks, then every 10 weeks</td>
<td>$900 per 3 ml vial</td>
</tr>
<tr>
<td>Natesto®</td>
<td>Intranasal gel in metered dose pump (5.5 mg per actuation)</td>
<td>11 mg (2 pump actuations), one per nostril TD</td>
<td>Not yet marketed</td>
</tr>
<tr>
<td>Vogelxo®</td>
<td>Testosterone topical gel in metered dose pump</td>
<td>50 mg (4 pump actuations) applied to shoulder or upper arm</td>
<td>$233.66 per 75g</td>
</tr>
</tbody>
</table>
New omega-3 products

**Epanova®**
- Omega-3-carboxylic acids
- 1 gram soft-gelatin capsules
- Dose - 2-4 caps once daily
- Indicated as an adjunct to diet to reduce triglycerides in adults with severe hypertriglyceridemia (≥500 mg/dl)
- 2014 - 4th quarter launch

**Omtryg®**
- Omega-3-acid ethyl esters A
- 1.2 gram soft-gelatin capsules
- Dose - 4 caps/day in 1-2 doses
- Indicated as an adjunct to diet to reduce triglycerides in adults with severe hypertriglyceridemia (≥500 mg/dl)
- Launch date not yet known

QUESTION #6
The new propranolol oral solution, Hemangeol®, is indicated to treat

A. Infantile hemangioma  
B. Hypertension  
C. Migraine headache  
D. Pheochromocytoma

**QUESTION #6**

The new propranolol oral solution, Hemangeol®, is indicated to treat

A. *Infantile hemangioma*
B. Hypertension
C. Migraine headache
D. Pheochromocytoma
Questions?

Arkansas Drug Information Center
Monday-Friday 8:30 AM to 5 PM
Local: 686-5072
Statewide Tollfree: (888) 228-1233