NEW ANTIMICROBIALS

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I have no disclosures or conflicts of interest.

OBJECTIVES

Pharmacists

For each new antimicrobial:
• Classify the agent based on pharmaceutical class and mechanism of action.
• Describe the microbiological spectrum of activity and indications for use.
• Review dosing adjustments for patients with hepatic and renal impairment.
• Identify common adverse effects and major drug interactions.
• Evaluate key clinical trials.

Pharmacy Technicians

For each new antimicrobial:
• Identify the brand and generic names and pharmaceutical class.
• Review indications for use and common adverse effects.
• Describe storage and preparation requirements.

OVERVIEW

Antifungals

• Isavuconazonium Sulfate (Cresemba®)

Gram Negative Antibacterials

• Ceftazidime/avibactam (Avycaz®)
• Ceftolozane/tazobactam (Zerbaxa®)

Gram Positive Antibacterials

• Tedizolid (Sivextro®)
• Dalbavancin (Dalvance®)
• Oritavancin (Orbactiv®)

LEGISLATION

Food and Drug Administration Safety and Innovation Act
• Generating Antibiotic Incentives Now (GAIN) Act (Title VIII)
• Passed by Congress in July 2012
• Qualified Infectious Disease Product (QIDP) designation
  • More lenient clinical trial requirements
  • Abbreviated New Drug Application
  • Expedited FDA review (priority/fast track)
  • 5 years of additional market exclusivity

ISAVUCONAZONIUM SULFATE

# ISAVUCONAZONIUM SULFATE (CRESEMBA®)

## Class: Triazole Antifungal
- **FDA Approval Date:** March 6, 2015
- **FDA Approved Indications:**
  - Invasive Aspergillosis
  - Invasive Mucormycosis
  - Orphan Drug Designation for Invasive Candidiasis (11/2014)

## Pharmacokinetics
- **Absorption**
  - 98% bioavailability, IV=PO
- **Distribution**
  - Extensive
  - >99% protein bound
- **Metabolism**
  - Hydrolysis to active drug by esterases in bloodstream
  - CYP3A4, CYP3A5
- **Elimination**
  - Hepatic

## Pharmacodynamics
- No association between plasma AUC or isavuconazole concentration and efficacy
- QTc interval
  - Shortens (13.1-24.6 msec)
  - Dose-dependent

## ISAVUCONAZONIUM SULFATE (CRESEMBA®):

### Loading Dose: 372 mg isavuconazonium sulfate Q8H x 6 doses

### Maintenance Dose: 372 mg isavuconazonium sulfate once daily

### Intravenous
- Vial: 372 mg isavuconazonium sulfate (200 mg isavuconazole)
  - Stored in the fridge
  - 250 mL NS or D5W
  - Administration: 1 hour
  - In line filter required
    - 0.2-1.2 micron pore size

### Oral
- Capsules: 186 mg isavuconazonium sulfate (100 mg isavuconazole)
- Blister packs
- Administer with or without food

## ISAVUCONAZONIUM SULFATE (CRESEMBA®):

### Hepatic Adverse Drug Reactions
- LFT elevations (generally reversible)
- Hepatitis, cholestasis, hepatic failure reported
- Severe underlying medical conditions

### Infusion-Related Reactions
- Hypotension, dyspnea, chills, dizziness, paresthesias reported

### Hypersensitivity Reactions
- Anaphylaxis and Stevens-Johnson syndrome with other azoles

### Embryo-Fetal Toxicity
- Increased perinatal mortality in animal models

### Drug Interactions

### Drug Particulates

## ISAVUCONAZONIUM SULFATE (CRESEMBA®):

### Common
- Nausea (26%)
- Vomiting (25%)
- Diarrhea (22%)
- Headache (17%)
- Elevated LFTs (16%)
- Hypokalemia (14%)
- Dyspnea & cough (12%)
- Peripheral edema (11%)
- Back pain (10%)

## Serious
- Occurred in 55% of patients in trials (223/403)
- 14% permanently discontinued treatment (56/403)
  - Altered mental status
  - Acute renal failure
  - Elevated bilirubin
  - Convulsion/epilepsy
  - Dyspnea
**ISAVUCONAZONIUM SULFATE (CRESEMBA): DRUG INTERACTIONS**

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>Immunosuppressants</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine, Sirolimus, Tacrolimus, Mycophenolate Mofetil</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Atorvastatin</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td></td>
<td>Bupropion</td>
</tr>
</tbody>
</table>

*Possible decreased exposure to lopinavir/ritonavir and loss of antiretroviral efficacy

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**ISAVUCONAZONIUM SULFATE (CRESEMBA): SPECIAL POPULATIONS**

- **Pregnancy Category C**
- **Not for lactating mothers**
- **No pediatric data**

- **Limited geriatric data**
- **No renal dose adjustment**
- **Not studied in severe hepatic impairment**

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**ISAVUCONAZONIUM SULFATE (CRESEMBA®): CLINICAL TRIALS**

**Invasive Aspergillosis**
- **Design:** Randomized, double-blind, non-inferiority, active control
  - Isavuconazonium sulfate versus *voriconazole*
  - Primary treatment of invasive fungal disease caused by *Aspergillus* spp.
  - Stratified by history of allogeneic bone marrow transplant, uncontrolled malignancy and geography
- **Patient Population**
  - Mean age: 51 years (17-87)
  - 78% Caucasian
  - 60% male
  - 95% with pulmonary disease
  - At least one species of *Aspergillus* identified in 30% of patients
    - *A. fumigatus* and *A. flavus* most common

**Results**
- Maximum treatment duration = 84 days
- Mean treatment duration = 47 days for both groups
- 8-9 days of IV administration before changing to PO
- All-Cause Mortality at Day 42
  - 18.6% isavuconazonium sulfate vs 20.2% voriconazole (95% CI -8.0% to 5.9%)
  - Overall Response Success at End of Treatment
    - 35% isavuconazonium sulfate vs 38.9% voriconazole (95% CI -16.3% to 8.4%)
- Non-inferior to *voriconazole* for the treatment of invasive aspergillosis

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**ISAVUCONAZONIUM SULFATE (CRESEMBA®): CLINICAL TRIALS**

**Invasive Mucormycosis**
- **Design:** Open-label, non-comparative
  - Safety and efficacy evaluation for isavuconazonium sulfate in patients with invasive mucormycosis
- **Patient Population (n=37)**
  - Mean age: 49 years (22-79)
  - 68% Caucasian
  - 81% male
- **Risk factors for mucormycosis:**
  - 60% hematologic malignancy, 35% HSCT, 27% neutropenic, 27% on corticosteroids, 49% on T cell immunosuppressant, 11% diabetes
  - *Rhizopus oryzae* most common pathogen
  - 59% pulmonary, 43% sinus, 19% ocular, 16% CNS, 14% bone

**Results**
- Median duration of treatment
  - 102 days for patients classified as primary
  - 33 days for patients classified as refractory
  - 85 days for patients classified as intolerant
- All-Cause Mortality at Day 42
  - 38% (14/37)
- Overall Response Success at End of Treatment
  - 31% (11/35)
Which of the following is false?

A. Isavuconazonium sulfate is a prodrug of isavuconazole, a difluorinated triazole antifungal
B. Isavuconazonium sulfate may be used as salvage therapy for refractory MRSA bacteremia
C. Isavuconazonium sulfate requires a loading dose that is given over 48 hours
D. Isavuconazonium sulfate causes drug-drug interactions primarily through CYP3A4 inhibition
E. Isavuconazonium sulfate must be administered with an in-line filter due to the potential for precipitate formation

Answer B (slides 6-18)
CEFTAZIDIME/AVIBACTAM (AVYCAZ®): DOSING & ADMINISTRATION

<table>
<thead>
<tr>
<th>Estimated CrCl</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>31-50 mL/min</td>
<td>1.25g (1g/0.25g) IV q8h</td>
</tr>
<tr>
<td>16-30 mL/min</td>
<td>0.84g (0.75g/0.19g) IV q12h</td>
</tr>
<tr>
<td>6-15 mL/min</td>
<td>0.94g (0.75g/0.19g) IV q24h</td>
</tr>
<tr>
<td>≤ 5 mL/min</td>
<td>0.94g (0.75g/0.19g) IV q48h</td>
</tr>
</tbody>
</table>

Duration of Treatment: cIAI 5-14 days, cUTI 7-14 days

Administration:
- Preparation
  - Compatible with NS, D5W, LR
  - Dilute in 50-250 mL
  - Stable 12-24 hours
- Give over 2 hours
- Compatibility with other drugs not established

CEFTAZIDIME/AVIBACTAM (AVYCAZ®): WARNING & PRECAUTIONS

- Decreased Efficacy in Patients with Baseline CrCl 30-50 mL/min
  - Monitor creatinine clearance at least daily in patients with changing renal function
  - Adjust dose accordingly

Hypersensitivity Reactions
- Anaphylaxis and serious skin reactions possible

Clostridium difficile-Associated Diarrhea

Central Nervous System Reactions
- Seizures and other neurologic events possible
- Adjust dose accordingly in patients with renal impairment

Development of Drug-Resistant Bacteria

CEFTAZIDIME/AVIBACTAM (AVYCAZ®): ADVERSE EFFECTS

Common
- Vomiting (14%)
- Nausea (10%)
- Constipation (10%)
- Anxiety (10%)
- Positive Direct Coombs' Test (7.3%)
  - Without evidence of hemolytic anemia

< 5%
- Rash
- Hypokalemia
- Elevated LFTs
- Prolonged PT
- Blood dyscrasias
  - Eosinophilia
  - Thrombocytopenia

CEFTAZIDIME/AVIBACTAM (AVYCAZ®): DRUG INTERACTIONS

Drug-Drug
- Probencid
  - Decreases elimination of avibactam by 56-70%
  - OAT inhibition
  - Co-administration not recommended

Drug-Lab
- False positive glucose in the urine
  - Enzymatic glucose oxidase reactions recommended

CEFTAZIDIME/AVIBACTAM (AVYCAZ®): SPECIAL POPULATIONS

- Pregnancy Category B: Ceftazidime excreted in milk
  - No pediatric data
  - Limited geriatric data
  - Renal dose adjustment required

CEFTAZIDIME/AVIBACTAM (AVYCAZ®): CLINICAL TRIALS

Design
- Ceftazidime/avibactam plus metronidazole versus meropenem for complicated intra-abdominal infections (cIAI)
  - 69.3% male
  - 55.4% Caucasian
- Ceftazidime/avibactam versus imipenem/cilastatin for complicated urinary tract infections (cUTI)
  - 75% female
  - 58.8% Caucasian

Results
- Similar overall rates of efficacy, adverse events, and mortality
- Increased mortality in cIAI studies for subgroup of patients with baseline CrCl 30-50 mL/min
  - 2.5% (8/31) on ceftazidime/avibactam + metronidazole vs 8.6% (3/35) on meropenem
  - Under-dosing
  - Delayed surgical intervention
  - Baseline pathogens unlikely to respond to study drug
CEFTOLOZANE/TAZOBACTAM

- **Class:** Novel Cephalosporin + Beta Lactamase Inhibitor
- **FDA Approval Date:** December 19, 2014
- **FDA Approved Indications:**
  - Complicated Intra-Abdominal Infections (cIAI)
  - Used in combination with metronidazole
  - Complicated Urinary Tract Infections (cUTI)
    - Including pyelonephritis

**Microbiological Spectrum:**
- Broad Gram negative coverage
  - Pseudomonas aeruginosa
  - Acinetobacter baumannii
  - Most ESBLs
  - No carbapenemases
    - Exception: Some strains of Pseudomonas
  - Gram positives: Streptococci

**Mechanism of Action**
- Target: Bacterial cell wall synthesis
- Binds penicillin binding proteins (PBPs)
- Bactericidal

**Pharmacokinetics**
- **Absorption:** IV only
- **Distribution:**
  - Ceftolozane: 16–21% protein bound
  - Tazobactam: 30% protein bound
- **Metabolism:**
  - Ceftolozane eliminated unchanged
  - Tazobactam is hydrolyzed to inactive metabolite (M1)
- **Elimination:** Renal

**Pharmacodynamics**
- **Time dependent killing**
- **Time > MIC**
- **No effect on cardiac electrophysiology**

**Renal Dose Adjustment Required**

<table>
<thead>
<tr>
<th>Estimated CrCl</th>
<th>Dose</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-50 mL/min</td>
<td>750 mg IV q8h</td>
<td></td>
</tr>
<tr>
<td>15-29 mL/min</td>
<td>375 mg IV q8h</td>
<td></td>
</tr>
<tr>
<td>ESRD or</td>
<td>750 mg IV x 1, then</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>150 mg IV q8h</td>
<td></td>
</tr>
</tbody>
</table>

**Duration of Treatment:**
- cIAI: 4-14 days
- cUTI: 7 days

**Decreased Efficacy in Patients with Baseline CrCl 30-49 mL/min**
- Monitor creatinine clearance at least daily in patients with changing renal function
- Adjust dose accordingly

**Hypersensitivity Reactions**
- Anaphylaxis possible

**Clostridium difficile-Associated Diarrhea**

**Development of Drug-Resistant Bacteria**
**CEFTOLOZANE/TAZOBACTAM (ZERBAXA®):**

**ADVERSE EFFECTS**

<table>
<thead>
<tr>
<th>Common</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea (7.9%)</td>
<td>2% permanently discontinued treatment (20/1032)</td>
</tr>
<tr>
<td>Diarrhea (6.2%)</td>
<td>1.9% in comparator arms</td>
</tr>
<tr>
<td>Headache (5.8%)</td>
<td>Renal impairment led to discontinuation in 0.5% (5/1015)</td>
</tr>
<tr>
<td>Pyrexia (5.6%)</td>
<td>None in comparator arms</td>
</tr>
</tbody>
</table>

**CLINICAL TRIALS**

**Complicated Intra-Abdominal Infections: ASPECT-cIAI**
- Design: Randomized, double-blind, multi-center phase III trial
  - Ceftolozane/tazobactam + metronidazole versus meropenem x 4-14 days
  - Appendicitis, cholecystitis, diverticulitis, gastric/duodenal/intestinal perforations, intra-abdominal abscess, peritonitis
- Patient Population (n=979)  
  - Mean age: 52 years  
  - 57.8% male  
  - 34.2% with diffuse peritonitis
- Results  
  - Ceftolozane/tazobactam non-inferior to meropenem  
  - 83% vs 87.3%  
  - Similar rates of adverse reactions

**Complicated Urinary Tract Infections: ASPECT-cUTI**
- Design: Randomized, double-blind, multi-center phase III trial
  - Ceftolozane/tazobactam versus levofloxacin x 7 days
  - Primary endpoint: Complete resolution or marked improvement and microbiologic eradication at test of cure visit 7±2 days after last dose
- Patient Population (n=1068)  
  - Mean age: 50.5 years  
  - 74% female  
  - 7.8% with bacteremia  
  - 82% with pyelonephritis
- Results  
  - Ceftolozane/tazobactam and levofloxacin response rates were similar when adjusted for baseline levofloxacin resistance  
  - 86.6% vs 79.7%  
  - Similar rates of adverse reactions

**SPECIAL POPULATIONS**

- Pregnancy Category B
- No lactation data
- No pediatric data
- Limited geriatric data
- Renal dose adjustment required
- No drug interactions!
TEDIZOLID PHOSPHATE

TEDIZOLID (SIVEXTRO®)

- Tedizolid phosphate is the prodrug of tedizolid
- Class: 2nd Generation Oxazolidinone
- FDA Approval Date: June 20, 2014
- FDA Approved Indications:
  - Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

Microbiological Spectrum:
- Gram positives
  - Staphylococci
  - MRSA
  - Streptococci
  - Enterococci
  - VRE
- No Gram negatives, obligate anaerobes or atypicals

Mechanism of Action
- Target: Bacterial protein synthesis
- Binds 50s subunit of bacterial ribosome
- Bacteriostatic

Pharmacokinetics
- Absorption
  - F=91%, IV=PO
  - Cmax reached 3 hours after oral dose, 1 hour after IV
- Distribution
  - 70-90% protein bound
- Metabolism
  - Converted to tedizolid by phosphatases
  - No other metabolism
- Elimination
  - Hepatic
  - 82% fecal, 18% urine

Pharmacodynamics
- AUC/MIC best correlates with activity
- No effect on cardiac repolarization

TEDIZOLID (SIVEXTRO®)

DOSING & ADMINISTRATION

- 200 mg IV/PO every 24 hours
- Duration of Treatment: 6 days

Preparation
- Reconstitute with 4 mL SWFI
- Dilute in 250 mL NS
- Shaking may cause foaming
- Only compatible with NS
- Stable for 24 hours

Administration
- Give IV over 1 hour
- Compatibility with other drugs not established
- Oral may be administered with or without food
- Missed doses
  - Take ASAP, anytime up to 8 hours prior to next dose

WARNINGS & PRECAUTIONS

Patients with Neutropenia
- Safety and efficacy not adequately evaluated
- Reduced activity in animal models

Clostridium difficile-Associated Diarrhea

Development of Drug Resistant Bacteria
TEDIZOLID (SIVEXTRO®): ADVERSE EFFECTS

Common
- Nausea (8%)
- Headache (6%)
- Diarrhea (4%)
- Vomiting (3%)
- Dizziness (2%)
- Median time to onset: 5 days
- Less myelosupression?
- Less optic and peripheral neuropathy?

Serious
- Occurred in 1.8% of patients in trials (12/662)
- 0.5% permanently discontinued treatment (3/662)
- Less than comparator (linezolid, 0.9%)

TEDIZOLID (SIVEXTRO®): DRUG INTERACTIONS

No clinically significant interactions

Weak MAOI

TEDIZOLID (SIVEXTRO®): SPECIAL POPULATIONS

Pregnancy Category C
No human lactation data
No pediatric data

Insufficient geriatric data
No dose adjustments

TEDIZOLID (SIVEXTRO®): CLINICAL TRIALS

ESTABLISH 1 & 2
- Design: Randomized, double-blind, multicenter, non-inferiority
  - ABSSSI
  - Tedizolid 200 mg PO daily x 6 days versus linezolid 600 mg PO twice daily x 10 days
    - ESTABLISH-2: Minimum 1 day of IV therapy before PO
- Primary Endpoint
  - Early clinical response
  - ESTABLISH-1: No increase from baseline lesion at 48-72 hours after first dose and oral temperature ≤ 99.7°F
  - ESTABLISH-2: ≥ 20% decrease in lesion area at 48-72 hours after first dose

TEDIZOLID (SIVEXTRO®): CLINICAL TRIALS

ESTABLISH-1
- Patient Population (n=667)
  - Median age: 43 years (18-86)
  - 84% Caucasian
  - 61% Male
- Results
  - Tedizolid non-inferior to linezolid
  - Early clinical response: 79.5% vs 79.4%
  - Similar rates of adverse events

ESTABLISH-2
- Patient Population (n=666)
  - Median age: 46 years (17-86)
  - 86% Caucasian
  - 68% Male
- Results
  - Tedizolid non-inferior to linezolid
  - Early clinical response: 85% vs 83%
  - Similar rates of adverse events

ORITAVANCIN
ORITAVANCIN (ORBACTIV®)

Class: 2nd Generation Lipoglycopeptide
FDA Approval Date: August 6, 2014

FDA Approved Indications:
• Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

Microbiological Spectrum: Gram positives
• Staphylococci
  • MRSA
• Streptococci
• Enterococci

Mechanism of Action
• Target: Bacterial cell wall synthesis
• Inhibits peptidoglycan synthesis
• Disrupts bacterial membrane integrity
• Bactericidal

Pharmacokinetics
• Absorption: IV only
• Distribution: 85% protein bound
• Metabolism: Not metabolized
• Elimination: Slowly excreted in feces and urine
  • Terminal half life = 245 hrs

Pharmacodynamics
• AUC/MIC
• No effect on QTc interval

Dose: 1200 mg IV x 1

Preparation
• 400 mg vials
• Reconstitute with 40 mL SWFI
• Dilute in 1000 mL D5W
  • Incompatible with NS
• Stable 6 hours (RT) or 12 hours (refrigerated)

Administration
• Give over 3 hours
• Compatibility with other drugs not established
  • Do not co-administer

Potential Risk of Bleeding with Concomitant Warfarin Use
• Warfarin exposure may be increased

Coagulation Test Interference
• Artificial prolongation of PT-INR for up to 24 hours and aPTT for up to 48 hours
• Non-phospholipid dependent test (chromogenic anti-Xa) may be used if unavoidable

Hypersensitivity
Infusion Reactions
Clostridium difficile-Associated Diarrhea
Osteomyelitis
Development of Drug Resistant Bacteria

Common
• Headache (7.1%)
• Nausea (9.9%)
• Vomiting (4.6%)
• Limb & subcutaneous abscesses (3.8%)
• Diarrhea (3.7%)

Serious
• Discontinued due to adverse reactions in 3.7% (36/976)
  • Cellulitis (4/976)
  • Ostemyelitis (3/976)
• Delayed hypersensitivity reactions?
  • Not reported
**ORITAVANCIN (ORBACTIV®): DRUG INTERACTIONS**

- Weak inhibitor: CYP 2C9, 2C19
- Weak inducer: CYP 3A4, 2D6
- Unfractionated Heparin Contraindicated
- Warfarin

**ORITAVANCIN (ORBACTIV®): SPECIAL POPULATIONS**

- Pregnancy Category C
- No human lactation data
- No pediatric data
- Insufficient geriatric data
- Caution in renal impairment
- Not studied in severe hepatic impairment

**ORITAVANCIN (ORBACTIV®): CLINICAL TRIALS**

**SOLO 1 & 2**
- **Design:** Randomized, double-blind, non-inferiority, phase III trial
- Oritavancin 1200 mg IV x 1 or vancomycin 1000 mg or 15 mg/kg IV q12h x 7-10 days
- Adults with ABSSSI (cellulitis, abscess, wound infection)
- Excluded if received antibiotics in 14 days prior to randomization
- **Primary Endpoint**
  - Cessation of the spread of erythema, temperature ≤ 99.7°F, and lack of use of rescue antibiotics 48-72 hours into treatment
- **Secondary Endpoints**
  - Clinical cure 7-14 days after treatment (investigator determined)
  - Lesion size reduction ≥ 20% 48-72 into treatment

**Patient Population**
- **SOLO-1** (n=954)
  - Mean age: 46 years
  - 63% male
  - 58% Caucasian
- **Results**
  - Primary: 82.3% vs 78.9%
  - Clinical cure: 79.6% vs 80%
  - Lesion size: 86.9% vs 82.9%
- **SOLO-2** (n=1005)
  - Mean age: 45 years
  - 67% male
  - 71% Caucasian
- **Results**
  - Primary: 80.1% vs 82.9%
  - Clinical cure: 82.7% vs 80.5%
  - Lesion size: 85.9% vs 85.3%

**ORITAVANCIN (ORBACTIV®): CLINICAL TRIALS**

**SOLO-1**
- **Patient Population** (n=954)
- **Results**
  - Primary: 82.3% vs 78.9%
  - Clinical cure: 79.6% vs 80%
  - Lesion size: 86.9% vs 82.9%

**SOLO-2**
- **Patient Population** (n=1005)
- **Results**
  - Primary: 80.1% vs 82.9%
  - Clinical cure: 82.7% vs 80.5%
  - Lesion size: 85.9% vs 85.3%

Oritavancin non-inferior to vancomycin.

**DALBAVANCIN (DALVANCE®)**

- **Class:** 2nd Generation Lipoglycopeptide
- **FDA Approval Date:** May 23, 2014
- **FDA Approved Indications:**
  - Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

[Image of Dalvance bottle]
**Microbiological Spectrum: Gram positives**
- Staphylococci
- MRSA
- Streptococci
- Enterococci

**Mechanism of Action**
- Target: Bacterial cell wall synthesis
- Inhibits peptidoglycan synthesis
- Disrupts bacterial membrane integrity
- Bactericidal

**Pharmacokinetics**
- Absorption: IV only
- Distribution: 93% protein bound
- Metabolism: Not a CYP substrate
- Minimal: Hydroxy-dalbavancin
- Elimination: Renal and fecal

**Pharmacodynamics**
- AUC/MIC: No effect on cardiac electrophysiology

**DOSING & ADMINISTRATION**
- Initial Dose: 1000 mg IV x 1
- Follow Up Dose (7 days later): 500 mg IV x 1
- CrCl < 30 mL/min: 750 mg IV x 1, then 375 mg IV x 1

**Preparation**
- 500 mg vials
- Reconstitute with 25 mL SWFI
- Dilute with D5W
  - Final concentration: 1-5 mg/mL
  - Stable 48 hours

**Administration**
- Give over 30 minutes
- Compatibility with other drugs not established

**ADVERSE EFFECTS**

<table>
<thead>
<tr>
<th>Common</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea (5.5%)</td>
<td>Occurred in 6.1% (109/1778)</td>
</tr>
<tr>
<td>Headache (4.7%)</td>
<td>6.5% in comparator arm</td>
</tr>
<tr>
<td>Diarrhea (4.4%)</td>
<td>Led to treatment discontinuation in 3% (53/1778)</td>
</tr>
<tr>
<td>Rash (2.7%)</td>
<td>ALT elevations &gt; 3x ULN more common</td>
</tr>
<tr>
<td>Pruritus (2.1%)</td>
<td>0.8% vs 0.2%</td>
</tr>
<tr>
<td>Median duration: 4 days</td>
<td></td>
</tr>
</tbody>
</table>

**WARNINGS & PRECAUTIONS**
- Hypersensitivity Reactions
- Infusion Reactions
- *Clostridium difficile*-Associated Diarrhea
- Hepatic Effects
- Development of Drug-Resistant Bacteria

**SPECIAL POPULATIONS**
- Pregnancy Category C
- No lactation data
- No pediatric data
- Limited geriatric data
- Renal dose adjustment, studied in HD
- No data for moderate to severe hepatic impairment

No drug-drug or drug-lab interactions!
**DISCOVER 1 & 2**
- **Design:** Randomized, double-blind, double-dummy, multi-center, non-inferiority phase III trials
  - Dalbavancin versus vancomycin for at least 3 days
  - Option to switch to oral linezolid to complete 10-14 days of treatment
  - Adults with ABSSSI (cellulitis, abscesses, wound infections)
- Excluded if used antibiotics within the previous 14 days
- **Primary Endpoint**
  - Early clinical response: Cessation of spread of infection-related erythema and the absence of fever at 48-72 hours
- **Secondary Endpoints**
  - Clinical status at end of therapy
  - Investigator’s assessment of outcome at end of therapy

**Patient Population (n=1312)**
- Mean age: 48.9 years (18-85)
- 90% Caucasian
- 60% male
- No significant differences between groups

**Results**
- Early clinical response: 79.7% dalbavancin vs 79.8%
- Secondary outcomes
  - Clinical status: 90.7% dalbavancin vs 92.1%
  - Assessment of outcome: 96% dalbavancin vs 96.7%
- Less adverse events and shorter duration in dalbavancin group

**DALBAVANCIN (DALVANCE®): CLINICAL TRIALS**

**ASSESSMENT**
The use of unfractionated heparin is contraindicated during the 48 hours following the administration of which of the following antimicrobials:

A. Oritavancin  
B. Ceftolozane/tazobactam  
C. Dalbavancin  
D. Tedizolid  
E. Ceftazidime/avibactam

Answer A (slide 62)

**FYI ONLY: NEW ANTIVIRALS**

<table>
<thead>
<tr>
<th>Influenza</th>
<th>HIV</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Peramivir (Rapivab) – 12/2014</td>
<td></td>
<td></td>
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<tr>
<td>• Dolutegravir/abacavir/lamivudine (Triumeq) – 8/2014</td>
<td></td>
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<tr>
<td>• Darunavir/cobicistat [Prezatix] – 1/2015</td>
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<tr>
<td>• Atazanavir/cobicistat [Evotaz] – 1/2015</td>
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</tr>
<tr>
<td>• Ledipasvir/sofosbuvir (Harvoni) – 10/2014</td>
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</tr>
<tr>
<td>• Paritaprevir/ritonavir/ombitasvir, dasabuvir (Viekkor Pak) – 12/2014</td>
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<td></td>
</tr>
</tbody>
</table>

**FYI ONLY: NEW TOPICAL AGENTS**

**Topical Antifungals**
- • Efinacozole (Jubia) solution – 6/2014  
- • Luliconozole (Luzu) cream – 11/2013

**Topical Antibacterials**
- • Finafloxacin Otic Suspension (Xtoro) – 12/2014
<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Phase</th>
<th>Enterobacteriaceae</th>
<th>Pseudomonas spp.</th>
<th>Acinetobacter spp.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>ESBL</td>
<td>KPC</td>
<td>NDM</td>
</tr>
<tr>
<td>Meropenem + RPX709</td>
<td>Carbapenem + BI1</td>
<td>3</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Ceftrazoline + avibactam</td>
<td>Cephalosporin + BI1</td>
<td>2</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
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<tr>
<td>Imipenem + relebactam</td>
<td>Carbapenem + BI1</td>
<td>2</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
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<tr>
<td>Plazomicin</td>
<td>Amino-glycoside</td>
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<td>Y</td>
<td>Y</td>
<td>?</td>
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<tr>
<td>Eravacycline</td>
<td>Fluorocycline</td>
<td>2</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
</tr>
<tr>
<td>Brilacidin</td>
<td>Peptide defense protein mimetic</td>
<td>2</td>
<td>Y</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

BLI = Beta Lactamase Inhibitor, NDM = New Delhi Metallo-Beta-Lactamase, WT = Wild Type, KPC = Klebsiella pneumoniae Carbapenemase, MDR = Multi-Drug Resistant