Qualified Infectious Disease Products (QIDP): Review of Recently Approved Anti-Infectives

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Unapproved Indications

– The material in this CME activity will include discussion of unapproved or investigational uses and will be noted where appropriate
  - Ceftazidime-Avibactam (Avycaz™)
  - Isavuconazonium (Cresemba®)

The opinions and content in this presentation are based on my personal views and do not reflect positions or policies of the FDA.

Learning Objectives

At the conclusion of this activity, the participant will be able to:
1. Define Qualified Infectious Disease Product (QIDP)
2. Review the clinical indications of recently approved QIDPs
3. Describe the pharmacology and pharmacokinetics of recently approved QIDPs
4. Identify potential adverse events, contraindications, and other safety precautions associated with the use of recently approved QIDPs

Centers for Disease Control and Prevention (CDC)

Each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections.


Part 1

QIDP
GAIN Act

Part 2

QIDPs Approved in 2015
Ceftazidime-Avibactam (Avycaz™)
Isavuconazonium (Cresemba®)

FDA Safety and Innovation Act of 2012 (FDASIA)

• Title IV
  - Biosimilar User Fee Act (BsUFA)
• Title VIII
  - Generating Antibiotic Incentives Now (GAIN)
• Title IX
  - Drug Approval and Patient Access
• Title XI
  - Other Provisions
Title VIII: GAIN

- Encourage development of antibacterial and antifungal drugs for the treatment of serious or life threatening infections
- Provide incentives for the development of certain antibacterial and antifungal drug products designated as QIDP
  - QIDP is “an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections”
  - Antibacterial or antifungal resistant pathogen, including novel or emerging infectious pathogens
  - Qualifying pathogens listed in FDASIA Title VIII

GAIN: Examples of Qualifying Pathogens

- Resistant Gram-positive bacteria
  - Methicillin-resistant Staphylococcus aureus (MRSA)
  - Vancomycin-resistant Staphylococcus aureus (VRSA)
  - Vancomycin-resistant enterococcus (VRE)
- Multi-drug resistant Gram-negative bacteria
  - Acinetobacter spp.
  - Klebsiella spp.
  - Pseudomonas spp.
  - Escherichia coli
- Clostridium difficile
- Multi-drug resistant tuberculosis (MDR-TB)

How often is the list updated?
“Every 5 years, or more often as needed, the Secretary shall review, provide modifications to, and publish the list of qualifying pathogens…”

GAIN: Incentives

- Additional 5 years exclusivity granted at the time of approval for products that have been granted a QIDP designation
- Priority review for marketing applications for products that have a QIDP designation
- Products that have been granted a QIDP designation are eligible for fast track designation

Fast Track Designation

- Fast Track accelerates new drug development and review
  - Drugs with the potential to address unmet medical needs
- FDA allocates increased level of communication to drug developers
  - Enables FDA/CDER to review portions of a drug application ahead of the submission of the complete application
- Seventeen of the 2014 novel new drugs (41%) were designated by FDA/CDER as Fast Track

GAIN: Other Provisions

- FDA
  - Review and update, as appropriate, at least 3 guidances per year for development of antibacterial and antifungal drugs
  - Provide written recommendations for nonclinical and clinical study protocols, and for nonclinical and clinical study requirements for products with QIDP designation
  - Publish a guidance on pathogen-focused antibacterial drug development
- HHS
  - Provide a report to Congress within 5 years of enactment

New Drug Applications (NDAs) Approved with QIDP Designation

1. Dalbavancin May 2014
2. Tedizolid June 2014
3. Oritavancin August 2014
4. Ceftolozane-Tazobactam December 2014
5. Ceftazidime-Avibactam February 2015
6. Isavuconazonium March 2015
**NDAs Approved with QIDP Designation**

**Gram-Positive Coverage**
Acute bacterial skin and skin structure infections (ABSSSI)

- **Dalbavancin (Dalvance™)**
  - Lipoglycopeptide (IV)
- **Tedizolid (Sivextro®)**
  - Oxazolidinone (oral and IV)
- **Oritavancin (Orbactiv™)**
  - Lipoglycopeptide (IV)

**Gram-Negative Coverage**
- Complicated intra abdominal infections plus metronidazole
- Complicated urinary tract infections including pyelonephritis

- **Ceftolozane-Tazobactam (Zerbaxa™)**
  - Cephalosporin/β-lactamase inhibitor (IV)
- **Ceftazidime-Avibactam (Avycaz™)**
  - Cephalosporin/β-lactamase inhibitor (IV)

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**NDAs Approved with QIDP Designation**

**Antifungal Coverage**

- **Isavuconazonium (Cresemba®)**
  - Triazole (oral and IV)

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**Ceftazidime-Avibactam Microbiology**

- **Ceftazidime**
  - 3rd generation cephalosporin
  - In vitro activity against certain Gram-negative and Gram-positive bacteria (%T>MIC)
  - Bactericidal action: penicillin binding proteins (PBP's)
- **Avibactam**
  - Non-beta-lactam, beta-lactamase inhibitor
  - Protects ceftazidime from degradation by certain beta-lactamase inhibitors
  - No direct antibacterial activity

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**Approved Beta-Lactamase Inhibitors**

- **Amoxicillin-Clavulanic acid** Augmentin®
- **Ticarcillin-Clavulanic acid** Timentin®
  - Discontinued in 2014
- **Ampicillin-Sulbactam** Unasyn®
- **Piperacillin-Tazobactam** Zosyn®

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**Imipenem-Cilastatin (Primaxin®)**

Cilastatin is NOT a beta-lactamase inhibitor
Ceftazidime-Avibactam

**Microbiology**
- What makes this a QIDP?
- In *vivo* activity:
  - *Pseudomonas aeruginosa*: Some AmpC beta-lactamases
- No activity against: metallo-beta-lactamases

**Pharmacokinetics**
- Absorption
  - IV only
- Distribution
  - Protein binding: <10% (both)
- Metabolism
  - Limited (both)
- Elimination
  - Ceftazidime: 80-90% renal, T1/2(h) = 2.76'
  - Avibactam: 85% renal, T1/2(h) = 2.71'

(terminal half-life, multiple doses 2.5 g IV Q8H as 2 hour infusions)

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Ceftazidime-Avibactam

**Approved Indications**
- Complicated intra-abdominal infections (+metronidazole)
  - Phase 2, randomized, blinded, multicenter
  - Comparator: meropenem
- Complicated UTIs, including pyelonephritis
  - Phase 2, randomized, blinded, multicenter
  - Comparator: imipenem-cilastatin
- Phase 2 studies were not designed with any formal hypotheses for inferential testing against the active comparator
- Efficacy supported in part by previous findings of efficacy and safety of Ceftazidime

Ceftazidime-Avibactam

**Approved Dosing**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommended Dose and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complicated intra-abdominal infections (±metronidazole)</td>
<td>2.0 g (1 g/12 h) intravenously over 1 hour, every 8 hours</td>
</tr>
<tr>
<td>Complicated urinary tract infections, <strong>including pyelonephritis</strong></td>
<td>2.0 g (1 g/12 h) intravenously over 1 hour, every 8 hours</td>
</tr>
<tr>
<td><strong>Hepatic Impairment:</strong> No change considered necessary</td>
<td></td>
</tr>
</tbody>
</table>

**Contraindications**
- Serious hypersensitivity to ceftazidime, avibactam, or other members of the cephalosporin class

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Ceftazidime-Avibactam

**Adverse Reactions** (≥10% in clinical studies)
- Vomiting
- Nausea
- Constipation
- Anxiety

**Drug Interactions**
- Probenecid: potential to decrease elimination of avibactam

**Pregnancy Category:** B
Ceftazidime-Avibactam
Unapproved Indication

- A Phase III, Randomized, Multicenter, Double-blind, Double-dummy, Parallel-group Comparative Study to Determine the Efficacy, Safety And Tolerability of Ceftazidime-Avibactam Versus Meropenem in the Treatment of Nosocomial Pneumonia Including Ventilator-Associated Pneumonia in Hospitalized Adults
- ClinicalTrials.gov Identifier: NCT01808092
- Currently recruiting

Part 2
NDAs approved in 2015 (QIDP)

Ceftazidime-Avibactam
(Avycaz™)

Isavuconazonium
(Cresemba®)

Isavuconazonium (Cresemba®)

- Pro-drug of isavuconazole
- Triazole antifungal agent

What makes this a QIDP?
- Invasive Aspergillosis
- Invasive Mucormycosis

Isavuconazonium Nomenclature

- Capsule
  - 186 mg of isavuconazonium sulfate
  - equivalent to 100 mg of isavuconazole
- Vial for Injection
  - 372 mg of isavuconazonium sulfate
  - equivalent to 200 mg of isavuconazole

Isavuconazonium Nomenclature

Challenges in Labeling Nomenclature

- USP Salt Policy (USP <1121>): When an active ingredient (drug substance) in a drug product is a salt, the nonproprietary (established) name of the drug product should contain the name of the active moiety and not the name of the salt. In addition, the strength also should be expressed in terms of the active moiety.
- Statute (FD&C Act; 21 U.S.C. 352(e) (1) (A) (ii)) requires name and the amount of the active ingredient (salt) to be provided

Isavuconazonium Nomenclature

<table>
<thead>
<tr>
<th>Table 1. Dosage Regimen for CREsemba</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting Dose</strong></td>
</tr>
<tr>
<td>1 capsule (372 mg)</td>
</tr>
<tr>
<td>every 5 hours for 6 doses (36 hours)</td>
</tr>
<tr>
<td>2 capsules (744 mg)</td>
</tr>
<tr>
<td>every 5 hours for 6 doses (36 hours)</td>
</tr>
</tbody>
</table>

Isavuconazonium Nomenclature

Cresemba® capsule formulation contains 186 mg of isavuconazonium sulfate equivalent to 100 mg of isavuconazole. The starting dose is 1 capsule every 5 hours for 6 doses (36 hours). After the sixth dose, the maintenance dose should be administered every 5 hours for 100 mg of isavuconazole.
Isavuconazonium Nomenclature

Searches Performed on 2/23/2015

- PubMed
  - Isavuconazonium: 1 result
  - Isavuconazole: 95 results
- Embase
  - Isavuconazonium: 48 results
  - Isavuconazole: 262 results
- Google Scholar
  - Isavuconazonium: 51 results
  - Isavuconazole: 893 results

Isavuconazonium Microbiology

- Inhibits the synthesis of ergosterol
  - Cytochrome P-450 dependent enzyme lanosterol 14-alpha demethylase (converts lanosterol to ergosterol)
  - Weakens the membrane structure and function
- In vitro activity and clinical infections
  - Aspergillus flavus
  - Aspergillus fumigatus
  - Aspergillus niger
  - Mucorales
    - Rhizopus oryzae
    - Mucormycetes species

Isavuconazonium Pharmacokinetics

- Absorption
  - Absolute bioavailability = 98%
- Distribution
  - 450 L, >99% protein bound
- Metabolism:
  - Isavuconazonium: esterases
  - Isavuconazole: cytochrome P450 enzymes 3A4 and 3A5
- Excretion:
  - Isavuconazole: <1% renal, T_{1/2} (h) = 130
- Pharmacokinetic/Pharmacodynamic Relationship
  - No significant association between plasma AUC or plasma concentration and efficacy

Isavuconazonium Pharmacokinetics

- Trial 1: Invasive Fungal Disease Caused by Aspergillus Species or Other Filamentous Fungi
  - Randomized, double-blind, non-inferiority
  - Comparator: Voriconazole

<table>
<thead>
<tr>
<th>Table 7. All-Cause Mortality Through Day 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRESEMBA</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>ITT</td>
</tr>
</tbody>
</table>

ITT = intent to treat population (≥ 1 dose)

Isavuconazonium Clinical Trials

- Trial 2: Invasive Mucormycosis (US: ~500 cases/year)
  - Prospective, open-label, non-comparative
  - No Comparator (historical control, untreated mucormycosis)
  - Efficacy not evaluated in controlled clinical trials

<table>
<thead>
<tr>
<th>Table 10. All-Cause Mortality and Overall Response Success in Mucormycosis Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
</tr>
<tr>
<td>All-cause Mortality Through Day 42</td>
</tr>
<tr>
<td>7 (13%)</td>
</tr>
</tbody>
</table>

Isavuconazonium Dosage and Administration

- IV: in-line filter (0.2 – 1.2 micron) over at least 1 hour, avoid vibration of vigorous shaking (do not use pneumatic transport)
- PO: with or without food

Renal Impairment: no dose adjustment (mild, moderate, severe)
Hepatic Impairment: no dose adjustment (mild, moderate)
Isavuconazonium

Contraindications

- Hypersensitivity to isavuconazonium
- Coadministration with strong CYP3A4 inhibitors
- Coadministration with strong CYP3A4 inducers
- Use in patients with familial short QT syndrome

Isavuconazonium QT Shortening

- Short QT syndrome (SQTS) is a rare genetic condition
  - Defined as a QT interval < 320 msec
- Dose-related shortening of QTc interval
  - 2 Capsules: -13.1 msec at 2 hours post-dose
  - 6 Capsules: -24.6 msec at 2 hours post-dose
- Not evaluated in combination with other agents known to reduce the QTc interval (additive effects unknown)
- Risk to general population unknown

  - Rufinamide (Banzel®)
    - ≥2400 mg twice daily: -20 msec

Isavuconazonium

Warnings and Precautions

- Hepatic adverse drug reactions
- Infusion-related reactions
- Hypersensitivity reactions
- Embryo-fetal toxicity
- Drug interactions
- Drug particulates
- Pregnancy Category: C

Isavuconazonium

Adverse Reactions

- ≥10% in two Phase 3 clinical studies (N=403)
  - Nausea (26%)
  - Vomiting (25%)
  - Diarrhea (22%)
  - Headache (17%)
  - Elevated liver tests (16%)
  - Hypokalemia (14%)
  - Constipation (13%)
  - Dyspnea (12%)
  - Cough (12%)
  - Peripheral edema (11%)
  - Back pain (10%)

- Discontinuation
  - 14% isavuconazonium
  - 23% voriconazole

- Elevated liver tests
  - 17% isavuconazonium
  - 24% voriconazole

Isavuconazonium

Drug Interactions

- Contraindicated
  - Ketoconazole
    - 5-fold ↑ in isavuconazonium exposure
  - Rifampin
    - 97% ↑ in isavuconazonium exposure

- Use with caution
  - Lopinavir/Ritonavir
  - Atorvastatin
  - Cyclosporine
  - Sirolimus
  - Tacrolimus
  - Midazolam
  - BuPROPion
  - Mycophenolate
  - Digoxin

Isavuconazonium

Unapproved Indication

- A Phase III, Double-blind, Randomized Study to Evaluate the Safety and Efficacy of BAL8557 (Isavuconazonium) Versus Caspofungin Followed by Voriconazole in the Treatment of Candidemia and Other Invasive Candida Infections
- ClinicalTrials.gov Identifier: NCT00413218
- Ongoing, not recruiting
Questions/Comments

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