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

Timothy Jancel, PharmD, BCPS (AQ-ID)
Safety Evaluator
FDA|CDER|OSE|DPV

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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

CDC Report: *Antibiotic Resistance Threats in the United States, 2013*

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)

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NDAs Approved with QIDP Designation
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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Part 2

NDAs approved in 2015 (QIDP)

Ceftazidime-Avibactam (Avycaz™)

Isavuconazonium (Cresemba®)

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Ceftazidime-Avibactam Microbiology

- **Ceftazidime**
  - 3rd generation cephalosporin
  - *In vitro* activity against certain Gram-negative and Gram-positive bacteria (%fT>MIC)
  - Bactericidal action: penicillin binding proteins (PBPs)
- **Avibactam**
  - **Non-beta-lactam,** beta-lactamase inhibitor
  - Protects ceftazidime from degradation by certain beta-lactamase inhibitors
  - No direct antibacterial activity

4:1 Ratio

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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®

Imipenem-Cilastatin (Primaxin®)
*Cilastatin is **NOT** a beta-lactamase inhibitor*

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Ceftazidime-Avibactam Microbiology

- What makes this a QIDP?
- *In vitro* activity:
  - **Enterobacteriaceae:** Some beta-lactamases and extended-spectrum beta-lactamases: TEM, SHV, CTX-M, *Klebsiella pneumoniae* carbapenemase (KPCs), AmpC, certain oxacillinases (OXA)
  - ***Pseudomonas aeruginosa:*** Some AmpC beta-lactamases
- No activity against: metallo-beta-lactamases, bacteria that overexpress efflux pumps or porin mutations

Ceftazidime-Avibactam Pharmacokinetics

- **A**bsorption
  - IV only
- **D**istribution
  - Protein binding: <10% (both)
- **M**etabolism
  - Limited (both)
- **E**limination
  - Ceftazidime: 80-90% renal, $T_{1/2}$ (h) = 2.76*
  - Avibactam: 85% renal, $T_{1/2}$ (h) = 2.71*

*terminal half-life, multiple doses 2.5 gm Q8H as 2 hour infusions

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 1. Dosage of AVYCAZ by Indication

Infection	*Dosage*	*Frequency*	*Infusion Time (hours)*	*Recommended Duration of Total Antimicrobial Treatment*
Complicated Intra-abdominal Infections [used in combination with metronidazole]	2.5 grams (2 grams/0.5 grams)	Every 8 hours	2	5 to14 days
Complicated Urinary Tract Infections including Pyelonephritis	2.5 grams (2 grams/0.5 grams)	Every 8 hours	2	7 to 14 days

DOSAGE AND ADMINISTRATION

Renal Dosing

Estimated Creatinine Clearance (mL/min)[a]	**Recommended Dosage Regimen for AVYCAZ** Infuse each dose intravenously over 2 hours
greater than 50	2.5 grams (2 grams/0.5 grams) every 8 hours
31 to 50	1.25 grams (1 grams/0.25 grams) every 8 hours
16 to 30	0.94 grams (0.75 grams/0.19 grams every 12 hours
6 to 15[b]	0.94 grams (0.75 grams/0.19 grams) every 24 hours
Less than or equal 5[b]	0.94 grams (0.75 grams/0.19 grams) every 48 hours

a As calculated using the Cockcroft-Gault formula.
b Both ceftazidime and avibactam are hemodialyzable; thus, administer AVYCAZ after hemodialysis on hemodialysis days.
Recommended duration of treatment: (2.1)
cIAI: 5 to 14 days
cUTI including pyelonephritis: 7 to 14 days

Hepatic Impairment: No change considered necessary

Ceftazidime-Avibactam

- **Warnings and Precautions**
  - Decreased efficacy in patients with baseline CrCl of 30-50 mL/min
    - Monitor CrCl at least daily in patients with changing renal function and adjust the dose accordingly
  - Hypersensitivity reactions
  - *Clostridium difficile*-associated diarrhea
  - Central nervous system reactions
  - Development of drug-resistant bacteria
- **Contraindications**
  - Serious hypersensitivity to ceftazidime, avibactam, or other members of the cephalosporin class

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

- 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

- **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

Table 1. Dosage Regimen for CRESEMBA

	Loading Dose	Maintenance Dose[c]
CRESEMBA for Injection 372 mg[a] of isavuconazonium sulfate per vial	1 reconstituted vial (372 mg[a]) intravenously every 8 hours for 6 doses (48 hours)	1 reconstituted vial (372 mg[a]) intravenously once daily
CRESEMBA Capsules 186 mg[b] of isavuconazonium sulfate per capsule	2 capsules (372 mg[a]) orally every 8 hours for 6 doses (48 hours)	2 capsules (372 mg[a]) orally once daily

[a] 372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole
[b] 186 mg of isavuconazonium sulfate is equivalent to 100 mg of isavuconazole
[c] Start maintenance doses 12 to 24 hours after the last loading dose

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

- **A**bsorption
  - Absolute bioavailability = 98%
- **D**istribution
  - 450 L, >99% protein bound
- **M**etabolism:
  - Isavuconazonium: esterases
  - Isavuconazole: cytochrome P450 enzymes 3A4 and 3A5
- **E**xcretion:
  - Isavuconazole: <1% renal, $T_{1/2}$ (h) = 130
- Pharmacokinetic/Pharmacodynamic Relationship
  - No significant association between plasma AUC or plasma concentration and efficacy

Isavuconazonium Clinical Trials

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

Table 7. All-Cause-Mortality Through Day 42

	CRESEMBA		Voriconazole	
	N	All-cause Mortality n (%)	N	All-cause Mortality n (%)
ITT	258	48 (18.6)	258	52 (20.2)

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 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%)

Isavuconazonium Dosage and Administration

Table 1. Dosage Regimen for CRESEMBA

	Loading Dose	Maintenance Dose[c]
CRESEMBA for Injection 372 mg[a] of isavuconazonium sulfate per vial	1 reconstituted vial (372 mg[a]) intravenously every 8 hours for 6 doses (48 hours)	1 reconstituted vial (372 mg[a]) intravenously once daily
CRESEMBA Capsules 186 mg[b] of isavuconazonium sulfate per capsule	2 capsules (372 mg[a]) orally every 8 hours for 6 doses (48 hours)	2 capsules (372 mg[a]) orally once daily

[a] 372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole
[b] 186 mg of isavuconazonium sulfate is equivalent to 100 mg of isavuconazole
[c] Start maintenance doses 12 to 24 hours after the last loading dose

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

*Circulation.2013;127:126-40

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%)

Trial 1 (N=516)
- 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

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