NEW FORCES IN THE MANAGEMENT OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

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Belgium

10 millions inhabitants …

10 Nobel prizes (10/850)

• **Peace**
  - Institute of International Law, Ghent (1904)
  - Auguste Beernaert (1909)
  - Henri Lafontaine (1913)
  - Father Dominique Pire (1958)

• **Literature**
  - Maurice Maeterlinck, Ghent (1911)

• **Medicine**
  - Jules Bordet, Brussels (1919)
  - Corneille Heymans, Ghent (1938)
  - Christian de Duve, Louvain (1974)
  - Albert Claude, Brussels (1974)

• **Chemistry**
  - Ilya Prigogyne, Brussels (1977)

• **Physics**
  - François Englert, Brussels (2013)
The Catholic University of Louvain in brief (1 of 4)

- originally founded in **1425** in the city of **Louvain** (in French and English; known as **Leuven** in Flemish)
The Catholic University of Louvain in brief (2 of 4)

- It was one of the major University of the so-called "Low Countries" in the 1500 – 1800 period, with famous scholars and discoverers (Vesalius for anatomy, Erasmus for philosophy, …). Teaching was in Latin, Greek, and Hebrew (College of the 3 languages…)

The University in the 1500's

Erasmus

Vesalius
The Catholic University of Louvain in brief (3 of 4)

• In the 19th century, teaching was in French but in the early 1900's, a Flemish-speaking section was opened. Courses were given in both languages, attracting many students and celebrities…

Professor C. de Duve, Professor of Biochemistry, obtained the Nobel Prize (Physiology and Medicine) in 1974 for his work on intracellular organelles (lysosomes, peroxisomes…)

(here in front of a centrifuge)

• in 1968, the University was divided into
  – a French-speaking Université catholique de Louvain
  – a Flemish-speaking Katholieke Universiteit Leuven…

Prof. G. Lemaitre, professor of Physics and Mathematics at the University who, in the 1930's, made the first suggestion of the continuous expansion of the Universe (“big bang”) (here in conversation with A. Einstein)
The Catholic University of Louvain in brief (4 of 4)

- The Flemish-speaking *Katholieke Universiteit Leuven* has remained in Louvain (Leuven) and is named in English *"Catholic Universiteit Leuven"*.
- The French-speaking *Université catholique de Louvain* has moved about 25 km South in a place called "Louvain-la-Neuve, with the "Health Sciences Sector" located in Brussels (Woluwe).

Together, the two Universities have about **55,000 students**
What do we do?

- Teaching of Pharmacology and Pharmacotherapy
- Post-graduate training on Drug Development
- Launching of Clinical Pharmacy in Europe
- Web-based courses on anti-infective Pharmacology
- 30 graduating students, doctoral fellows and post-graduate fellows working on anti-infective therapy (laboratory and clinical applications)

- Toxicity, medicinal chemistry, and improved schedules of aminoglycosides
- Novel antibiotics
  - beta-lactams (ceftaroline…)
  - fluoroquinolones (finafloxacine…)
  - ketolides (solithromycin…)
  - oxazolidinones (tedizolid …)

www.facm.ucl.ac.be

- Editorial board of AAC and IJAA
- Member of the General Committee of EUCAST (for ISC) and of its Steering committee (2008-10)
- Member of the Belgian Antibiotic Policy Coordination Committee
- Founder and Past President of the International Society of Antiinfective Pharmacology (ISAP)

www.isap.org

A partial view of our University Clinic (900 beds) and the Education and Research buildings (5,000 students), in the outskirts of Brussels, Belgium.
New antibiotics: what is your own view of the pipeline?

- dry?
- hopeless?
- messy?
- under repair?
- seamless?
- in good shape?
- of global concern?
New antibiotics: where are we?

Approvals by FDA/EMA – systemic antibiotics

DECLINING ANTIBACTERIAL APPROVALS (PAST 25 YEARS)

1983-1987  16
1988-1992  14
1993-1997  10
1998-2002  7
2003-2007  4
2008-2012  2

→ telavancin
→ ceftaroline
New antibiotics: where are we?

Approvals by FDA/EMA – systemic antibiotics

- dalbavancin
- oritavancin
- tedizolid
- ceftazidime/avibactam
- ceftolozane/tazobactam
- telavancin
- ceftaroline

Shall we succeed?
**Tedizolid**

**Synthesis and antibacterial activity of oxazolidinones containing pyridine substituted with heteroaromatic ring**

Yeong Woo Jo, a,b Weon Bin Im, b Jae Keol Rhee, b Mi Ja Shim, c Won Bae Kim b and Eung Chil Cho, a,*

a College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, Seoul 151-742, Korea
b Dong-A Pharmaceutical Co., Ltd., Research Laboratories, Yongin, Kyunggi 449-905, Korea
c Department of Life Science, The University of Seoul, Seoul 130-743, Korea

Received 29 July 2004; revised 18 August 2004; accepted 18 August 2004
Available online 11 September 2004

**Original article**

**Discovery of torezolid as a novel 5-hydroxymethyl-oxazolidinone antibacterial agent**

Weon Bin Im a,b, Sun Ho Choi b, Ju-Young Park a, Sung Hak Choi b, John Finn c, Sung-Hwa Yoon a,*

a Department of Molecular Science and Technology, Ajou University, San 5, Woncheon, Yeongtong, Suwon 443-749, Republic of Korea
b Dong-A Pharmaceutical Co., Ltd., Research Laboratories, Yongin 449-905, Republic of Korea
c Trius Therapeutics, 6310 Nancy Ridge Drive Suite 101, San Diego, CA 92121, USA
Dong-A pharmaceuticals and tedizolid: step #1

Replacing the morpholinyl by a pyridinyl and adding a methyl-tetrazolyl moiety
- increases activity
- prolongs half-life
Tedizolid has more interactions with the ribosome...

Fig. 2. Models of 11 (blue) and linezolid (yellow) binding to the *Escherichia coli* ribosome.
Tedizolid is systematically 3-4x more active than linezolid against LSD^S strains.

Table 1. Susceptibility of the strains of *S. aureus, L. monocytogenes* and *L. pneumophila* used in this study to linezolid and torezolid

<table>
<thead>
<tr>
<th>Species, phenotype and strain no.</th>
<th>MIC (mg/L)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>linezolid</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td></td>
</tr>
<tr>
<td>MSSA ATCC 25923^b</td>
<td>2</td>
</tr>
<tr>
<td>HA-MRSA ATCC 33591^b</td>
<td>1</td>
</tr>
<tr>
<td>SA 238^c</td>
<td>2</td>
</tr>
<tr>
<td>CM 05^d</td>
<td>8</td>
</tr>
<tr>
<td>CA-MRSA NRS 192^e</td>
<td>2</td>
</tr>
<tr>
<td>NRS 384 (US300)^e</td>
<td>2</td>
</tr>
<tr>
<td>VISA NRS 52^e</td>
<td>2</td>
</tr>
<tr>
<td>VRSA VRS 1^e</td>
<td>1–2</td>
</tr>
<tr>
<td>VRS 2^e</td>
<td>1–2</td>
</tr>
<tr>
<td>animal MRSA N7112046^f</td>
<td>2</td>
</tr>
<tr>
<td><strong>Listeria monocytogenes</strong></td>
<td></td>
</tr>
<tr>
<td>EGD^g</td>
<td>1–2</td>
</tr>
<tr>
<td><strong>Legionella pneumophila</strong></td>
<td></td>
</tr>
<tr>
<td>ATCC 33153^b</td>
<td>4–8</td>
</tr>
</tbody>
</table>

LZD^R, resistant to linezolid.
^aRepresentative values of at least two determinations.
^bFrom the American Tissue Culture Collection (Manassas, VA, USA).
^cProvided by P. C. Appelbaum.\[^36\]
^dProvided by J. P. Quinn, John H. Stroger Jr. Hospital, Rush University, Chicago, IL, USA.
^eFrom the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) programme (operated by Eurofins Medinet, Inc., Hendon, VA, USA; supported under NIAID/NIH contract no. HHSN2722007 00055C); details on each strain are available at http://www.narsa.net/content/horne.jsp.
^fProvided by Y. Glupczynski, Cliniques universitaires UCL de Mont Godinne, Yvoir, Belgium.
^gProvided by P. Berche, Hôpital Necker, Paris, France.\[^28\]

Lemaire et al. JAC 2009; 64:1035–1043
And even for *S. aureus* of different epidemiological origin…

**Activity of Tedizolid (TR-700) against Well-Characterized Methicillin-Resistant *Staphylococcus aureus* Strains of Diverse Epidemiological Origins**

*Kenneth S. Thomson, Richard V. Goering
Creighton University, Omaha, Nebraska, USA*

**TABLE 1 Drug activity against all MRSA isolates and epidemiological groups**

<table>
<thead>
<tr>
<th>Isolate(s)</th>
<th>Drug(s)</th>
<th>MIC range (µg/ml)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All isolates (<em>n = 111</em>)</td>
<td>Tedizolid</td>
<td>0.12 to 0.5</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>0.5 to 4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim/sulfamethoxazole</td>
<td>≤0.5/9.5 to &gt;2/38</td>
<td>&gt;2/38</td>
</tr>
<tr>
<td></td>
<td>Tigecycline</td>
<td>0.06 to &gt;1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin</td>
<td>0.12 to &gt;4</td>
<td>&gt;4</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>0.06 to &gt;16</td>
<td>&gt;16</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>≤0.25 to 4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Daptomycin</td>
<td>≤0.5 to 2</td>
<td>≤0.5</td>
</tr>
<tr>
<td></td>
<td>Oxacillin</td>
<td>0.12 to &gt;4</td>
<td>&gt;4</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>0.12 to &gt;8</td>
<td>&gt;8</td>
</tr>
<tr>
<td></td>
<td>Gentamicin</td>
<td>≤0.06 to &gt;16</td>
<td>&gt;16</td>
</tr>
</tbody>
</table>
Dong-A pharmaceuticals and tedizolid: step #2

2. replacing the acetamido by an hydroxyl maintains the increased activity vs. linezolid!
Tedizolid and linezolid resistance
Oxazolidinones: 1st mechanism of resistance

Chloramphenicol-florfenicol resistance (Cfr)

- First identified in several staphylococcal species (cattle, swine) (Schwarz 2000; Kehrenberg 2006)
- CM05 (Colombia) - first clinical isolate documented to carry the cfr gene (Toh 2007)
- C-8 methylation of ribosome target at A2503 (Kehrenberg 2005; Giessing 2009)
- PhLOPS_A phenotype leads to cross resistance to 6 drug classes!
  - Phenicols, Lincosamides, Oxazolidinones, Pleuromutilins, Streptogramin A and 16 membered macrolides (Long, 2006; Smith & Mankin 2008)
- Tedizolid retains potency against cfr strains and demonstrates 8 fold better activity than linezolid (Shaw 2008, Jones 2009, Livermore 2009, Locke 2009)
Activity against Cfr$^+$ resistant strains … (cfr$^+$ bacteria)

<table>
<thead>
<tr>
<th>Strain</th>
<th>Reference</th>
<th>Presence of cfr</th>
<th>MIC (µg/ml)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RN4220(pLI50)</td>
<td>68</td>
<td>−</td>
<td>2</td>
</tr>
<tr>
<td>RN4220(pLXM1)$^b$</td>
<td>68</td>
<td>+</td>
<td>8</td>
</tr>
<tr>
<td>CM05Δ$^c$</td>
<td>44</td>
<td>−</td>
<td>2</td>
</tr>
<tr>
<td>CM05$^c$</td>
<td>68</td>
<td>+</td>
<td>8</td>
</tr>
<tr>
<td>29213</td>
<td>ATCC</td>
<td>−</td>
<td>2</td>
</tr>
<tr>
<td>29213(p42262)$^d$</td>
<td>45</td>
<td>+</td>
<td>16</td>
</tr>
<tr>
<td>42262$^e$</td>
<td>51</td>
<td>+</td>
<td>16</td>
</tr>
</tbody>
</table>

$^a$ MICs (broth microdilution: CLSI)

$^b$ The pLXM1 cfr-containing plasmid is isogenic to the empty pLI50 vector.

$^c$ CM05Δ is isogenic to the CM05 clinical cfr-positive strain but lacks cfr and one copy of ermB.

$^d$ 29213(p42262) was generated through transformation of ATCC 29213

$^e$ 42262 is a clinical cfr-positive isolate from a 2008 hospital outbreak in Madrid, Spain.

Locke et al. AAC 2010;54:5337-5343
Why is tedizolid active against LZD\textsuperscript{R} strains (cfr) ?

![Chemical structures of LZD and TR700](image)

**FIG. 2.** Structural analysis of oxazolidinone binding in the presence of Cfr methylation. (A) Crystal structure of LZD-bound *H. marismortui* 50S ribosome (30). (B) Model of LZD binding in the Cfr-methylated state. (C and D) Proposed models of TR-700 bound to wild-type (C) or Cfr-methylated (D) ribosome. Substantial steric hindrance between the LZD C-5 acetamide group and the 23S rRNA base A2503 carbon-8 methyl (bonds shown in brown) likely contributes to reduced binding affinity (B). As modeled, the TR-700 hydroxymethyl substituent does not display this steric clash with the A2503 methyl group (D), explaining its retained activity against cfr strains. A group of PTC bases were removed from the images to improve clarity. Images were generated with PyMOL (16).

Locke et al. AAC 2010;54:5337-5343
Why is tedizolid active against LzdR strains (cfr) ?

Locke et al. AAC 2010;54:5337-5343
Do we need to be afraid of the \textit{cfr}+ linezolid resistance?

Clinical Outbreak of Linezolid-Resistant \textit{Staphylococcus aureus} in an Intensive Care Unit

Miguel Sánchez García, MD, PhD
Maria Angeles De la Torre, MD
Gracia Morales, PhD
Beatriz Peláez, PhD
María José Tolón, MD
Sara Domingo, MD
Francisco Javier Candela, MD, PhD
Raquel Andrade, PhD
Ana Arribi, MD, PhD
Nicolás García, MD
Fernando Martínez Sagasti, MD, PhD
José Ferreres, MD, PhD
Juan Picazo, MD, PhD

Context
Linezolid resistance is extremely uncommon in \textit{Staphylococcus aureus}.

Objective
To report an outbreak with linezolid and methicillin-resistant \textit{S. aureus} (LRSA) in an intensive care department and the effective control measures taken.

Design, Setting, and Patients
Outbreak study of consecutive critically ill patients colonized and/or infected with LRSA at an intensive care department of a 1000-bed tertiary care university teaching hospital in Madrid, Spain. Patients were placed under strict contact isolation. Daily updates of outbreak data and recommendations for the use of linezolid were issued. Extensive environmental sampling and screening of the hands of health care workers were performed.

Main Outcome Measures
Linezolid use and clinical and epidemiological characteristics and outcomes using minimal inhibitory concentrations, pulsed-field gel electrophoresis, and polymerase chain reaction of LRSA isolates.

Results
Between April 13 and June 26, 2008, 12 patients with LRSA were identified. In 6 patients, LRSA caused ventilator-associated pneumonia and in 3 patients it caused bacteremia.


BRIEF REPORT

Multicity Outbreak of Linezolid-Resistant \textit{Staphylococcus epidermidis} Associated with Clonal Spread of a \textit{cfr}-Containing Strain

Hector Bonilla,1 Michael D. Huband,2 Joan Seidel,1 Helen Schmidt,2 MaryKay Lescoe,3 Sandra P. McCurdy,2 M. Megan Lemmon,3 Lori A. Brennan,1 A. Tait-Kamradt,2 Laura Puzniak,4 and John P. Quinn1

1Summa Health System, Akron, and 2Robinson Memorial Hospital, Ravenna, Ohio; and 3Pfizer Global Research and Development, Groton, Connecticut

We report a multicity outbreak of \textit{cfr}-containing linezolid-resistant \textit{Staphylococcus epidermidis} in Ohio. Thirty-nine isolates were obtained from 2 hospitals. Two clones with different mechanisms of linezolid resistance were circulating in hospital A. One of these contained the \textit{cfr} gene, and the other a ribosomal mutation. The clone containing \textit{cfr} was identical in both hospitals.

Clin Infect Dis. 2010 Oct 1;51(7):796-800
Do we need to be afraid of the cfr+ linezolid resistance?

Horizontal gene transmission of the cfr gene to MRSA and Enterococcus: role of Staphylococcus epidermidis as a reservoir and alternative pathway for the spread of linezolid resistance

Fabio Cafini¹,²*, Le Thuy Thi Nguyen²,³, Masato Higashide⁴, Federico Román⁵, José Prieto¹ and Kazuya Morikawa²

¹Division of Microbiology, Department of Medicine, School of Medicine, Universidad Complutense, Avda Complutense s/n, 28040 Madrid, Spain; ²Division of Biomedical Science, Faculty of Medicine, University of Tsukuba, Tsukuba 305-8575, Japan; ³Human Biology Program, School of Integrative and Global Majors, University of Tsukuba, 1-1-1 Tennodai, Tsukuba 305-8577, Japan; ⁴Kotobiken Medical Laboratories, Inc., Kamiyokoba, Tsukuba 305-0584, Japan; ⁵Laboratory of Nosocomial Infections, Department of Bacteriology, Centro Nacional de Microbiologia, Instituto de Salud Carlos III, Majadahonda, Madrid, Spain

lates were obtained from 2 hospitals. Two clones with different mechanisms of linezolid resistance were circulating in hospital A. One of these contained the cfr gene, and the other a ribosomal mutation. The clone containing cfr was identical in both hospitals.

Clin Infect Dis. 2010 Oct 1;51(7):796-800
Oxazolidinones: 2d mechanism of resistance

Chromosomal 23S rRNA mutations

- Low frequency, but local outbreaks have been observed
- First clinical cases of resistant staphylococci and enterococci reported soon after linezolid approval in 2000 (Gonzales 2001; Tsiodras 2001)
- Tedizolid demonstrates 8-fold better potency against these strains (Shaw 2008, Jones 2009, Livermore 2009, Locke 2009)
- Mutations also observed in ribosomal proteins L3 and L4

loses about 2 to 4-fold activity but still
Tedizolid and ribosomal mutations

**TABLE 1. Oxazolidinone MICs for S. aureus ribosomal mutants**

<table>
<thead>
<tr>
<th>Strain&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Source or reference</th>
<th>Resistance mechanism&lt;sup&gt;b&lt;/sup&gt;</th>
<th>MIC (µg/ml)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>LZD</td>
</tr>
<tr>
<td>29213</td>
<td>ATCC</td>
<td>23S (G2447T ×3)</td>
<td>2</td>
</tr>
<tr>
<td>29213-1</td>
<td>43</td>
<td>23S (T2500A ×2)</td>
<td>32</td>
</tr>
<tr>
<td>29213-2</td>
<td>43</td>
<td>23S (T2500A ×2)</td>
<td>8</td>
</tr>
<tr>
<td>29213-3</td>
<td>43</td>
<td>L3 (ΔPhe127-His146)</td>
<td>8</td>
</tr>
<tr>
<td>33591</td>
<td>ATCC</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>33591-1</td>
<td>43</td>
<td>23S (G2576T ×3)</td>
<td>16</td>
</tr>
<tr>
<td>33591-2</td>
<td>43</td>
<td>23S (G2576T/T2571C ×3)</td>
<td>16</td>
</tr>
<tr>
<td>33591-3</td>
<td>43</td>
<td>L4 (Lys68Gln)</td>
<td>2</td>
</tr>
<tr>
<td>NRS127</td>
<td>NARSA&lt;sup&gt;d&lt;/sup&gt;</td>
<td>L3 (ΔSer145)</td>
<td>8</td>
</tr>
</tbody>
</table>

<sup>a</sup> ATCC 29213 and ATCC 33591 isogenic mutant panels were generated through selection in the presence of LZD and/or TR-700. NRS127 is an LZD<sup>e</sup> clinical isolate.

<sup>b</sup> Mutations in 23S rRNA genes (and mutant allele copy number) or in the ribosomal protein L3 or L4 are shown.

<sup>c</sup> MICs (broth microdilution; CLSI) were determined against the oxazolidinone panel.

<sup>d</sup> Network of Antimicrobial Resistance in *Staphylococcus aureus*.

Locke et al. AAC 2010;54:5337-5343

TDZ MICs are 8x < than LZD but 2-4x > than for wild type bacteria
Tedizolid has lower propensity to induce resistance

- Spontaneous frequency of resistance is 16-fold lower for tedizolid vs linezolid
- Serial passage experiment (30 cycles of selection)
  - Much more difficult to select resistance to tedizolid vs linezolid

Single mutation leads to resistance
Mutation frequency = $3 \times 10^{-9}$

Double mutation required
Mutation frequency = $2 \times 10^{-10}$

To sum up: what are the main differences between linezolid and tedizolid of interest at this point?

- **Linezolid (LZD)**
  - Additional methyl-tetrazolyl

- **Tedizolid (TR-700)**
  - Morpholinylin vs. pyridinyl
  - Acetamido vs. free -OH

Substantial differences that DO impact on:
- **intrinsic activity** (*more potent*)
- Full activity against *cfr+* resistant strains
- MICs < LZD for ribosomal mutants
Pharmacokinetics / Pharmacodynamics
Tedizolid clinical formulations

Tedizolid phosphate (pro-drug releasing tedizolid in vivo)

- stable at room temp for >2 yrs
- 2 formulations:
  - **IV** Lyophile: TR-701 FA Lyophilized Vial for Injection, 200 mg
  - **Oral** Tablet: TR-701 FA Immediate Release Tablet, 200 mg
Tedizolid vs Linezolid human pharmacokinetics:
oral doses (200 mg TR-701* q24h vs 600 mg linezolid q12h for 21 days.

Tedizolid:
- mean $t_{1/2} > 2 \times$ greater than linezolid
- longer initial presence at $> 0.5 \text{ mg/L}$ (vs. 4 mg/L for linezolid).

* TR-701: tedizolid phosphate

Human pharmacokinetics:
multiple doses and bioavailability

- Single-dose mean $C_{\text{max}}$ and AUC$_{0\text{-inf}}$ values of TR-700 increased in a dose proportional manner for TR-701 FA dose levels of 100 to 400 mg (1.16 to 5.13 µg/mL and 17.36 to 58.70 µg·hr/mL, respectively).

- A slight accumulation of ~28% was observed following multiple dosing and was predicted from single dose data.

- TR-700 concentrations were generally similar on Day 7 compared to Day 1 at the 200 mg dose level.

- The absolute bioavailability of TR-700 from TR-701 FA 200 mg tablets was 91.7%.

Tedizolid elimination …

- When using $^{14}$C-labelled tedizolid phosphate in humans, most of the radioactivity is excreted in feces.

Mean cumulative percentage of radioactive dose was recovered in urine and feces after single 204-mg (100-mCi) oral $^{14}$C-tedizolid phosphate to healthy male subjects. (+/- SD)

Dreskin H. et al, ICAAC 2011; Poster A2-033.
AUC$_{24h}$ and activity tedizolid

TZD activity depends on actual AUC$_{24h}$/MIC value, and is independent of the dosing schedule (in the limits investigated)

Louie et al. AAC 2011; 55:3453-3460
Tedizolid breakpoints… a matter of dispute?

1 mg/L for S. aureus is resistant

1 mg/L for S. aureus is intermediate

**Table 5 Susceptibility Test Interpretive Criteria for SIVEXTRO**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Minimum Inhibitory Concentrations (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Staphylococcus aureus (methicillin-resistant and methicillin-susceptible isolates)</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Streptococcus anginosus Group*</td>
<td>≤0.25</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>≤0.5</td>
</tr>
</tbody>
</table>

S=susceptible, I=intermediate, R=resistant

* Includes S. anginosus, S. intermedius, S. constellatus

2. SIVEXTRO (tedizoid) US prescription information (FDA defined breakpoint). Available at [http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205435s000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205435s000lbl.pdf)
Distribution of tedizolid in tissues
Activity of tedizolid towards intracellular bacteria

Cellular pharmacokinetics and intracellular activity of torezolid (TR-700): studies with human macrophage (THP-1) and endothelial (HUVEC) cell lines

Sandrine Lemaire¹, Françoise Van Bambeke¹, Peter C. Appelbaum² and Paul M. Tulkens¹*

¹Unité de Pharmacologie cellulaire et moléculaire & Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium; ²Hershey Medical Center, Hershey, PA 17033, USA
Accumulation and activity of tedizolid in macrophages

doi:10.1093/jac/dkp267
Advance Access publication 16 September 2009

Cellular pharmacokinetics and intracellular activity of torezolid (TR-700): studies with human macrophage (THP-1) and endothelial (HUVEC) cell lines

Sandrine Lemaire¹, Françoise Van Bambeke¹, Peter Kitovski²

¹Unité de Pharmacologie cellulaire et moléculaire & Louvain, Brussels, Belgium; ²Hershey Medical Center, Hershey, PA, USA
Tedizolid is active intracellularly against MRSA disregarding resistance phenotypes

Concentration-dependent effects of torezolid (TR-700) towards *S. aureus* with different resistance phenotypes after phagocytosis by THP-1 macrophages

Lemaire et al. JAC 2010; 64:1035–1043
Tedizolid accumulates in lung macrophages (and fluid) of healthy adults volunteers (200 mg dose)

Tedizolid distributes equally in muscle and adipose tissue (microdialysis) compared to plasma

The median ratios of $fAUC_{0-12h}$ in tissue / $fAUC_{0-12h}$ in plasma were

1.08 ± 0.22 for adipose and 1.22 ± 0.18 for muscle tissues, respectively.
Tedizolid safety
(preclinical and "experimental human")
Linezolid known adverse effects *

- Drug interactions:
  - cytochrome P450: no special effect
  - antibiotics: rifampin causes a 21 % drop in LZD serum levels
  - Monoamine Oxidase Inhibition (reversible, nonselective inhibitor):
    - adrenergic and serotonergic agents (PRECAUTIONS)

- Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) (WARNING)

- Hypoglycemia

- Lactic acidosis (PRECAUTION – Immediate medical attention)

- Peripheral and Optic Neuropathy (> 28 days)

- Convulsions

* Zyvox (linezolid) US Prescribing Information
Available at [http://www.accessdata.fda.gov/drugsatfda_docs lbl/2008/021130s016,021131s013,021132s014lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/lbl/2008/021130s016,021131s013,021132s014lbl.pdf)
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* Zyvox (linezolid) US Prescribing Information
Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021130s016,021131s013,021132s014lbl.pdf
Monoamine Oxidase (MAO) Substrate Specificity

Consequences of MAO-A Inhibition

Serotonin Syndrome

Hypertensive crisis

<table>
<thead>
<tr>
<th>MAO-A</th>
<th>MAO-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin</td>
<td>Noradrenaline</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>Adrenaline</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>Octopamine</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Tyramine&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tryptamine</td>
<td>Kynuramine</td>
</tr>
<tr>
<td>Kynuramine</td>
<td>3-methoxytyramine</td>
</tr>
<tr>
<td>Benzylamine</td>
<td>Phenylethylamine</td>
</tr>
<tr>
<td>N-phenylamine</td>
<td>Octylamine</td>
</tr>
<tr>
<td>N-acetylpumtrescine</td>
<td>Milacemide</td>
</tr>
<tr>
<td>N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> MAO-A is the predominate form for oxidation of tyramine. Elmer and Bertoni. *Expert Opin Pharmacother.* 2008;9:2759-2772
This is what we tell the pharmacists in Belgium ....

Interactions linezolid - médicaments

- Anti-migraineux: triptans, dihydroergotamine
- Anti-Parkinsoniens: L-Dopa, bromocryptine, selegiline
- Sympathomimétiques: bronchodilatatateurs, pseudoéphédrine
- Anti-psychotiques: clozapine, olanzapine, risperidone, lithium
- Anti-émétiques: setrons, metoclopramide
- Antitussifs: dextromethorphan, codéine
- Anxiolytiques: buspirone
- Anti-dépresseurs: tricycliques, IMAO, ISRS

Lawrence et al., CID (2006) 42:1578-83
5-HTP Mouse Head Twitch (Model of Serotonergic Effects)

**FIG 3** Mouse head twitch rate following tedizolid phosphate, linezolid, fluoxetine, or moclobemide treatment. Twitch frequency is shown as means ± SD (n = 8 mice/group). Tedizolid refers to tedizolid phosphate. *, P < 0.05 versus the control group.


Lack of MAO interactions at multiples ~30-fold above therapeutic tedizolid clinical peak exposure
Human data for blood pressure elevation

**FIG 2** Blood pressure response to 60 mg pseudoephedrine in placebo- and tedizolid phosphate-pretreated study populations. Patients \( n = 18 \) were randomized to oral placebo or oral tedizolid phosphate doses of 200 mg per day for 4 days; on the fifth day, 60 mg pseudoephedrine was administered with the morning dose of placebo or tedizolid phosphate, and blood pressure was recorded over the subsequent 24 h. Blood pressure was measured within 15 min prior to drug administration (Pre), every hour for 8 h after study drug administration, and at 10, 12, and 24 h.


Tedizolid has no effect on blood pressure vs placebo.
Linezolid known adverse effects *

- Drug interactions:
  - cytochrome P450: no special effect
  - antibiotics: rifampin causes a 21% decrease in LZD serum levels
  - Monoamine Oxidase Inhibition (reversible, nonselective inhibitor): adrenergic and serotonergic agents (PRECAUTIONS)

- Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) (WARNING)
- Hypoglycemia
- Lactic acidosis (PRECAUTION – Immediate medical attention)
- Peripheral and Optic Neuropathy (> 28 days)
- Convulsions

* Zyvox (linezolid) US Prescribing Information Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021130s016,021131s013,021132s014lbl.pdf
TEDIZOLID Phase I: platelets at 21 days *

* treatment duration in phase III is limited to 6 days
Summary of Tedizolid Non-clinical Safety Attributes

**No Drug-Drug Interactions**

- No inhibition or induction of human hepatic cytochrome P450 activities at high concentrations
- No tyramine or noradrenergic "Pressor potentiation Effect" (vs significant effect for linezolid)
- No serotonergic effect in head twitch model

**No Safety Pharmacology Issues Identified**

- No effects in pivotal cardiovascular, neurobehavioral, respiratory, or gastrointestinal systems
- No IKr or QTc signal with TR-700 at highest soluble dose
- No non-clinical genetic toxicology signals: Ames, Chrom Ab, Micronucleus, UDS
- No genotoxicity or reprotoxicity issues
- No effect on spermatogenesis
Tedizolid
Clinical development
Tedizolid phase III studies

Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections
The ESTABLISH-1 Randomized Trial

Philipp Prokocimer, MD
Carisa De Anda, PharmD
Edward Fang, MD
Purvi Mehta, MD
Anita Das, PhD

Importance Acute bacterial skin and skin structure infections (ABSSSIs), including cellulitis or erysipelas, major cutaneous abscesses, and wound infections, can be life-threatening and may require surgery and hospitalization. Increasingly, ABSSSIs are associated with drug-resistant pathogens, and many antimicrobial agents have adverse effects restricting their use. Tedizolid phosphate is a novel oxazolidinone in development for the treatment of ABSSSIs.


Articles

Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial

Gregory J Moran, Edward Fang, G Ralph Corey, Anita F Das, Carisa De Anda, Philippe Prokocimer

Background New antibiotics are needed to treat infections caused by drug-resistant bacteria. Tedizolid is a novel oxazolidinone antibacterial drug designed to provide enhanced activity against Gram-positive pathogens. We aimed to assess the efficacy and safety of intravenous to oral tedizolid for treatment of patients with acute bacterial skin and skin-structure infections.

## FDA new clinical guidance

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>cSSSI</td>
<td></td>
<td>ABSSSI</td>
</tr>
<tr>
<td>Infection Type</td>
<td>Large Abscess, Wound, Cellulitis, DFI, Chronic Ulcer</td>
<td>Large Abscess, Wound, Cellulitis – min. 75 cm²</td>
</tr>
<tr>
<td>Infection Severity</td>
<td>Intermediate/Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Primary Endpoints</td>
<td>Subjective Clinicians Assessment at 7-14 Days After EOT</td>
<td>Objective ≥20% reduction in lesion size at 48–72 hours</td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td>Varied</td>
<td>Higher Potential for differentiation</td>
</tr>
</tbody>
</table>

- ABSSI = acute bacterial skin and skin structure infections
- cSSSI = complicated skin and skin structure infections; including chronic ulcers, diabetic foot infections, and burns – very different in nature, treated differently (polymicrobial) and chronic

* The 2010 FDA Guidance primary endpoint: "Cessation of lesion spread & fever at 48-72 h" was updated in 2013

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# FDA new clinical guidance

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>ABSSI</td>
<td>cSSSI</td>
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<tbody>
<tr>
<td>Intermediate/Severe</td>
<td></td>
<td>Severe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>• Diffuse skin infection characterized by spreading of edema, redness, and heat ¹,²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• May accompany lymphangitis and regional lymph node inflammation ²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Erysipelas may be differentiated with raised skin lesions and clear demarcation line of affected and unaffected areas ²</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>• Purulent drainage with edema, redness, and/or induration of the surrounding wound ¹</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Involves the dermis and deeper skin tissues in the presence of pus collections ¹,²</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. see note * in the bottom of the slide  

* Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment (FDA - CDER -- October 2013)  
Measurement of Lesions

Measurement for All Lesions
Head-to-toe vs largest perpendicular width

Additional Measurement for Abscesses and Wounds* (at screening only)
Abscess/wound margin to perimeter of erythema, oedema, and/or induration/cellulitis

*Erythema extending at least 5cm in the shortest distance from the peripheral margin of the abscess or wound

ESTABLISH-1 (PO) and -2 (IV/PO) Phase 3 Trial Design: combining FDA and EMA endpoints

(double-blind, double-dummy)

<table>
<thead>
<tr>
<th>Day 1</th>
<th>48–72 hours after initial dose</th>
<th>End of Therapy Day 11</th>
<th>Post-Therapy Evaluation Day 18–25</th>
<th>Late Follow-Up Day 29–36</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=667 ABSSSI patients</td>
<td>N=666 ABSSSI patients</td>
<td>ESTABLISH-1 (112): All oral</td>
<td>ESTABLISH-2 (113): IV initiated with option of switching to oral</td>
<td></td>
</tr>
</tbody>
</table>

**ESTABLISH-1 (112): All oral**
- 6 days, Oral Tedizolid qD
- 10 days, Oral Linezolid BID

**ESTABLISH-2 (113): IV initiated with option of switching to oral**
- 6 days IV/Oral Tedizolid qD
- 10 days, IV/Oral Linezolid BID

Post-treatment evaluations

- **FDA 1° endpoint**: Sustained clinical response
- **FDA 2° endpoint**: Investigator’s assessment of clinical response
- **EMA 1° endpoint**: Sustained clinical success
- **EMA 2° endpoint**: EMA 2° endpoint

- **Cessation of spread and absence of fever**
- **≥20% decrease from baseline in lesion area**

22/03/2016 New Forces in Management of MRSA infections
ESTABLISH-1 and -2 Integrated Efficacy: All Efficacy Endpoints Achieved

ITT Analysis Set*

- Early Clinical Response (≥20% lesion area Reduction)
- End of therapy (Programmatic clinical response)
- Days 7-14 post-EOT (Investigator assessed response)

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Tedizolid N=664</th>
<th>Linezolid N=669</th>
</tr>
</thead>
<tbody>
<tr>
<td>48-72 hours</td>
<td>81.6</td>
<td>79.4</td>
</tr>
<tr>
<td>Day 11</td>
<td>87.0</td>
<td>87.9</td>
</tr>
<tr>
<td>Days 7-14 post-EOT</td>
<td>86.7</td>
<td>86.8</td>
</tr>
</tbody>
</table>

* Pooled data

Tedizolid vs Linezolid

- 2.2 (-2.0; 6.5) for 48-72 hours
- -0.8 (-4.4; 2.7) for Day 11
- -0.1 (-3.8; 3.6) for Days 7-14 post-EOT

ESTABLISH-1 and -2 Integrated Efficacy: Non-inferiority Achieved in Each Infection Type

Early Clinical Response Rate at 48–72 h. ITT Analysis Set*

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Tedizolid N=664</th>
<th>Linezolid N=669</th>
<th>Difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulitis/erysipelas</td>
<td>75.7</td>
<td>74.3</td>
<td>1.4</td>
<td>(-5.4; 8.3)</td>
</tr>
<tr>
<td>Major cutaneous abscess</td>
<td>85.7</td>
<td>86.7</td>
<td>-1.0</td>
<td>(-8.6; 6.5)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>87.2</td>
<td>81.1</td>
<td>6.0</td>
<td>(-1.2; 13.4)</td>
</tr>
</tbody>
</table>

* Pooled data

ESTABLISH-1 and -2 Integrated Efficacy

Non-inferiority was Achieved at 48-72 hours in All Subgroups

<table>
<thead>
<tr>
<th>ITT analysis set</th>
<th>Tedizolid, % (n/N)</th>
<th>Linezolid, % (n/N)</th>
<th>Treatment difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>82.6 (489/592)</td>
<td>79.5 (485/610)</td>
<td>3.1 (-1.3; 7.6)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>73.6 (53/72)</td>
<td>78.0 (46/59)</td>
<td>-4.9 (-19.4; 10.1)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>83.0 (356/429)</td>
<td>80.1 (330/412)</td>
<td>2.8 (-2.4; 8.1)</td>
</tr>
<tr>
<td>Female</td>
<td>79.1 (186/235)</td>
<td>78.2 (201/257)</td>
<td>1.0 (-6.4; 8.2)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 kg/m^2</td>
<td>83.8 (389/464)</td>
<td>79.4 (347/437)</td>
<td>4.4 (-0.6; 9.5)</td>
</tr>
<tr>
<td>≥30 kg/m^2</td>
<td>76.5 (153/200)</td>
<td>79.3 (184/232)</td>
<td>-2.8 (-10.8; 5.0)</td>
</tr>
<tr>
<td>IV drug use</td>
<td>82.5 (151/183)</td>
<td>79.6 (164/206)</td>
<td>2.9 (-5.0; 10.7)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>70.7 (41/58)</td>
<td>82.1 (55/67)</td>
<td>-10.9 (-26.1; 4.0)</td>
</tr>
<tr>
<td>Bacteraemia at baseline</td>
<td>100 (11/11)^a</td>
<td>69 (11/16)</td>
<td>ND</td>
</tr>
</tbody>
</table>

^Pathogens isolated included: *Staphylococcus aureus* (methicillin-resistant *S. aureus*, 2 patients; methicillin-sensitive *S. aureus*, 4 patients; eradication confirmed for all), *Streptococcus pyogenes* (2 patients), *Streptococcus constellatus* (1 patient), *Staphylococcus hominis* (1 patient), *Streptococcus agalactiae* (1 patient).

BMI = body mass index; CI = confidence interval; ND = not done; ITT = intent to treat; IV = intravenous.

MRSA and MSSA eradication rates are equivalent for tedizolid 200 mg 6 days vs linezolid 600 mg 10 days

* Pooled data

**ESTABLISH-1 and -2 Integrated Per-pathogen Microbiological Response at PTE**

<table>
<thead>
<tr>
<th>MITT Analysis Set</th>
<th>ESTABLISH-1 &amp; ESTABLISH-2</th>
<th>Rival</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tedizolid 200mg qD for 6 days % (n)</td>
<td>Linezolid 600mg BID for 10 days % (n)</td>
<td></td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>88.8 (292/329)</td>
<td>88.9 (304/342)</td>
<td>-0.1 (-5.0; 4.7)</td>
</tr>
<tr>
<td><strong>MRSA</strong></td>
<td>84.4 (119/141)</td>
<td>82.2 (120/146)</td>
<td>2.2 (-6.6; 10.9)</td>
</tr>
<tr>
<td><strong>MSSA</strong></td>
<td>92.0 (173/188)</td>
<td>93.9 (186/198)</td>
<td>-1.9 (-7.4; 3.3)</td>
</tr>
<tr>
<td><strong>Streptococcus pyogenes</strong></td>
<td>90.9 (30/33)</td>
<td>95.0 (19/20)</td>
<td>-4.1 (-19.8; 16.1)</td>
</tr>
<tr>
<td><strong>S. anginosus-milleri group</strong></td>
<td>73.3 (22/30)</td>
<td>89.3 (25/28)</td>
<td>-15.7 (-35.4; 5.7)</td>
</tr>
</tbody>
</table>

High potency against Gram + pathogens

### ESTABLISH-1 and -2 Integrated Safety: Overall Adverse Events

<table>
<thead>
<tr>
<th>Treatment-Emergent Adverse Event (TEAE)</th>
<th>Tedizolid % (n=662)</th>
<th>Linezolid % (n=662)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>283 (42.7)</td>
<td>286 (43.2)</td>
</tr>
</tbody>
</table>

Most Adverse Events Reported were Mild or Moderate in Severity

Tedizolid (N=662): 58% Mild, 29% Moderate, 11% Mild, 2% Severe, 2% None

Linezolid (N=662): 57% Mild, 29% Moderate, 12% Mild, 2% Severe, 2% None

---

## ESTABLISH-1 and -2 Integrated Safety: Overall Adverse Events

<table>
<thead>
<tr>
<th>Treatment-Emergent Adverse Event (TEAE)</th>
<th>Tedizolid % (n=662)</th>
<th>Linezolid % (n=662)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-related TEAE</td>
<td>148 (22.4)</td>
<td>185 (27.9)</td>
</tr>
<tr>
<td>TEAE leading to discontinuation of study drug</td>
<td>3 (0.5)</td>
<td>6 (0.9)</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>12 (1.8)</td>
<td>13 (2.0)</td>
</tr>
<tr>
<td>Drug-related serious TEAE</td>
<td>0 (0.0)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Any TEAE leading to death*</td>
<td>2 (0.3)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

Overall TEAE rates were similar between tedizolid- and linezolid-treated patients

* Not related to study drug

---

## ESTABLISH-1 and -2 Integrated Safety: TEAEs ≥ 1% in "Preferred Terms"

<table>
<thead>
<tr>
<th>System Organ Class &quot;Preferred Term&quot;</th>
<th>Tedizolid % (n=662)</th>
<th>Linezolid % (n=662)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>106 (16.0)*</td>
<td>152 (23.0)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>54 (8.2)*</td>
<td>81 (12.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26 (3.9)</td>
<td>35 (5.3)</td>
</tr>
<tr>
<td></td>
<td>19 (2.9)*</td>
<td>37 (5.6)</td>
</tr>
<tr>
<td>General disorders and administration site conditions (IV site reactions &lt;2% both groups)</td>
<td>36 (5.4)</td>
<td>39 (5.9)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td>91 (13.7)</td>
<td>78 (11.8)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>35 (5.3)</td>
<td>26 (3.9)</td>
</tr>
<tr>
<td></td>
<td>17 (2.6)</td>
<td>14 (2.1)</td>
</tr>
</tbody>
</table>

*P<0.05

**Lower incidence of gastrointestinal TEAEs in tedizolid- vs linezolid-treated patients**

**ESTABLISH-1 and -2 Integrated Safety**

Tedizolid treatment was associated with a lower incidence of GI Adverse Events

Tedizolid was associated with a significantly lower incidence of GI adverse events irrespective of duration of therapy.

Patients with GI TEAEs (%)

- **Overall GI TEAEs**: 
  - Tedizolid 200 mg qD, 6 days: 16.0
  - Linezolid 600 mg BID, 10 days: 23.0
  - *p*=0.0018

- **GI TEAEs Day 0 - Day 6**: 
  - Tedizolid 200 mg qD, 6 days: 13.0
  - Linezolid 600 mg BID, 10 days: 18.9
  - *p*=0.0042

**Tedizolid was associated with a significantly lower incidence of GI adverse events irrespective of duration of therapy**

TEAE = treatment-emergent adverse events; GI = gastrointestinal.

Tedizolid Use was Associated with Overall Reduced Risk of Myelosuppression

Patients with reduced platelet counts during the entire study period

Tedizolid was associated with a significantly lower risk of developing thrombocytopenia

Tedizolid is not known to increase the risk of anemia, leukopenia, or pancytopenia

LLN = lower limit of normal.

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Summary – Clinical

- Non-inferior to linezolid overall and in all infection types
  - with a shorter duration of therapy (6 days vs 10 days)
  - a lower daily dose (200 mg/day vs 1200 mg/day)
  - a simplified schedule of administration (once daily)

- High eradication rates against Gram-positive pathogens

- Well tolerated with no serious AE occurring related to tedizolid

- Significantly lower incidence of gastrointestinal adverse events vs linezolid; irrespective of treatment duration

- Significantly lower risk of developing thrombocytopenia vs linezolid
Can we make a comparison list for ABSSI?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Availability</th>
<th>Points to Consider *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>All generics</td>
<td>- IV only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- &gt; 7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- BID or continuous infusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Nephrotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Failures if MIC &gt; 2 (MIC creep)</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Generics coming</td>
<td>- IV only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ≥ 7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Beware of VISA (susceptibility)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Beware of rhabdomyolysis (check CPK)</td>
</tr>
<tr>
<td>Ceftarolone</td>
<td>Branded</td>
<td>- IV only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ≥ 7 day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Tested only against vancomycin</td>
</tr>
<tr>
<td>Tedizolid</td>
<td>Branded</td>
<td>- IV and oral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 6 days (against linezolid 10 days)</td>
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<tr>
<td></td>
<td></td>
<td>- Active against cfr+ linezolidR strains</td>
</tr>
</tbody>
</table>

* Based on analysis of the prescription information and literature data.
What about the future?