The new antibiotics: useful improvement of our current armamentarium ... but can we pay for them?

Paul M. Tulkens, MD, PhD
Françoise Van Bambeke, PharmD, PhD

Pharmacologie cellulaire et moléculaire
Louvain Drug Research Institute,
Université catholique de Louvain,
Brussels, Belgium
http://www.facm.ucl.ac.be

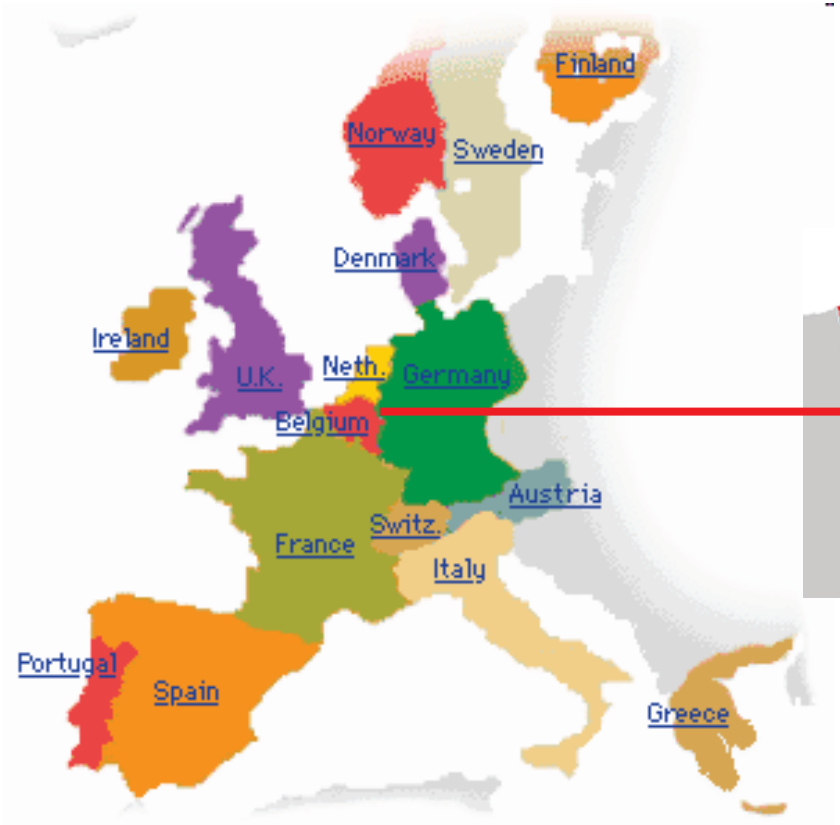
Medellin, Colombia, 1 December 2015

Disclosures and slides availability

- Research grants
  - Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica, Debiopharm
  - Belgian Science Foundation (*F.R.S.-FNRS*), Ministry of Health (*SPF*), Walloon and Brussels Regions, European Union (*FP7 programme*)
- Speaking fees
  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma
- Decision-making and consultation bodies
  - European Committee for Antimicrobial Susceptibility Testing [EUCAST] (General Assembly and steering committee (2010-2012))
  - European Medicines Agency (external ad-hoc expert)
  - US National Institutes of Health (grant reviewing)
  - **Drive-AB [*Driving reinvestment in R&D and responsible use for antibiotics*]** (governance)

Slides: http://www.facm.ucl.ac.be → Lectures

Belgium


Finland
Norway
Sweden
Denmark
Ireland
U.K.
Neth.
Germany
Belgium
Austria
Switz.
France
Italy
Portugal
Spain
Greece


FLANDERS
BRUSSELS
WALLONIA

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)

A partial view of our University Clinic (900 beds) and the Education and Research buildings (5,000 students), in the outskirts of Brussels, Belgium

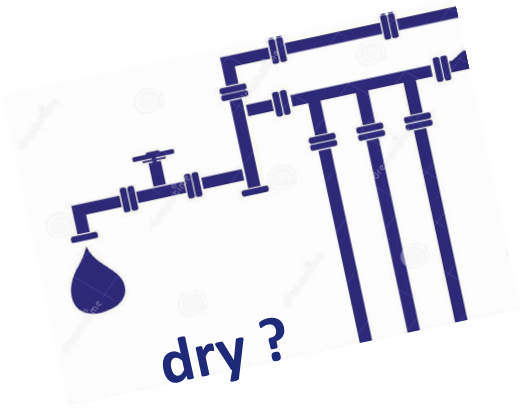
- improved schedules of aminoglycosides and β-lactams
- assessment of novel antibiotics
  - beta-lactams (e.g., ceftaroline…)
  - fluoroquinolones (e.g., delafloxacin…)
  - lipoglycopeptides (e.g., oritavancin)
  - ketolides (e.g., solithromycin…)
  - oxazolidinones (e.g., tedizolid …)
  - others…

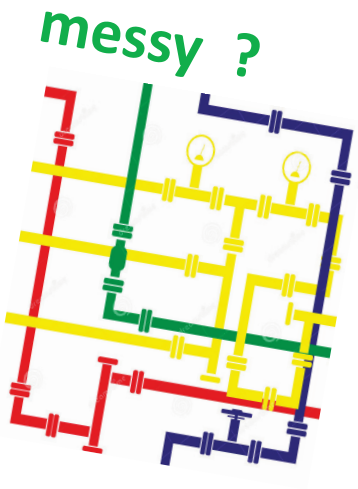
www.facm.ucl.ac.be

- 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

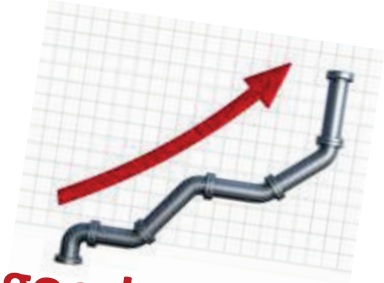
New antibiotics: what is your own view of the pipeline ?





of global concern?

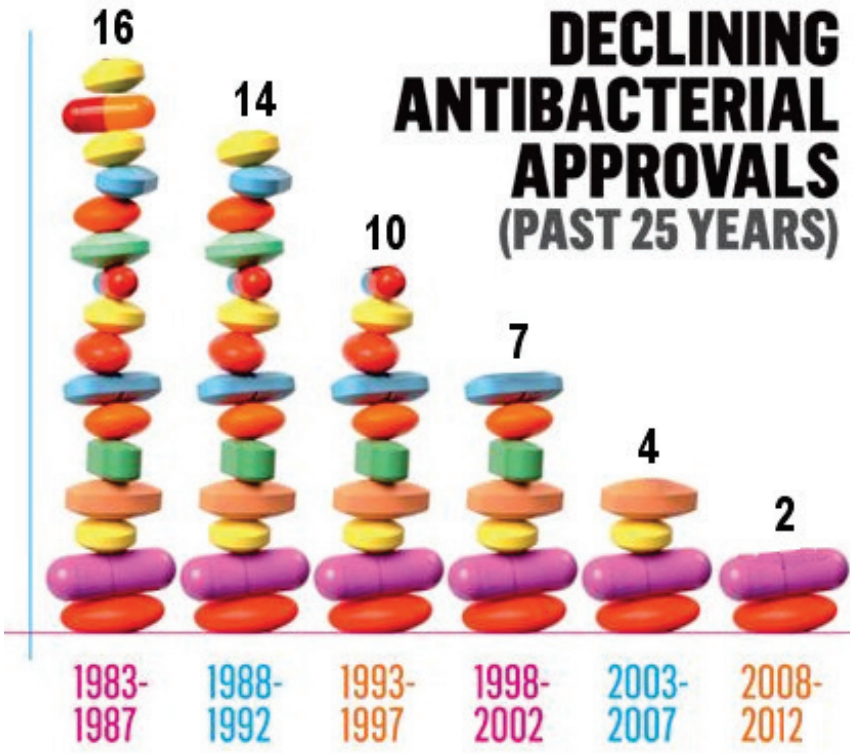
under repair?



in good shape ?

New antibiotics: where are we ?

Approvals by FDA/EMA – systemic antibiotics

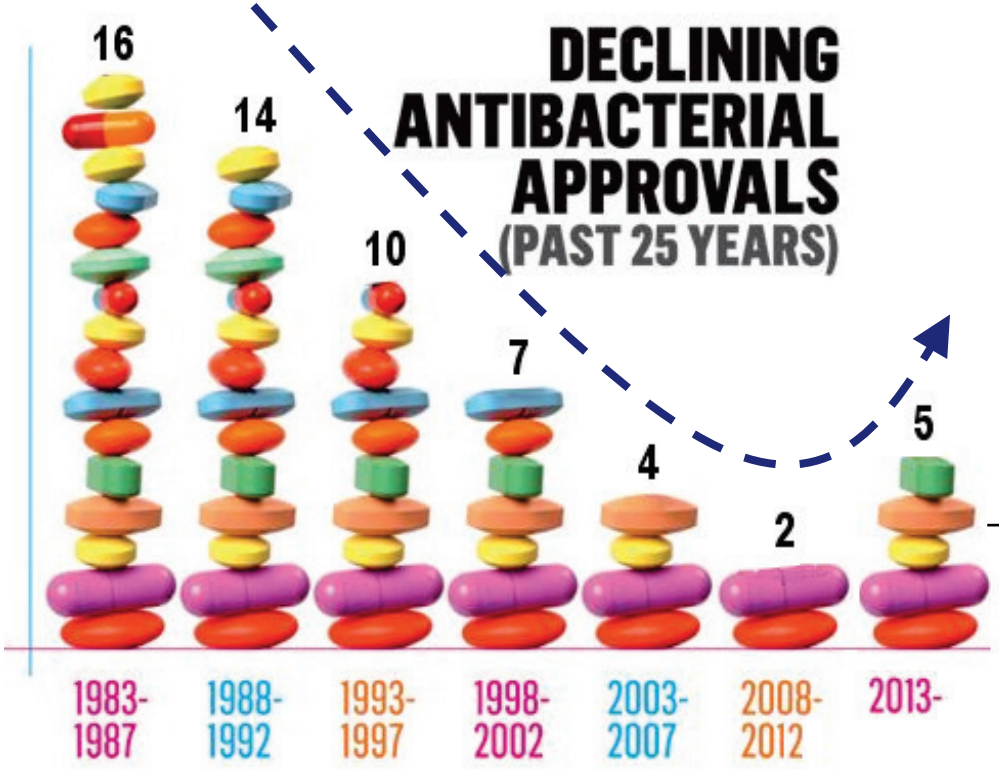


→ telavancin

→ ceftaroline

New antibiotics: where are we ?

Approvals by FDA/EMA – systemic antibiotics



Shall we succeed ?

- dalbavancin
- oritavancin
- tedizolid
- ceftazidime/avibactam *
- ceftolozane/tazobactam

FDA only so far

- telavancin
- ceftaroline

Why do see that in the US ?

1. Definition of the "**Qualified infectious disease product (QIDP) qualifying pathogens: pathogens that have the highest unmet medical need**" by the FDA *

   → list of 21 microorganisms from <u>both hospital and community</u>

* US eCFR Title 21, Chapter I, Subchapter D, §317.2 List of qualifying pathogens that have the potential to pose a serious threat to public health. 2014 [12.01.2015].
Available from: http://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=8508abd4d5a913bee24de949bb1920d2&ty=HTML&h=L&r=PART&n=pt21.5.317

Why do see that in the US ?

Table 1: Qualified infectious disease product (QIDP) qualifying pathogens: pathogens that have the highest unmet medical need.

QIDP qualifying pathogen names [20]		**Type of infection**		
Bacteria	**Gram**	**Opportunistic**	**Hospital acquired**	**Community acquired**
Acinetobacter species[1]	Gram–	X	X	
Burkholderia cepacia complex	Gram–	X	X	
Campylobacter species	Gram-		X	X
Clostridium difficile[1]	Gram+		X	X
Enterobacteriaceae[1] (especially *Citrobacter, Enterobacter cloacae, Klebsiella pneumoniae, Escherichia coli, Proteus vulgaris, Salmonella, Serratia marcescens, Shigella*)	Gram–	X	X	X
Enterococcus species	Gram+		X	X
Helicobacter pylori	Gram–			X
Mycobacterium tuberculosis complex[1]	NA	X		X
Neisseria gonorrhoeae[1]	Gram–			X
Neisseria meningitidis	Gram–			X
Nontuberculous mycobacteria species	NA	X		X
Pseudomonas species[1]	Gram–	X	X	
Staphylococcus aureus[1, 2]	Gram+	X	X	X
Streptococcus agalactiae (group B)	Gram+			X
Streptococcus pneumoniae	Gram+	X		X
Streptococcus pyogenes (group A)	Gram+			X
Vibrio cholerae	Gram–			X
Fungi				
Aspergillus species	NA	X		
Candida species	NA	X		X
Coccidioides species	NA			X
Cryptococcus species	NA	X		

[1] Key unmet need due to high and increasing prevalence of XDR or PDR strains [21]
[2] Unmet need primarily for blood, bone and prosthesis infections and not for skin infection.
NA = Not applicable.

* US eCFR Title 21, Chapter I, Subchapter D, §317.2 List of qualifying pathogens that have the potential to pose a serious threat to public health. 2014 [12.01.2015].
Available from: http://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=8508abd4d5a913bee24de949bb1920d2&ty=HTML&h=L&r=PART&n=pt21.5.317

Why do see that in the US ?

1. Definition of the "**Qualified infectious disease product (QIDP) qualifying pathogens: pathogens that have the highest unmet medical need**" by the FDA *
   → list of 21 microorganisms from both hospital and community

2. The GAIN act … ("***G**enerating **A**ntibiotic **I**ncentive **N**ow*") at the US House of Representatives in 2011 *

   – **additional five years of exclusivity** for those new antibiotics designated under the law as a "qualified infectious disease product," … in addition to any existing exclusivity, including that which may be applicable under Hatch-Waxman (five years or three years), orphan drug (seven years), or pediatric exclusivity (six months).

   – **Fast track and priority review status** and **expedited regulatory approval process** with FDA.

   – **FDA-issued new guidance** on the development of pathogen-focused antibiotics

*Available from: http://www.gpo.gov/fdsys/pkg/BILLS-112hr2182ih/pdf/BILLS-112hr2182ih.pdf
See also: http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2013/11/07/gain-how-a-new-law-is-stimulating-the-development-of-antibiotics

Why do see that in the US ?

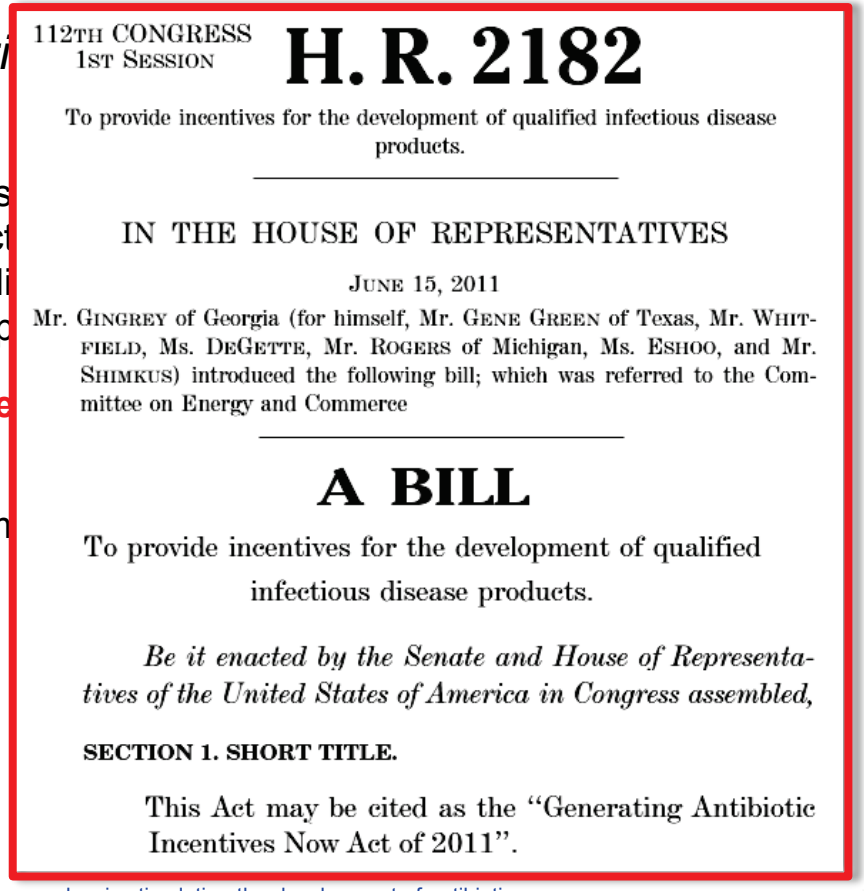
1. Definition of the "**Qualified infectious disease product (QIDP) qualifying pathogens: pathogens that have the highest unmet medical need**" by the FDA *
   → list of 21 microorganisms from both hospital and community

2. The GAIN act … ("*Generating Antibioti*
   House of Representatives in 2001 *

   – **additional five years of exclusivity** for thos
   law as a "qualified infectious disease product
   exclusivity, including that which may be appli
   three years), orphan drug (seven years), or p

   – **Fast track and priority review status** and e
   with FDA.

   – **FDA-issued new guidance** on the developn



112TH CONGRESS
1ST SESSION

H. R. 2182

To provide incentives for the development of qualified infectious disease products.

IN THE HOUSE OF REPRESENTATIVES

JUNE 15, 2011

Mr. GINGREY of Georgia (for himself, Mr. GENE GREEN of Texas, Mr. WHITFIELD, Ms. DEGETTE, Mr. ROGERS of Michigan, Ms. ESHOO, and Mr. SHIMKUS) introduced the following bill; which was referred to the Committee on Energy and Commerce

A BILL

To provide incentives for the development of qualified infectious disease products.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Generating Antibiotic Incentives Now Act of 2011".

*Available from: http://www.gpo.gov/fdsys/pkg/BILLS-112hr2182ih/pdf/BILLS-112hr2182ih.pdf
See also: http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2013/11/07/gain-how-a-new-law-is-stimulating-the-development-of-antibiotics

Why do see that in the US ?

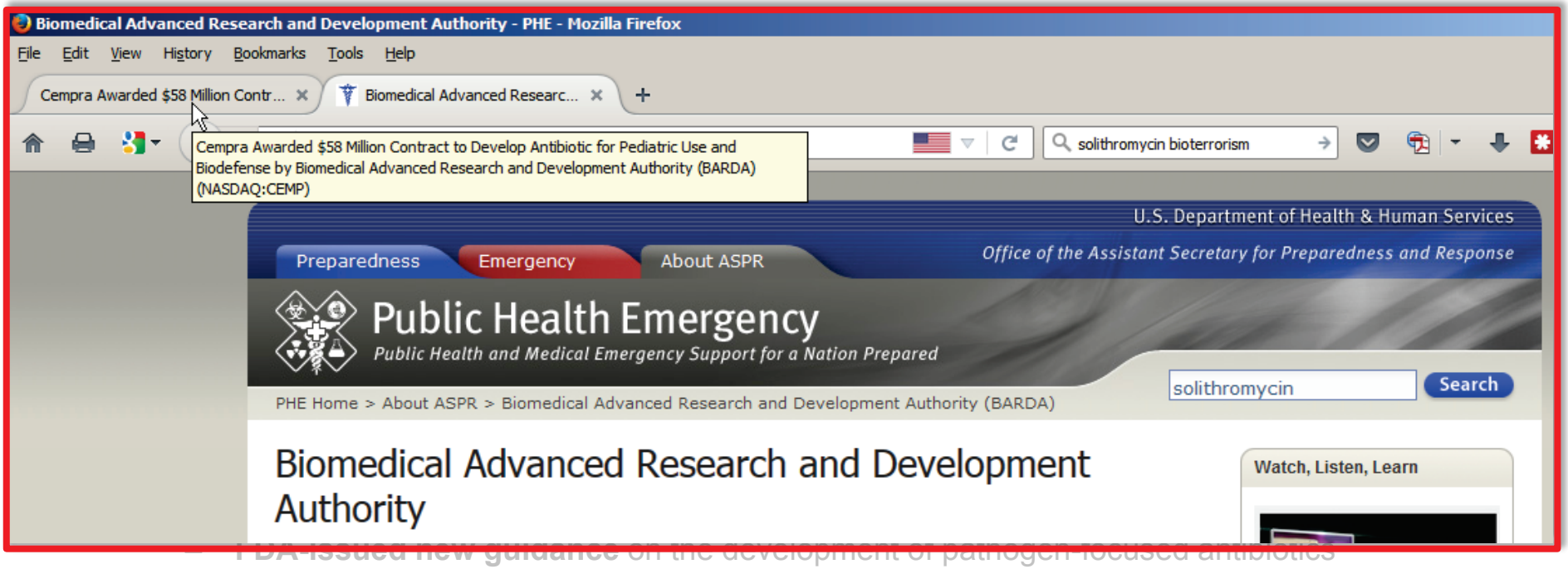
1. Definition of the "**Qualified infectious disease product (QIDP) qualifying pathogens: pathogens that have the highest unmet medical need**" by the FDA *
   → list of 21 microorganisms from both hospital and community
2. The GAIN act … ("*Generating Antibiotic Incentive Now*") at the US House of Representatives *
   - **additional five years of exclusivity** for those new antibiotics designated under the law as a "qualified infectious disease product," … in addition to any existing exclusivity, including that which may be applicable under Hatch-Waxman (five years or three years), orphan drug (seven years), or pediatric exclusivity (six months).
   - **Fast track and priority review status** and **expedited regulatory approval process** with FDA.
   - **FDA-issued new guidance** on the development of pathogen-focused antibiotics

3. The **Biomedical Advanced Research and Development Authority** (BARDA) activities *

   - integrated, systematic approach to the **development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies**

* http://www.phe.gov/about/barda/Pages/default.aspx

Why do see that in the US ?



3. The **Biomedical Advanced Research and Development Authority** (BARDA) activities *

   – integrated, systematic approach to the **development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies**

* http://www.phe.gov/about/barda/Pages/default.aspx

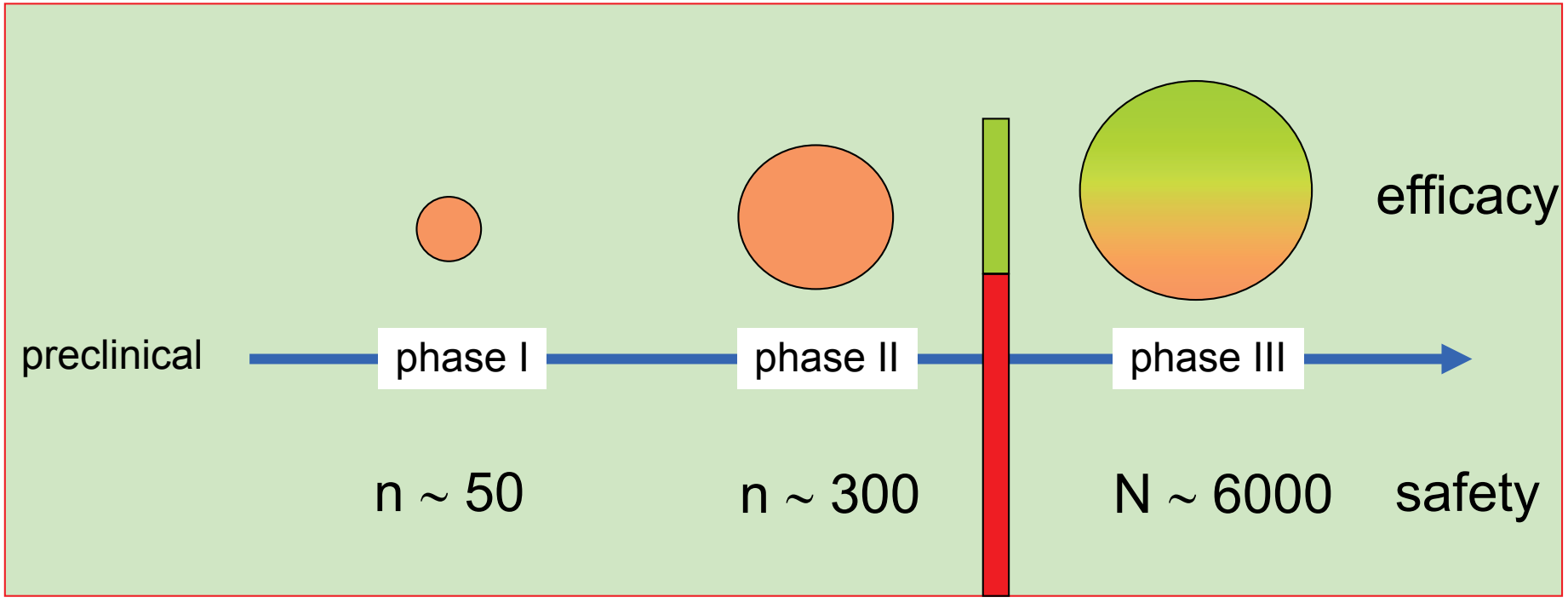
A view from Europe

- €2 billions euro budget…
- collaborative research projects and networks of industrial and academic experts…
- collaborative ecosystem for pharmaceutical research and development (R&D)…
- increase Europe's competitiveness globally…
- establish Europe as **the most attractive place for pharmaceutical R&D**

http://www.imi.europa.eu/
Last accessed: 26 May 2015

Early registering at FDA and EMA for efficacy …

- Registration: proposed new scheme
  - Provisional registration at phase II level (solving the unmet medical need)
  - Continue evaluation through commercialization until reaching a number of patients equivalent to a phase III to get full registration



As a result…

Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Review article: Current opinion | Published 31 July 2015, doi:10.4414/smw.2015.14167

Cite this as: Swiss Med Wkly. 2015;145:w14167

Development of new antibiotics: taking off finally?

Esther Bettiol[a], *Stephan Harbarth*[a,b]

[a] Infection Control Programme, Geneva University Hospitals and Faculty of Medicine, Switzerland

[b] Division of Infectious Diseases, Geneva University Hospitals and Faculty of Medicine, Switzerland

As a result…

Established in 1871

Swiss Medica

Formerly: Schweizerische Medizinische Wochensch

An open access, online journal • www.smw.ch

Review article: Current opinion | Published 31

Cite this as: Swiss Med Wkly. 2015;145:w14167

Development of new

Esther Bettiol[a], *Stephan Harbarth*[a,b]

[a] Infection Control Programme, Geneva University Hospita

[b] Division of Infectious Diseases, Geneva University Hospi

Table 2: Late-stage pipeline: systemic antibiotics recently approved, in registration or in phase III of clinical development.

Drug (brand name) - Company	Antibiotic class	Activity spectrum/resistant pathogens targeted	Phase and indication[1]	Regulatory status		
				US	European Union	Switzerland
Ceftazidime+ avibactam [44] (AvycazTM) – AstraZeneca/ Actavis	Cephalosporin + new BLI	Gram–, including MDR *P. aeruginosa*, ESBL-producing strains and KPC	Approved February 2015 for cIAI in combination with metronidazole, and for cUTI in patients who have limited or no alternative treatment options, in phase III for HAP/VAP and cIAI	Approved February 2015	Not submitted yet	Not submitted yet
Ceftolozane+ tazobactam [41] (ZerbaxaTM) – Cubist Pharmaceuticals / Merck Sharp & Dohme	Cephalosporin + BLI	Gram–, including carbapenem, piperacillin+tazobactam and ceftazidime-resistant *Pseudomonas aeruginosa*, ESBL-producing strains	Approved for cUTI and cIAI, in phase III for VAP and phase I for paediatric use	Approved December 2014	Under review since August 2014	Under review since September 2014[2]
Ceftobiprole medocaril [45] (Zevtera®/Mabelio®) – Basilea Pharmaceutica/Quintiles	Cephalosporin	Gram+ and –, including MRSA, VRSA, penicillin- and ceftriaxone-resistant *Streptococcus pneumoniae*, *Enterobacteriaceae*, *P. aeruginosa*	Approved for CABP and HAP, excluding VAP	Not submitted (additional phase III data required	Approved October 2013	Approved December 2014
Oritavancin [42] (OrbactivTM) – The Medicines Company	Glycopeptide	Gram+, including MRSA	Approved for ABSSSI, in phase I for paediatric use	Approved August 2014	Approved May 2015	Under review[2]
Tedizolid phosphate [43] (SivextroTM) – Cubist Pharmaceuticals / Merck Sharp & Dohme	Oxazolidinone	Gram+, including MRSA and linezolid-resistant MRSA	Approved for ABSSSI, in phase III for HAP/VAP and for ABSSSI in adolescents	Approved June 2014	Approved March 2015	Under review since second quarter 2014[2]
Dalbavancin [42] (DalvanceTM/ XydalbaTM) – Actavis / Durata Therapeutics	Glycopeptide	Gram+, including MRSA	Approved for ABSSSI, in phase III for CABP and phase I and III for paediatric use	Approved May 2014	Approved March 2015	Unknown
Meropenem+RPX7009 [54, 55] (CarbavanceTM) – The Medicines Company	Carbapenem + new class of BLI	Gram–, including CRE and particularly KPC	Phase III for cUTI and infections caused by CRE[3]	NA	NA	NA
Eravacycline [56] – Tetraphase Pharmaceuticals	Tetracycline	Gram+ and –, including CRE, ESBL-producing strains, MDR *Acinetobacter baumanii*, VRE, MRSA	Phase III for cUTI and cIAI[4]	NA	NA	NA
Plazomicin [57] – Achaogen	Aminoglycoside	Gram–, including CRE	Phase III for bloodstream infection and nosocomial pneumonia caused by CRE[5]	NA	NA	NA
Delafloxacin [51] – Melinta Therapeutics	Fluoroquinolone	Gram+ and –, including MRSA	Phase III for ABSSSI	NA	NA	NA
Solithromycin [52] – Cempra Pharmaceuticals	Macrolide	Gram+, including macrolide-resistant strains	Phase III for CABP and uncomplicated gonorrhoea, in phase I for paediatric use	NA	NA	NA

[1] Information retrieved from clinicaltrials.gov as of March 2015.
[2] Personal communication.
[3] Completion of trial expected in 2016; clinicaltrial.gov identifiers: NCT02168946 and NCT02166476.
[4] Completion of trial expected in 2015; clinicaltrial.gov identifiers: NCT01978938 and NCT0184485.
[5] Completion of trial expected in 2017; clinicaltrial.gov identifiers: NCT01970371.
ABSSSI = acute bacterial skin and skin structure infections; BLI =: β-lactamase inhibitor; CABP = community-acquired bacterial pneumonia; cIAI = complicated intra-abdominal infections; CRE = carbapenem-resistant *Enterobacteriaceae*; cUTI = complicated urinary tract infections; ESBL = extended spectrum β-lactamase; Gram+ = Gram-positive; Gram– = Gram-negative; HAP = hospital-acquired pneumonia; KPC = *Klebsiella pneumoniae* carbapenemase; MRSA = meticillin-resistant *Staphylococcus aureus*; VAP = ventilator-acquired pneumonia; VRSA = vancomycin-resistant *Staphylococcus aureus*

As a result…

Established in 1871

Swiss Medica

Formerly: Schweizerische Medizinische Wochensch

1. ceftazidime-avibactam
2. ceftozolane-tazobactam
3. ceftobiprole
4. oritavancin
5. tedizolid
6. dalbavancin
7. meropenem-RPX7009
8. eravacycline
9. plazomycin
10. delafoxacin
11. solithromycin

Table 2: Late-stage pipeline: systemic antibiotics recently approved, in registration or in phase III of clinical development.

Drug (brand name) - Company	Antibiotic class	Activity spectrum/resistant pathogens targeted	Phase and indication[1]	Regulatory status		
				US	European Union	Switzerland
Ceftazidime+ avibactam [44] (AvycazTM) – AstraZeneca/ Actavis	Cephalosporin + new BLI	Gram–, including MDR *P. aeruginosa*, ESBL-producing strains and KPC	Approved February 2015 for cIAI in combination with metronidazole, and for cUTI in patients who have limited or no alternative treatment options, in phase III for HAP/VAP and cIAI	Approved February 2015	Not submitted yet	Not submitted yet
Ceftolozane+ tazobactam [41] (ZerbaxaTM) – Cubist Pharmaceuticals / Merck Sharp & Dohme	Cephalosporin + BLI	Gram–, including carbapenem, piperacillin+tazobactam and ceftazidime-resistant *Pseudomonas aeruginosa*, ESBL-producing strains	Approved for cUTI and cIAI, in phase III for VAP and phase I for paediatric use	Approved December 2014	Under review since August 2014	Under review since September 2014[2]
biprole medocaril [45] era®/Mabelio®) – Basilea haceutica/Quintiles	Cephalosporin	Gram+ and –, including MRSA, VRSA, penicillin- and ceftriaxone-resistant *Streptococcus pneumoniae*, *Enterobacteriaceae*, *P. aeruginosa*	Approved for CABP and HAP, excluding VAP	Not submitted (additional phase III data required	Approved October 2013	Approved December 2014
ancin [42] (OrbactivTM) – ledicines Company	Glycopeptide	Gram+, including MRSA	Approved for ABSSSI, in phase I for paediatric use	Approved August 2014	Approved May 2015	Under review[2]
olid phosphate [43] troTM) – Cubist haceuticals / Merck Sharp me	Oxazolidinone	Gram+, including MRSA and linezolid-resistant MRSA	Approved for ABSSSI, in phase III for HAP/VAP and for ABSSSI in adolescents	Approved June 2014	Approved March 2015	Under review since second quarter 2014[2]
vancin [42] (DalvanceTM/ baTM) – Actavis / Durata peutics	Glycopeptide	Gram+, including MRSA	Approved for ABSSSI, in phase III for CABP and phase I and III for paediatric use	Approved May 2014	Approved March 2015	Unknown
enem+RPX7009 [54, 55] avanceTM) – The ines Company	Carbapenem + new class of BLI	Gram–, including CRE and particularly KPC	Phase III for cUTI and infections caused by CRE[3]	NA	NA	NA
cycline [56] – Tetraphase haceuticals	Tetracycline	Gram+ and –, including CRE, ESBL-producing strains, MDR *Acinetobacter baumanii*, VRE, MRSA	Phase III for cUTI and cIAI[4]	NA	NA	NA
micin [57] – Achaogen	Aminoglycoside	Gram–, including CRE	Phase III for bloodstream infection and nosocomial pneumonia caused by CRE[5]	NA	NA	NA
oxacin [51] – Melinta peutics	Fluoroquinolone	Gram+ and –, including MRSA	Phase III for ABSSSI	NA	NA	NA
romycin [52] – Cempra haceuticals	Macrolide	Gram+, including macrolide-resistant strains	Phase III for CABP and uncomplicated gonorrhoea, in phase I for paediatric use	NA	NA	NA

[1] Information retrieved from clinicaltrials.gov as of March 2015.
[2] Personal communication.
[3] Completion of trial expected in 2016; clinicaltrial.gov identifiers: NCT02168946 and NCT02166476.
[4] Completion of trial expected in 2015; clinicaltrial.gov identifiers: NCT01978938 and NCT0184485.
[5] Completion of trial expected in 2017; clinicaltrial.gov identifiers: NCT01970371.
ABSSSI = acute bacterial skin and skin structure infections; BLI =: β-lactamase inhibitor; CABP = community-acquired bacterial pneumonia; cIAI = complicated intra-abdominal infections; CRE = carbapenem-resistant *Enterobacteriaceae*; cUTI = complicated urinary tract infections; ESBL = extended spectrum β-lactamase; Gram+ = Gram-positive; Gram– = Gram-negative; HAP = hospital-acquired pneumonia; KPC = *Klebsiella pneumoniae* carbapenemase; MRSA = meticillin-resistant *Staphylococcus aureus*; VAP = ventilator-acquired pneumonia; VRSA = vancomycin-resistant *Staphylococcus aureus*

What shall I focus on ?

Drugs that are now registered in the US and in Europe
(* or will be soon) …

a) Lipoglycopeptides (*from vancomycin*)
   - telavancin (old but renewed…)
   - dalbavancin
   - oritavancin

b) Oxazolidinones (*from linezolid*)
   - tedizolid

c) cephalosporines anti-MRSA (*from ceftazidime*)
   - ceftaroline
   - ceftobiprole

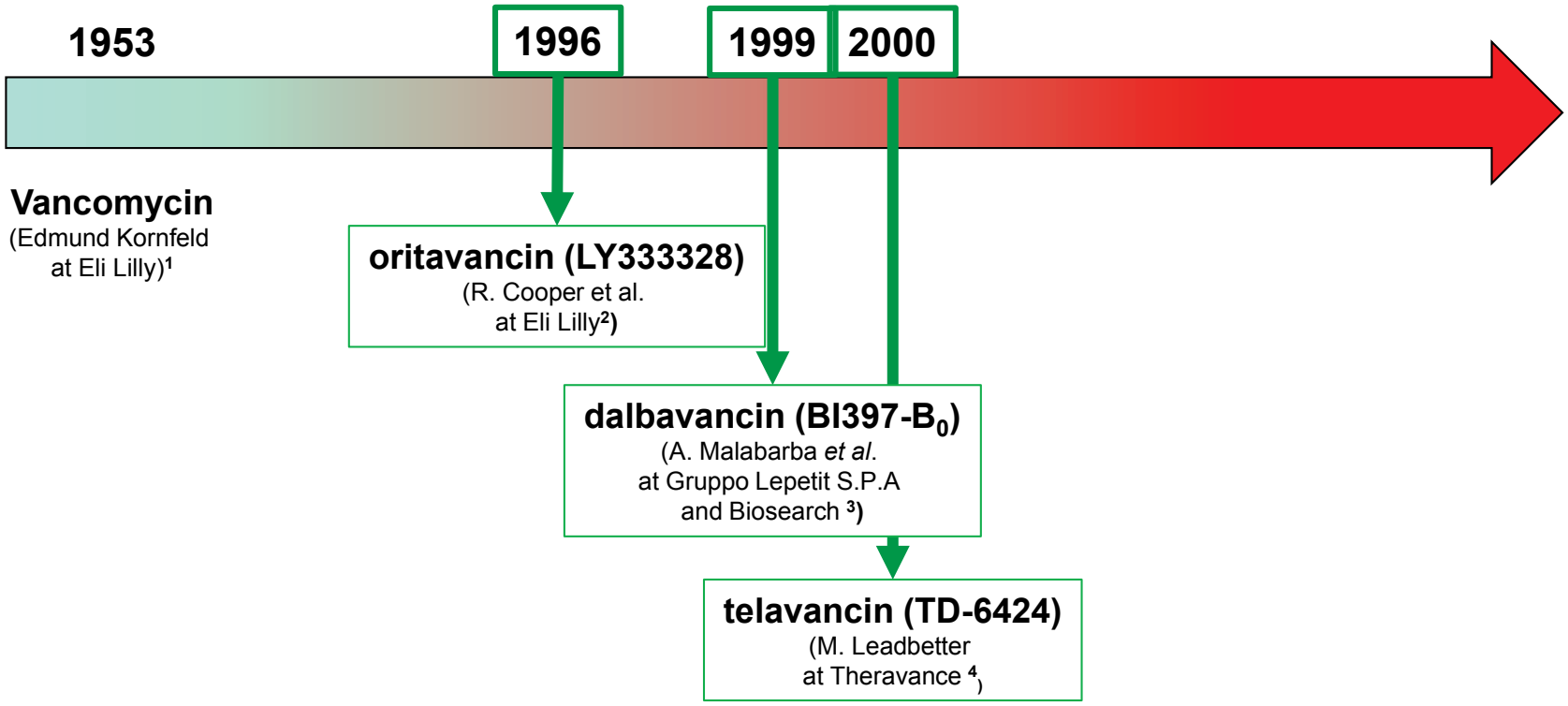
d) Ketolides (*from telithromycine*)
   - solithromycin *

anti Gram (+)

e) cephalosporins x β-lactamase inhibitors
   - ceftozolane x tazobactam
   - ceftzidime x avibactam *

anti Gram (-)

Lipoglycopeptides history: the discovery



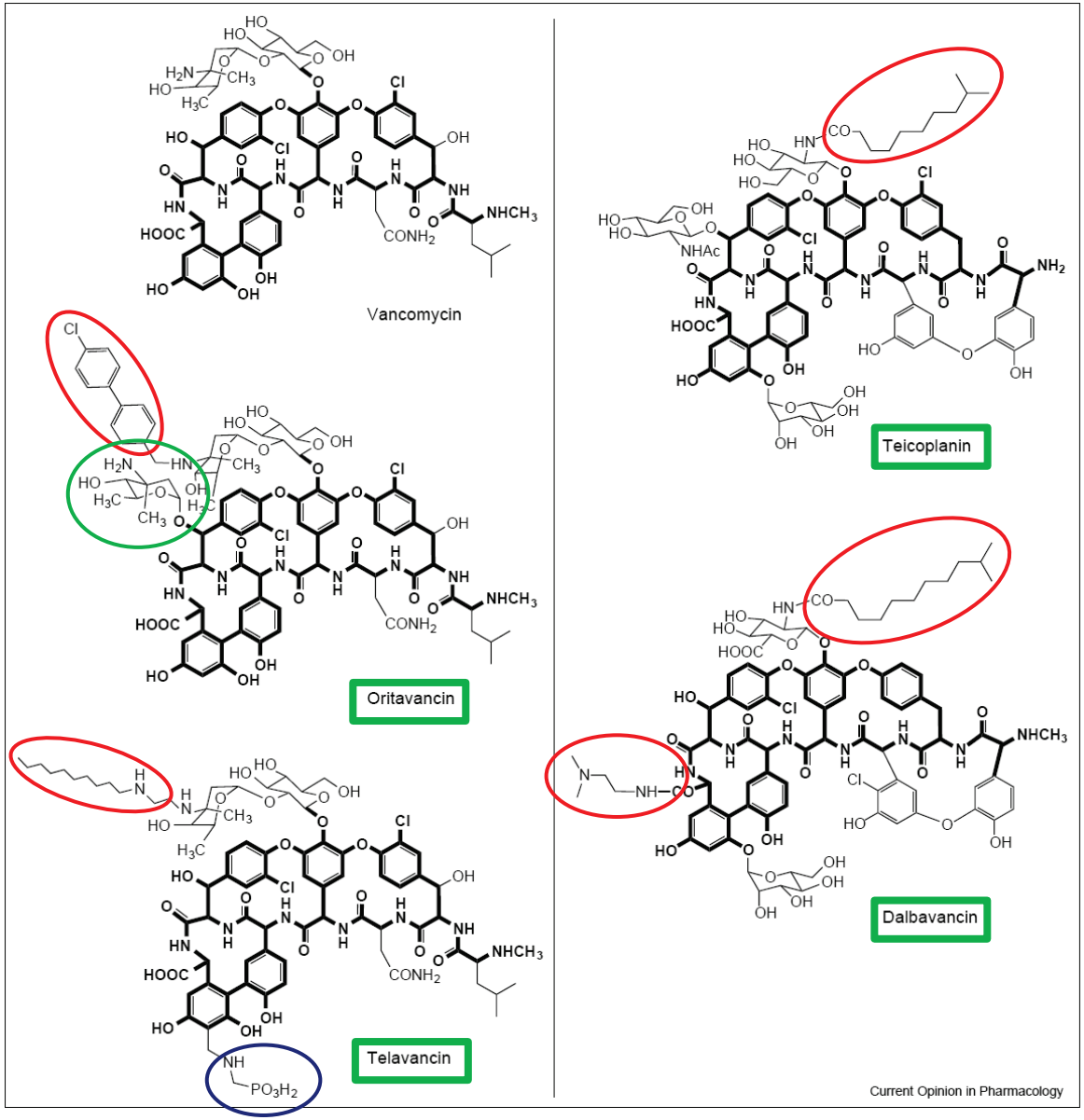
1 McCormick *et al.* Vancomycin, a new antibiotic. I. Chemical and biologic properties. Antibiot Annu. 1955-1956;3:606-11
2 Cooper *et al.* Journal of Antibiotics (1996), 49(6), 575-581.
3 Malabarba *et al.* Drugs of the Future (1999), 24(8), 839-846
4 Leadbetter et al. PCT Int. Appl. (2001), WO 2001098328 A2 20011227.
See also: Van Bambeke Drugs, in press
(unedited typescript available at http://www.facm.ucl.ac.be/Full-texts-FACM/in-press/vanbambeke-Lipoglycopeptides-drugs-accepted.pdf)

Lipoglycopeptides

- very prolonged half-life
- membrane anchoring (bactericidal)

dimerization → increased activity

- moderate half-life
- membrane anchoring (bactericidal)

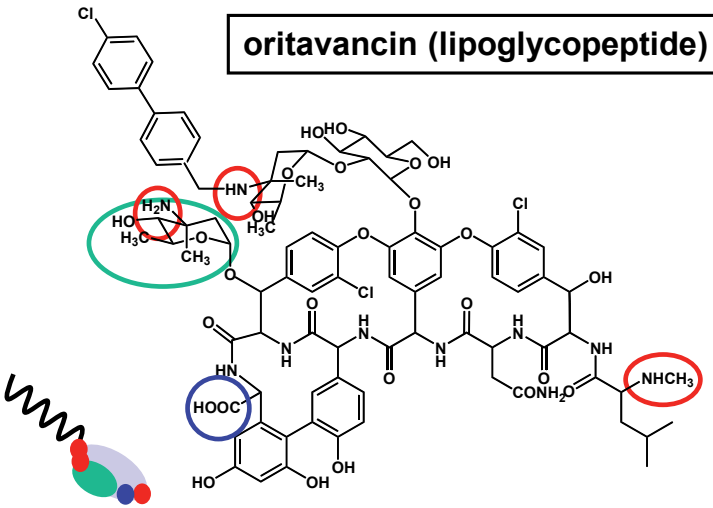


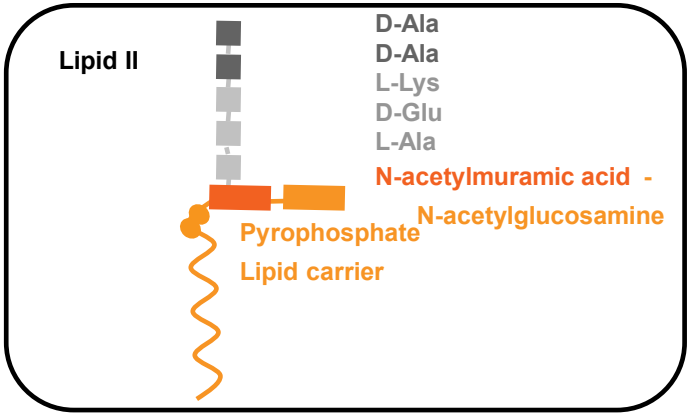
prolonged half-life

very prolonged half-life

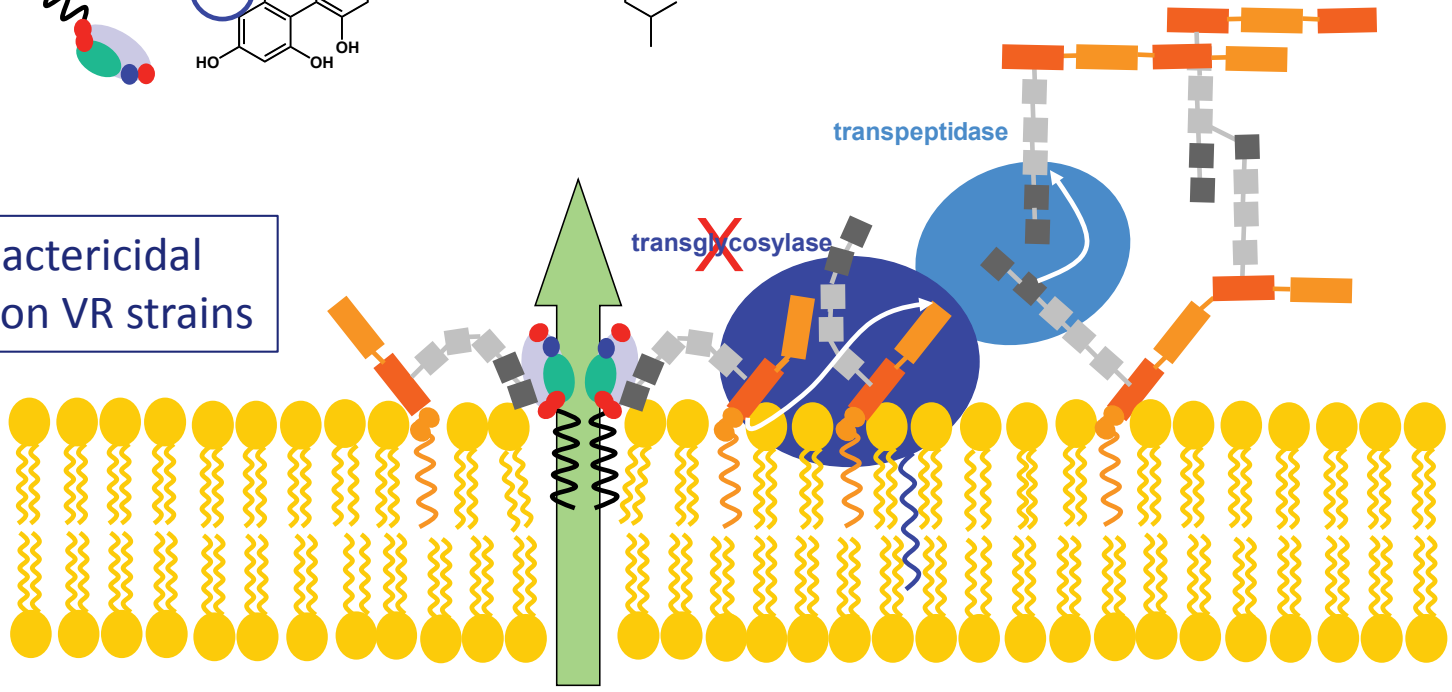
Van Bambeke, Cur. Op. Pharmacol. 2004, 4:471–478

Lipoglycopeptides: dual mode of action





- highly bactericidal
- activity on VR strains



Van Bambeke et al, TIPS 2008, 29:124-134

Lipoglycopeptides: microbiology (median MICs)

organism	VAN	TEC	TLV	DAL	ORI
MSSA	1	0.5	0.06 a	0.06 a	0.0.3
MRSA	1	1.0	0.12 a	0.06 a	0.03
E. faecalis	2	0.5	0.25	0.03	0.015

very low MICs

	S. aureus		*E. faecalis*	
	FDA	EMA	FDA	EMA
TLV	≤ 0.12	≤ 0.125	≤ 0.25	I.E.
DAL	≤ 0.12	≤ 0.125	--	--
ORI	≤ 0.12	≤ 0.125	≤ 0.12	I.E.

current breakpoints
(set at maximum MIC observed in clinical trials)

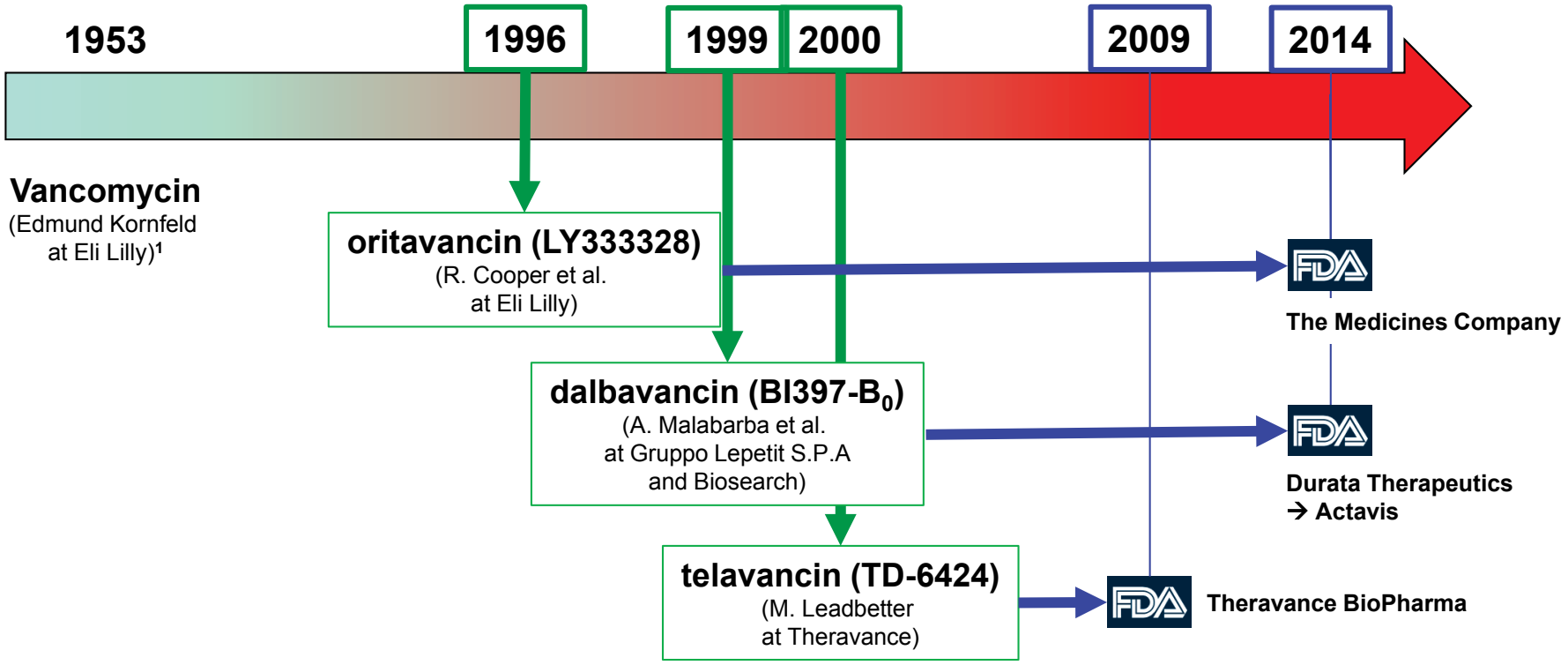
http://www.eucast.org
http://www.vibativ.com/docs/VIBATIV_PI_Final.pdf
http://www.orbactiv.com/pdfs/orbactiv-prescribing-information.pdf
http://pi.actavis.com/data_stream.asp?product_group=1973&p=pi&language=E

Lipoglycopeptides: pharmacokinetics

parameter	VAN	TEC	TLV	DAL	ORI
Dosage	15 mg/kg	6 mg/kg	10 mg/kg [a]	1000 mg	1200 mg
C_{max} (mg/L)	20-50	43	108±26	287±13.9	138±23
AUC (mg.h/L)	260	600	780±125	3185 (24h) 23443 (tot)	1110 (24h) 2800 (tot)
(%) prot. binding	55	88-94	~90	99	85
T ½ (h)	1 (β) 3-9 (γ)	10 (β) 168 (γ)	**8.1±1.5**	**346±16.5** (γ)	13.4 ± (β) **245±10.5** (γ)

twice daily | every 2 days | once daily | once-a-week | once !

Lipoglycopeptides: towards registration



[1] Wenzler E, Rodvold KA. Telavancin: The Long and Winding Road From Discovery to Food and Drug Administration Approvals and Future Directions. Clin Infect Dis 2015;61 Suppl 2:S38-S47.

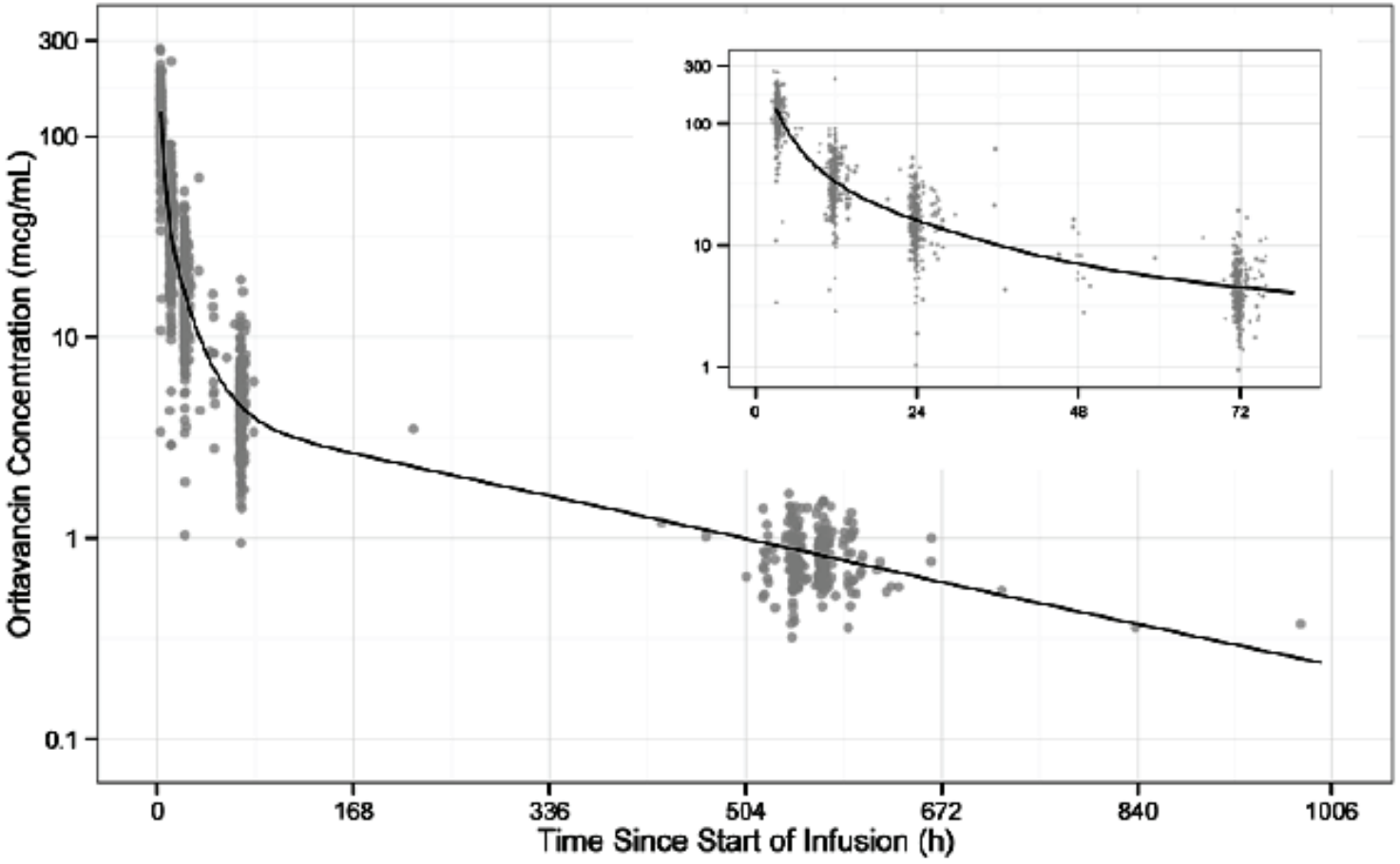
[2] Butler MS, Hansford KA, Blaskovich MAT et al. Glycopeptide antibiotics: back to the future. J Antibiot (Tokyo) 2014;67(9):631-44.

[3] Van Bambeke *et al.* Glycopeptides (Dalbavancin, Oritavancin, Teicoplanin, Telavancin, Vancomycin) - Update 2009. Antimicrobial Therapy and Vaccines. Vol. II: Antimicrobial Agents (2009) 42pp; available at http://www.antimicrobe.org

[4] Van Bambeke Lipoglycopeptide antibacterial agents in Gram-positive infections: A comparative review. Drugs, *in press* (unedited typescript available at http://www.facm.ucl.ac.be/Full-texts-FACM/in-press/vanbambeke-Lipoglycopeptides-drugs-accepted.pdf)

Oritavancin: a unusual development based on pharmacokinetics…

Population Mean Plasma Concentration-Time Profile after a Single 1200 mg dose of Oritavancin Administered Intravenously Over 3 Hours – Semi-Log Scale



http://www.orbactiv.com/pdfs/orbactiv-prescribing-information.pdf

Oritavancin: a unusual development based on pharmacokinetics…

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Single-Dose Oritavancin in the Treatment of Acute Bacterial Skin Infections

G. Ralph Corey, M.D., Heidi Kabler, M.D., Purvi Mehra, M.D., Sandeep Gupta, M.D., J. Scott Overcash, M.D., Ashwin Porwal, M.D., Philip Giordano, M.D., Christopher Lucasti, M.D., Antonio Perez, M.D., Samantha Good, Ph.D., Hai Jiang, Ph.D., Greg Moeck, Ph.D., and William O'Riordan, M.D., for the SOLO I Investigators*

N Engl J Med 2014;370:2180-90 (http://www.nejm.org/doi/full/10.1056/NEJMoa1310422)

Participants underwent randomization in a 1:1 ratio to receive either

- a single intravenous dose of 1200 mg of oritavancin followed by intravenously administered placebo, or
- an intravenous dose of vancomycin (1 g, or 15 mg per kilogram of body weight) every 12 hours for 7 to 10 days

Oritavancin: a unusual development based on pharmacokinetics…

Subgroup	Oritavancin	Vancomycin	Percentage-Point Difference (95% CI)
	no. of events/total no. (%)		
Modified intention-to-treat population			
Primary efficacy outcome at ECE	391/475 (82.3)	378/479 (78.9)	3.4 (–1.6 to 8.4)
Investigator-assessed clinical cure at PTE	378/475 (79.6)	383/479 (80.0)	–0.4 (–5.5 to 4.7)
Lesion size reduction ≥20% at ECE	413/475 (86.9)	397/479 (82.9)	4.1 (–0.5 to 8.6)
CE population			
Primary efficacy outcome at ECE	344/394 (87.3)	342/397 (86.1)	1.2 (–3.6 to 5.9)
Investigator-assessed clinical cure at PTE	357/394 (90.6)	352/397 (88.7)	1.9 (–2.3 to 6.2)
Lesion size reduction ≥20% at ECE	362/394 (91.9)	370/397 (93.2)	–1.3 (–5.0 to 2.3)
Patients infected with MRSA in intention-to-treat population with microbiologic evaluation			
Primary efficacy outcome at ECE	84/104 (80.8)	80/100 (80.0)	0.8 (–10.1 to 11.7)
Investigator-assessed clinical cure at PTE	86/104 (82.7)	83/100 (83.0)	–0.3 (–10.7 to 10.0)
Lesion size reduction ≥20% at ECE	94/104 (90.4)	84/100 (84.0)	6.4 (–2.8 to 15.5)
Patients infected with MSSA in intention-to-treat population with microbiologic evaluation			
Primary efficacy outcome at ECE	96/116 (82.8)	92/110 (83.6)	–0.9 (–10.6 to 8.9)
Investigator-assessed clinical cure at PTE	89/116 (76.7)	88/110 (80.0)	–3.3 (–14.0 to 7.4)
Lesion size reduction ≥20% at ECE	98/116 (84.5)	94/110 (85.5)	–1.0 (–10.3 to 8.3)

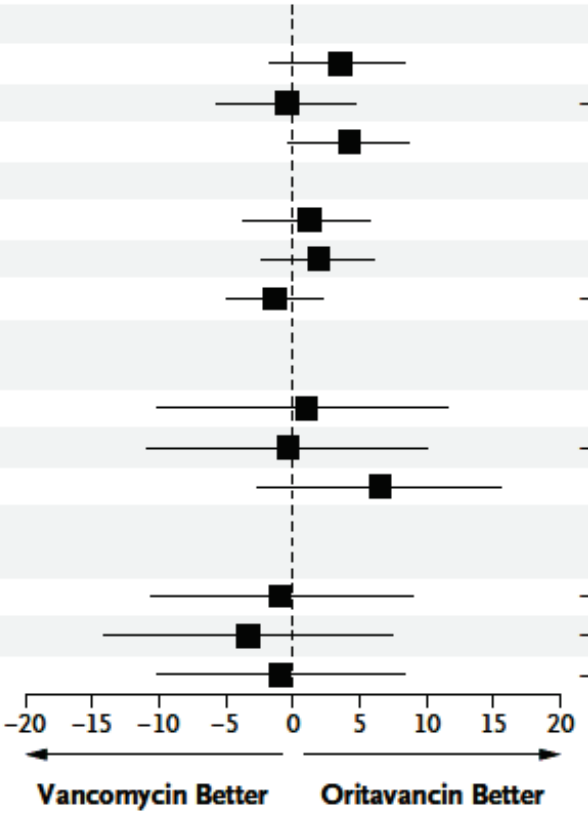


Figure 2. Primary and Secondary Efficacy End Points According to Analysis Population and MRSA Subgroup.

CE denotes clinical evaluation, ECE early clinical evaluation, MRSA methicillin-resistant *Staphylococcus aureus*, MSSA methicillin-susceptible *S. aureus*, and PTE post-therapy evaluation.

N Engl J Med 2014;370:2180-90 (http://www.nejm.org/doi/full/10.1056/NEJMoa1310422)

Oritavancin: a unusual development based on pharmacokinetics…

Table 2. Primary Efficacy Outcome at Early Clinical Evaluation According to Pathogen Detected at Baseline (Intention-to-Treat Population Who Could Be Evaluated Microbiologically).*

Pathogen	Oritavancin (N=244)	Vancomycin (N=242)	Difference (95% CI)†
	no./total no. (%)		*percentage points*
Detection of at least one pathogen	201/244 (82.4)	196/242 (81.0)	1.4 (–5.5 to 8.3)
Staphylococcus aureus	180/220 (81.8)	172/210 (81.9)	–0.1 (–7.4 to 7.2)
MRSA	84/104 (80.8)	80/100 (80.0)	0.8 (–10.1 to 11.7)
MSSA	96/116 (82.8)	92/110 (83.6)	–0.9 (–10.6 to 8.9)
Streptococcus species	25/31 (80.6)	31/38 (81.6)	–0.9 (–19.5 to 17.6)
S. anginosus group‡	12/13 (92.3)	14/16 (87.5)	
S. agalactiae	6/7 (85.7)	8/8 (100.0)	
S. pyogenes	5/8 (62.5)	5/10 (50.0)	
S. dysgalactiae	2/3 (66.7)	3/3 (100.0)	
Enterococcus faecalis	6/7 (85.7)	4/5 (80.0)	

* The pathogens listed are gram-positive pathogens known to cause acute bacterial skin and skin-structure infections, whether isolated from an infection site-culture or a blood culture. The pathogens listed include only those detected in both treatment groups. Patients with multiple pathogens were counted once in the rows for each pathogen. MSSA denotes methicillin-susceptible *S. aureus*.

† Differences and 95% confidence intervals are shown only for speciated pathogens identified from 10 or more patients in each treatment group.

‡ This group includes *S. anginosus*, *S. intermedius*, and *S. constellatus*.

N Engl J Med 2014;370:2180-90 (http://www.nejm.org/doi/full/10.1056/NEJMoa1310422)

Oritavancin: a unusual development based on pharmacokinetics…

Table 2. Primary Efficacy Outcome at Early Clinical Evaluation According to Pathogen Detected at Baseline (Intention-to-Treat Population Who Could Be Evaluated Microbiologically).*

Pathogen
Detection of at least one pathogen
Staphylococcus aureus
MRSA
MSSA
Streptococcus species
S. anginosus group‡
S. agalactiae
S. pyogenes
S. dysgalactiae
Enterococcus faecalis

* The pathogens listed are gram-pos
whether isolated from an infection
in both treatment groups. Patients
denotes methicillin-susceptible S.
† Differences and 95% confidence in
in each treatment group.
‡ This group includes *S. anginosus*, *S. intermedius*, and *S. constellatus*.

But important exclusions:

- Severe sepsis or refractory shock
- Known or suspected bacteremia at time of screening
- Concomitant infection at another site not including a secondary ABSSSI lesion (eg, septic arthritis, endocarditis, osteomyelitis)
- Infections known to be caused by a Gram-positive organism with a vancomycin minimum inhibitory concentration (MIC) >2 µg/mL or clinically failing prior therapy with glycopeptides.

See all exclusions at
http://www.nejm.org/doi/suppl/10.1056/NEJMoa1310422/suppl_file/nejmoa1310422_appendix.pdf

N Engl J Med 2014;370:2180-90 (http://www.nejm.org/doi/full/10.1056/NEJMoa1310422)

Oritavancin: a unusual development based on pharmacokinetics…

Table 3. Patients with Adverse Events (Safety Population).*

Adverse Event	Oritavancin (N=473)	Vancomycin (N=481)
	no. of patients (%)	
At least 1 adverse event that developed during treatment	284 (60.0)	307 (63.8)
Related to study drug	108 (22.8)	151 (31.4)
Leading to discontinuation of study drug	18 (3.8)	28 (5.8)
Serious adverse event†	35 (7.4)	35 (7.3)
Related to study drug	3 (0.6)	3 (0.6)
Leading to discontinuation of study drug	11 (2.3)	13 (2.7)
Death	1 (0.2)	2 (0.4)

N Engl J Med 2014;370:2180-90 (http://www.nejm.org/doi/full/10.1056/NEJMoa1310422)

Oritavancin: a unusual d

Table 3. Patients with Adverse Event

Adverse Event		
At least 1 adverse event that develop during treatment		
Related to study drug		
Leading to discontinuation of stu		
Serious adverse event†		
Related to study drug		
Leading to discontinuation of stu		
Death		
Most frequently reported adverse events‡		
Nausea	52 (11.0)	43 (8.9)
Headache	34 (7.2)	38 (7.9)
Pruritus	16 (3.4)	44 (9.1)
Infusion-site reaction	19 (4.0)	34 (7.1)
Infusion-site extravasation	18 (3.8)	23 (4.8)
Vomiting	23 (4.9)	18 (3.7)
Constipation	19 (4.0)	21 (4.4)
Diarrhea	23 (4.9)	17 (3.5)
Cellulitis	20 (4.2)	17 (3.5)
Pyrexia	15 (3.2)	20 (4.2)
Dizziness	15 (3.2)	15 (3.1)
Insomnia	14 (3.0)	13 (2.7)
Chills	10 (2.1)	12 (2.5)
Urticaria	7 (1.5)	15 (3.1)
Pruritus, generalized	11 (2.3)	9 (1.9)
Subcutaneous abscess	9 (1.9)	11 (2.3)
Abscess on limb	13 (2.7)	5 (1.0)
Infusion-site phlebitis	8 (1.7)	10 (2.1)
Alanine aminotransferase elevation	11 (2.3)	5 (1.0)
Fatigue	10 (2.1)	6 (1.2)

* A study investigator determined whether there was a causal relationship between an adverse event and the study drug.

N Engl J Med 2014;370:2180-90 (http://www.nejm.org/doi/full/10.1056/N

N Engl J Med 2014;370:2180-90.

Oritavancin: a unusual d

Table 3. Patients with Adverse Event

Adverse Event		
At least 1 adverse event that de during treatment		
Related to study drug		
Leading to discontinuation		
Serious adverse event†		
Related to study drug		
Leading to discontinuation of stu		
Death		

N Engl J Med 2014;370:2180-90 (http://www.nejm.org/doi/full/10.1056/N

Most frequently reported adverse events‡		
Nausea	52 (11.0)	43 (8.9)
Headache	34 (7.2)	38 (7.9)
Pruritus	16 (3.4)	44 (9.1)
Infusion-site reaction	19 (4.0)	34 (7.1)
Urticaria	7 (1.5)	15 (3.1)
Pruritus, generalized	11 (2.3)	9 (1.9)
Subcutaneous abscess	9 (1.9)	11 (2.3)
Abscess on limb	13 (2.7)	5 (1.0)
Infusion-site phlebitis	8 (1.7)	10 (2.1)
Alanine aminotransferase elevation	11 (2.3)	5 (1.0)
Fatigue	10 (2.1)	6 (1.2)

* A study investigator determined whether there was a causal relationship between an adverse event and the study drug.

But an important exclusion:

- Patients that required anticoagulant monitoring with an activated partial thromboplastin time (aPTT)

→ oritavancin interferes with these tests…

See all exclusions at
http://www.nejm.org/doi/suppl/10.1056/NEJMoa1310422/suppl_file/nejmoa1310422_appendix.pdf

N Engl J Med 2014;370:2180-90.

FDA indications and dosages of new lipoglycopeptides

- **Telavancin** (VIBATIV®) [1]
  - adults with **complicated Skin and Skin Structure Infections** (cSSSI) caused by **susceptible** Gram-positive isolates (*S. aureus* [including MRSA], *S. pyogenes*, *S. agalactiae*, *S. anginosus* group or *E. faecalis* (vancomycin-susceptible isolates only).
  - adults with **hospital-acquired and ventilator-associated bacterial pneumonia** (HABP/VABP), caused by susceptible isolates (*S. aureus* [including MRSA].
    VIBATIV should be reserved for use when alternative treatments are not suitable.
  - ➢ 10 mg/kg once daily (7 to 21 days) and 7.5 mg/kg if CrCl 30-50.

- **Oritavancin** (ORBACTIV®) [2]
  - adults with **acute bacterial skin and skin structure infections (ABSSSI)** caused by **susceptible** Gram-positive isolates (*S. aureus* [including MRSA], *S. pyogenes*, *S. agalactiae*, *S. dysgalactiae*, *S. anginosus* group *E. faecalis* (vancomycin-susceptible isolates only).
    If osteomyelitis is suspected or diagnosed → appropriate alternate antibacterial therapy
  - ➢ 1200 mg single dose by intravenous infusion over 3 hours (no dosage adaptation for age, kidney or hepatic dysfunction)

- **Dalbavancin** (**DALVANCE®**) [3,*]
  - adults with **bacterial skin and skin structure infections** (ABSSSI) caused by **susceptible** Gram-positive isolates (*S. aureus* [including MRSA], *S. pyogenes*, *S. agalactiae*, *S. anginosus group*).
    Serious hypersensitivity (anaphylactic) and skin reactions have been reported with DALVANCE.
  - ➢ 1000 mg once-weekly followed one week later by 500 mg (750/375 mg if CrCl < 30 ml/min; no impact of haemodialysis)

[1] http://www.vibativ.com/docs/VIBATIV_PI_Final.pdf
[2] http://www.orbactiv.com/pdfs/orbactiv-prescribing-information.pdf
[3] http://pi.actavis.com/data_stream.asp?product_group=1973&p=pi&language=E
(dalbavancin is a mixture of five closely related active homologs (A0, A1, B0, B1, and B2) with B0 being the major one).

Pros and cons of the new lipoglycopeptides ?

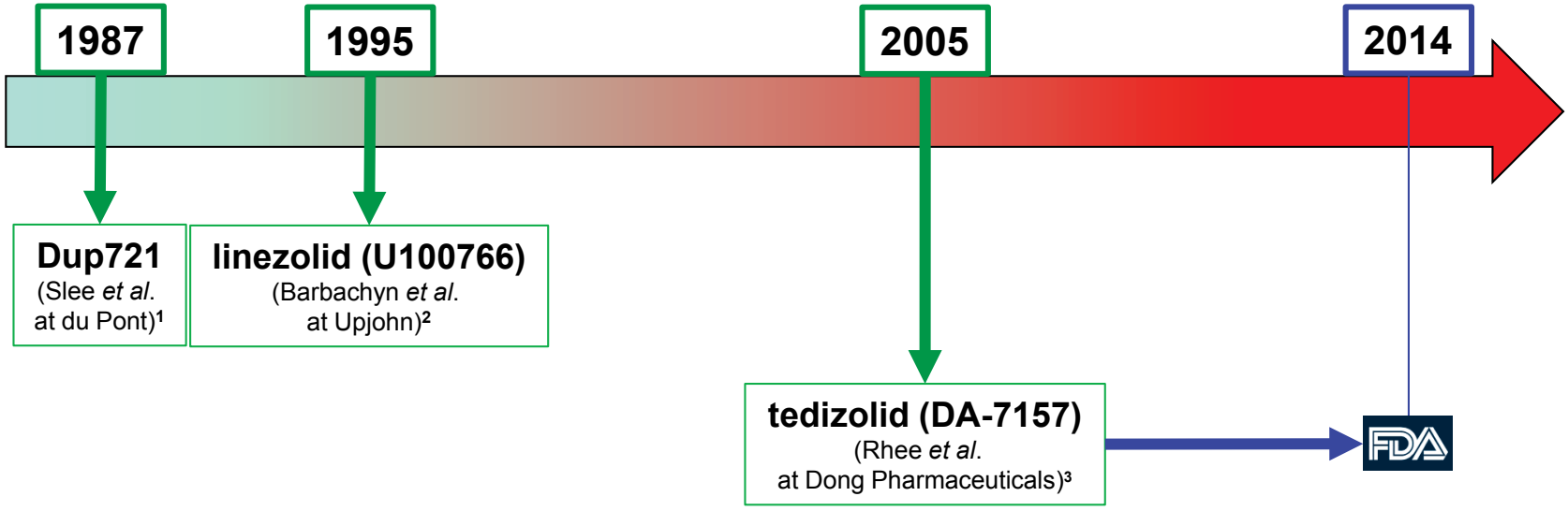
Pros

- Preference for once daily (telavancin), once a week (dalbavancin), or once (oritavancin) *vs* twice daily for 7-14 days (vancomycin)
- No need (or provision) for monitoring (so far…)
- Patients with MRSA or *Enterococcus faecalis* with reduced susceptibility to vancomycin (MIC ≥ 2 mg/L [MRSA] or ≥ 4 mg/L [*Enterococci*]) and susceptible to the new lipoglycopeptide intended for use
  → **documented therapy AND not proven clinically !**

Cons

- Limited indications (at present)
- Insufficient knowledge about toxicity risks related to long half-lives (dalbavancin, oritavancin) and potential increase in mortality in patients with renal insufficiency (tealavancin)
- Price (but low clinical burden than vancomycin)

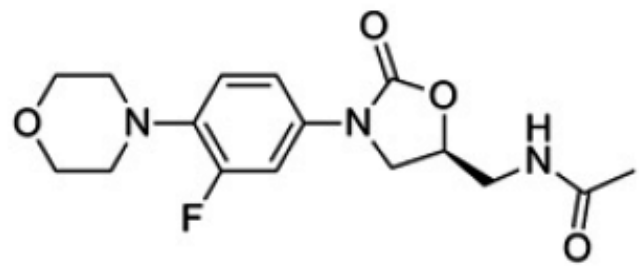
Oxazolidinones: a successor for linezolid ?



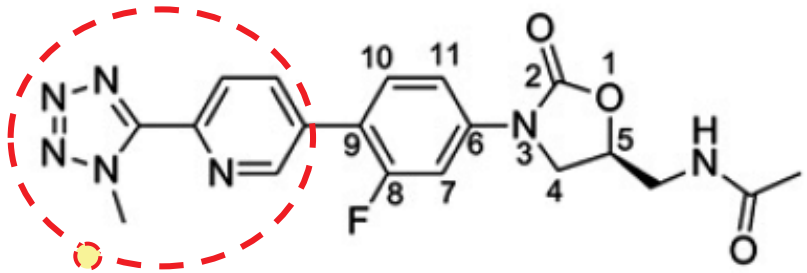
1 Slee et *al.* Antimicrob Agents Chemother. 1987;31:1791-97
2 Barbachyn et al. PCT Int. Appl., WO 9507271 A1 Mar 16, 1995
3 Rhee *et al*. PCT Int. Appl. (2005), WO 2005058886 A1 Jun 30, 2005
See also: Ford et al. Curr Drug Targets Infect Disord. 2001;1:181-99
Zhanel *et al.* Drugs. 2015;75:253-70.

Dong-A pharmaceuticals and tedizolid: step #1

Available online at www.sciencedirect.com
SCIENCE DIRECT
Bioorganic & Medicinal Chemistry



Linezolid



DA-7867

	MIC
MSSA	0.78 ug/ml
MRSA	0.78 ug/ml
VRE	0.125 ug/ml
PRSP	0.39 ug/ml

Replacing the morpholinyl by a **pyridinyl** and adding a **methyl-tetrazolyl** moiety

- **increases activity**
- **prolong half-life**

rial potency of lead compound (DA-7867).

a novel 5-hydroxymethyl-oxazolidinone

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

Tedizolid has more interactions with the ribosome…

W.B. Im et al. / European Journal of Medicinal Chemistry 46 (2011) 1027–1039

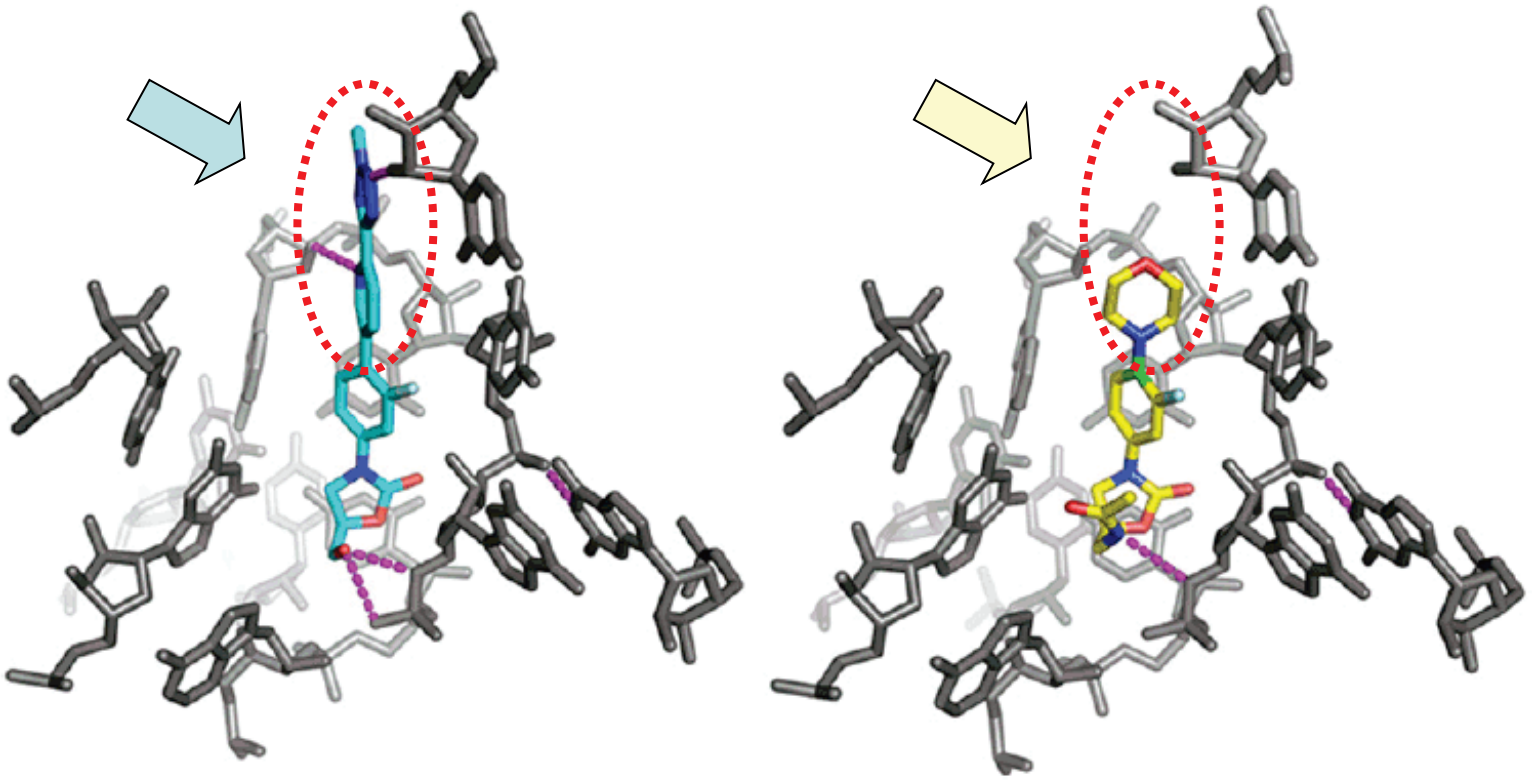
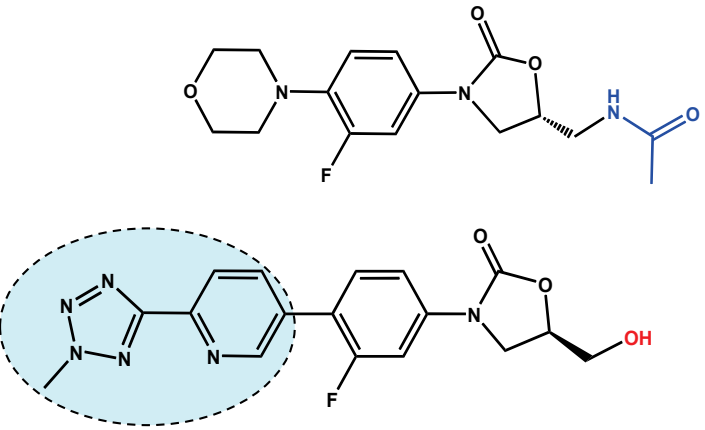


Fig. 2. Models of **11** (blue) and linezolid (yellow) binding to the *Escherichia coli* ribosome.

tedizolid

Tedizolid is systematically 3-4-x more active than linezolid against LSD^S strains



potential role of the tetrazolyl moiety

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

Species, phenotype and strain no.		MIC (mg/L)[a] linezolid	torezolid
Staphylococcus aureus			
MSSA	ATCC 25923[b]	2	0.25
HA-MRSA	ATCC 33591[b]	1	0.125–0.25
	SA 238[c]	2	0.25–0.5
	CM 05[d]	8	0.25–0.5
CA-MRSA	NRS 192[e]	2	0.125–0.25
	NRS 384 (US300)[e]	2	0.25
VISA	NRS 52[e]	2	0.125
VRSA	VRS 1[e]	1–2	0.125–0.25
	VRS 2[e]	1–2	0.25
animal MRSA	N7112046[f]	2	0.125
Listeria monocytogenes			
	EGD[g]	1–2	0.125
Legionella pneumophila			
	ATCC 33153[b]	4–8	0.25–0.5

LZD^R, resistant to linezolid.
[a]Representative values of at least two determinations.
[b]From the American Tissue Culture Collection (Manassas, VA, USA).
[c]Provided by P. C. Appelbaum.[36]
[d]Provided by J. P. Quinn, John H. Stroger Jr. Hospital, Rush University, Chicago, IL, USA.
[e]From the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) programme (operated by Eurofins Medinet, Inc., Hendon, VA, USA; supported under NIAID/NIH contract no. HHSN272200700055C); details on each strain are available at http://www.narsa.net/content/home.jsp.
[f]Provided by Y. Glupczynski, Cliniques universitaires UCL de Mont Godinne, Yvoir, Belgium.
[g]Provided by P. Berche, Hôpital Necker, Paris, France.[28]

Lemaire et al. JAC 2009; 64:1035–1043

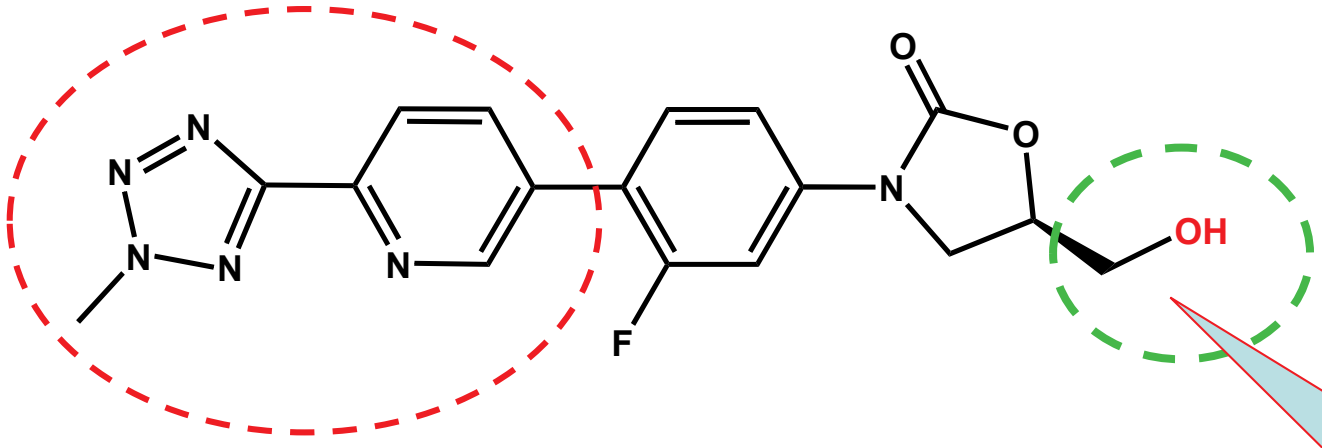
Tedizolid: global susceptibility profile

Table 1 In vitro activity (MIC mg/L) of tedizolid and comparators against aerobic Gram-positive organisms

Bacteria	Tedizolid			Linezolid			Vancomycin		
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
Staphylococcus aureus (MS)	0.25	0.5	≤0.015–8	2	2	≤0.25 to >8	1	1	0.25–2
Staphylococcus aureus (MR)	0.25	0.5	≤0.015–16	2	2	≤0.25 to >8	1	2	0.25–2
CoNS (MS)	0.25	0.5	0.06–1	1	2	≤0.25–4	2	2	1–2
CoNS (MR)	0.25	0.5	≤0.03–4	1	2	≤0.25–8	2	4	1–4
Enterococcus faecalis (VS)	0.5	0.5	0.12–1	2	2	0.5–4	1	2	0.5–4
Enterococcus faecalis (VR)	0.5	0.5	0.25–1	2	2	0.5–4	512	512	8 to >512
Enterococcus faecium (VS)	0.5	0.5	0.06–2	2	4	0.5–4	0.5	1	0.5–2
Enterococcus faecium (VR)	0.5	0.5	0.06–2	2	4	0.5 to >8	512	512	8 to >512
Streptococcus pyogenes (group A)	0.25	0.25	0.06–0.5	1	1	0.06–2	0.5	1	0.5–1
Streptococcus agalactiae (group B)	0.25	0.25	0.06–1	2	2	1–2	0.25	0.5	0.25–0.5
Streptococcus pneumoniae (PS)	0.25	0.25	0.03–0.5	1	2	0.12–2	0.25	0.5	0.06–1
Streptococcus pneumoniae (PI)	0.25	0.25	0.06–0.5	1	2	0.5–4	0.5	1	0.25–1
Streptococcus pneumoniae (PR)	0.25	0.25	0.06–0.5	1	2	0.25–2	0.25	0.5	0.06–2
Listeria monocytogenes	0.25	0.25	0.25–0.5	2	2	2	0.5	1	0.06–2

MR methicillin-resistant, *MS* methicillin-susceptible, *CoNS* coagulase-negative staphylococci, *PS* penicillin-susceptible (MIC ≤0.06 mg/L), *PI* penicillin-intermediate (MIC: 0.12–1 mg/L), *PR* penicillin-resistant (MIC ≥2 mg/L), *VS* vancomycin-susceptible (MIC ≤4 mg/L), *VR* vancomycin resistant (MIC ≥32 mg/L). Adapted from references [26–46]

Dong-A pharmaceuticals and tedizolid: step #2



#	R	X	MIC (μg/mL)		
			MSSA	MRSA	VRE
Linezolid			2	2	1
11	2-Methyl-2*H*-tetrazol-5-yl	—OH	0.5	0.5	0.125

2. replacing the **acetamido** by an **hydroxyl** maintains the increased activity *vs.* linezolid !

[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

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)

full

to 16

Activity against Cfr+ resistant strains … (*cfr*+ bacteria)

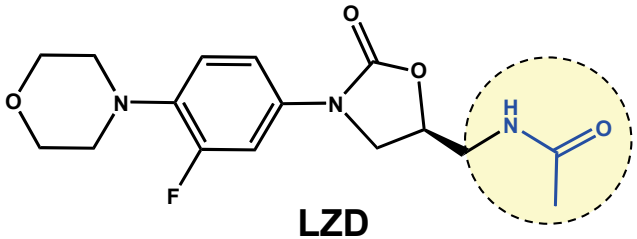
Oxazolidinone MICs for *S. aureus cfr* strains

Strain	Reference	Presence of *cfr*	MIC (μg/ml)[a]	
			LZD	TR-700
RN4220(pLI50)	68	−	2	0.5
RN4220(pLXM1)[b]	68	+	8	0.5
CM05Δ[c]	44	−	2	0.5
CM05[c]	68	+	8	0.5
29213	ATCC	−	2	0.5
29213(p42262)[d]	45	+	16	0.5
42262[e]	51	+	16	0.5

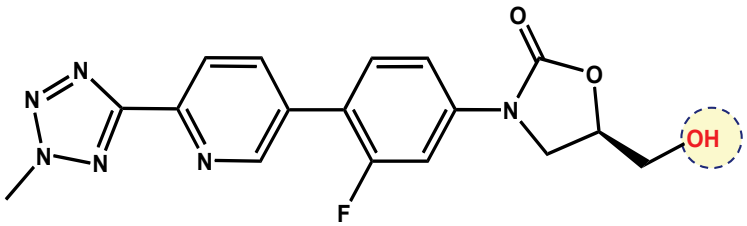
[a] MICs (broth microdilution: CLSI)
[b] The pLXM1 *cfr*-containing plasmid is isogenic to the empty pLI50 vector.
[c] CM05Δ is isogenic to the CM05 clinical *cfr*-positive strain but lacks *cfr* and one copy of *ermB*.
[d] 29213(p42262) was generated through transformation of ATCC 29213
[e] 42262 is 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^R strains (*cfr*) ?



LZD



TR700

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

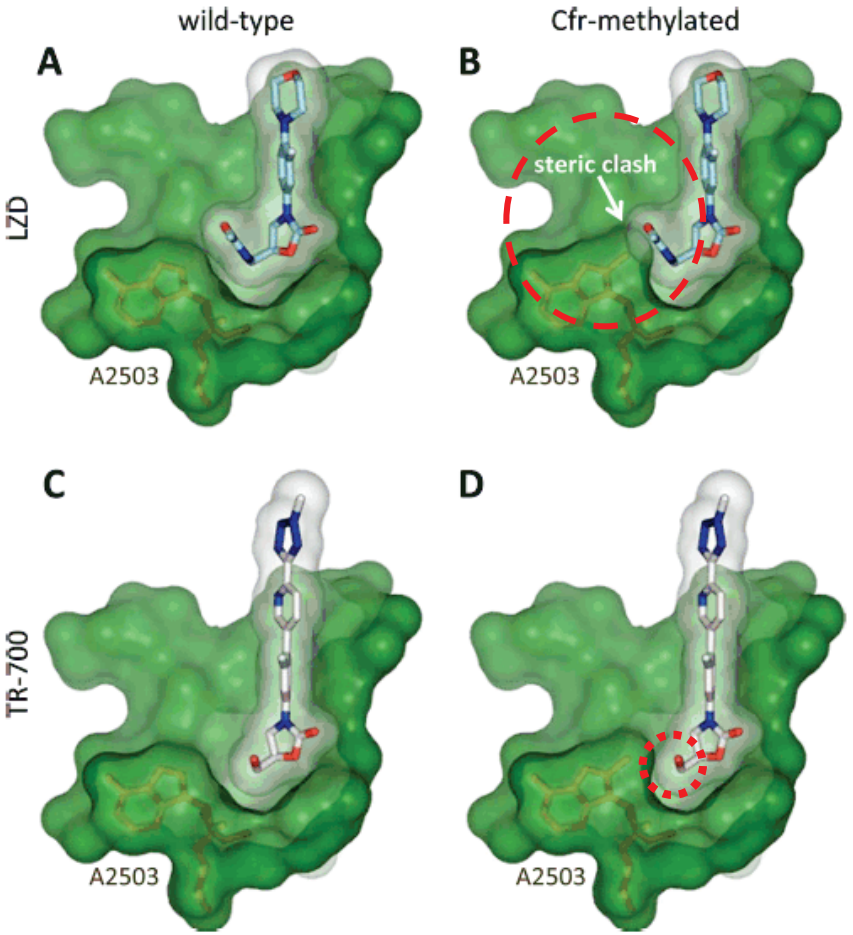
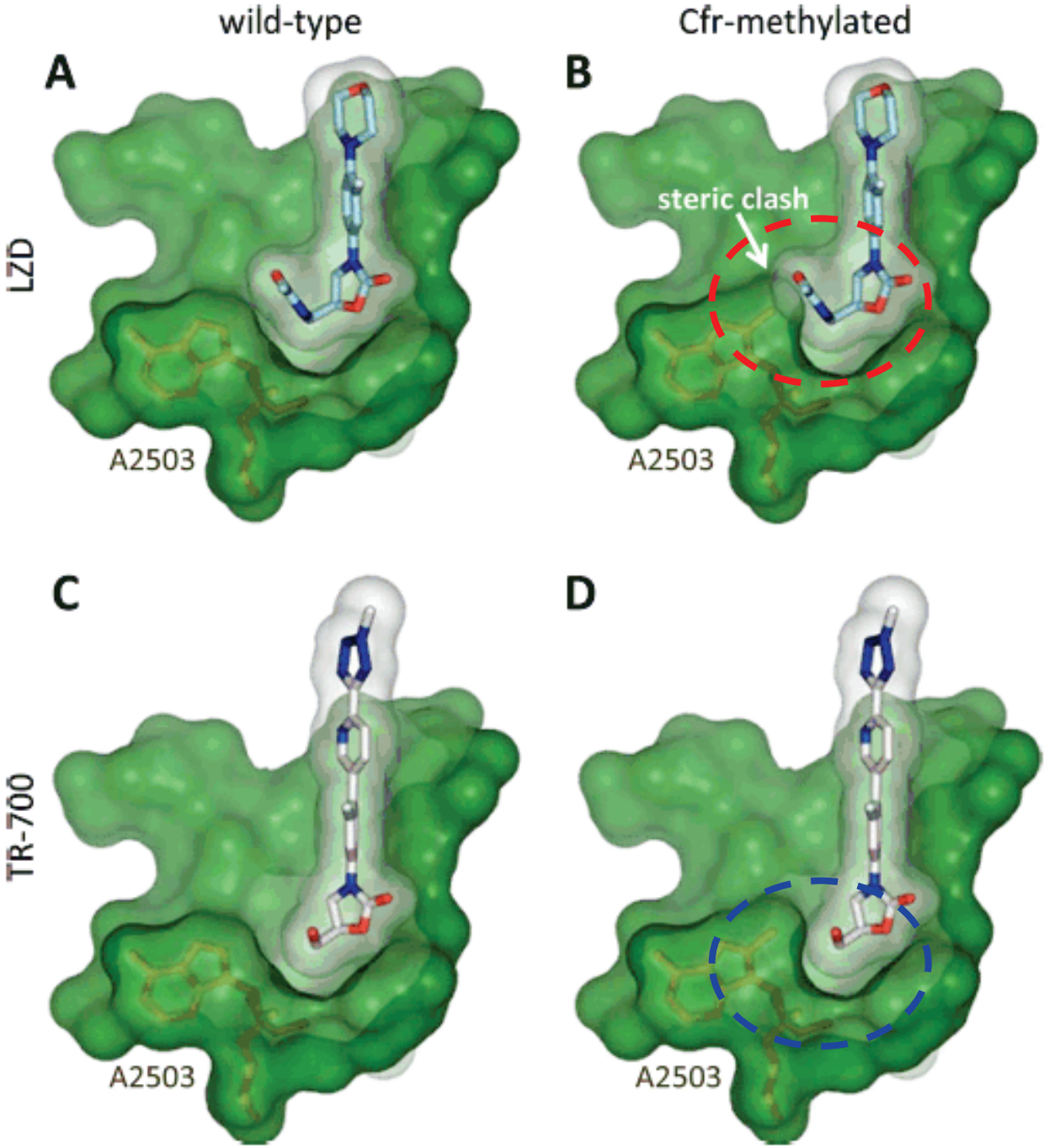


FIG. 2. Structural analysis of oxazolidinone binding in the presence of Cfr methylation. (A) Crystal structure of LZD-bound *H. marismortui* 50S ribosome (30). (B) Model of LZD binding in the Cfr-methylated state. (C and D) Proposed models of TR-700 bound to wild-type (C) or Cfr-methylated (D) ribosome. 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).

Why is tedizolid active against LZD^R strains (*cfr*) ?

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



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 ribo[illegible]mal proteins L3 and L4

But the MIC may exceed the EUCAST breakpoint !

Tedizolid and ribosomal mutations

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

Strain[a]	Source or reference	Resistance mechanism[b]	MIC (μg/ml)[c]	
			LZD	TR-700
29213	ATCC		2	0.5
29213-1	43	23S (G2447T ×3)	32	4
29213-2	43	23S (T2500A ×2)	8	2
29213-3	43	L3 (ΔPhe127-His146)	8	2
33591	ATCC		1	0.25
33591-1	43	23S (G2576T ×3)	16	2
33591-2	43	23S (G2576T/T2571C ×3)	16	2
33591-3	43	L4 (Lys68Gln)	2	0.5
NRS127	NARSA[d]	L3 (ΔSer145)	8	1

[a] 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^r clinical isolate.

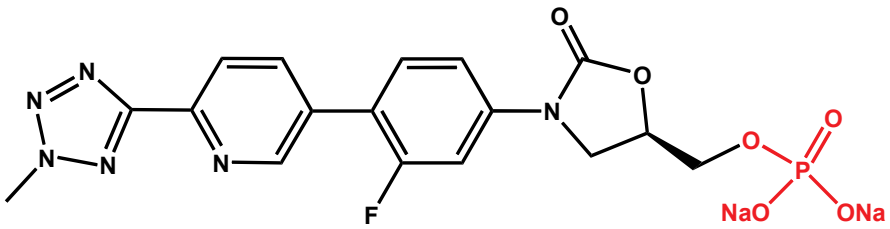
[b] Mutations in 23S rRNA genes (and mutant allele copy number) or in the ribosomal protein L3 or L4 are shown.

[c] MICs (broth microdilution; CLSI) were determined against the oxazolidinone panel

[d] Network of Antimicrobial Resistance in *Staphylococcus aureus*.

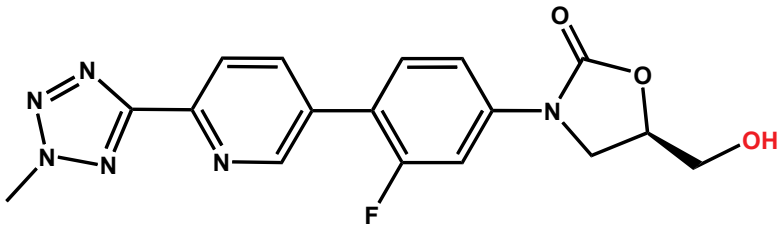
Locke et al. AAC 2010;54:5337-5343

Tedizolid is always administered as a prodrug…



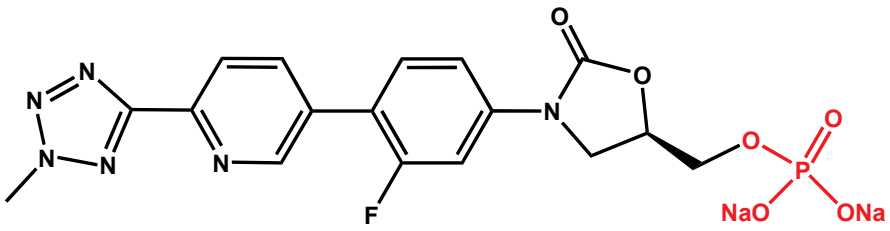
tedizolid phosphate

tedizolid



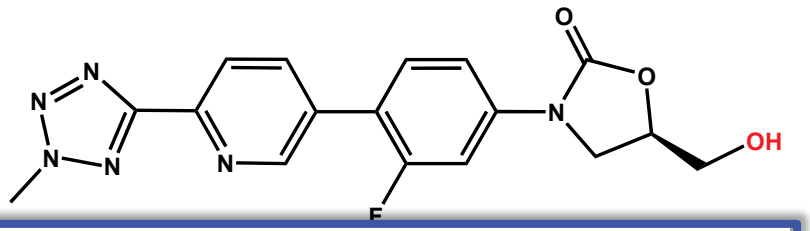
- **Tedizolid phosphate** is a water soluble **phosphate prodrug**
- **Phosphatases** rapidly cleave it *in vivo* to its **active moiety (tedizolid)**

Tedizolid is always administered as a prodrug…



tedizolid phosphate

tedizolid



- **Tedizolid phosphate** is a water soluble p
- **Phosphatases** rapidly cleave it *in vivo* to

Percentage of prodrug tedizolid phosphate remaining and tedizolid formed in plasma after incubation with 2 μg/ml tedizolid phosphate for 2 hours at 37°C

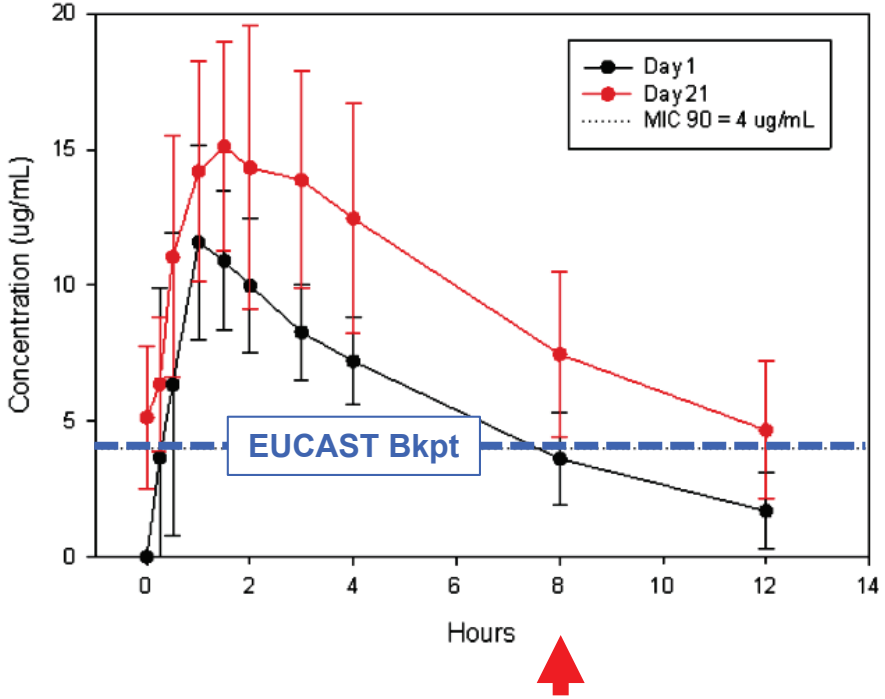
Samples were analyzed for tedizolid phosphate and tedizolid content by HPLC with UV detection.

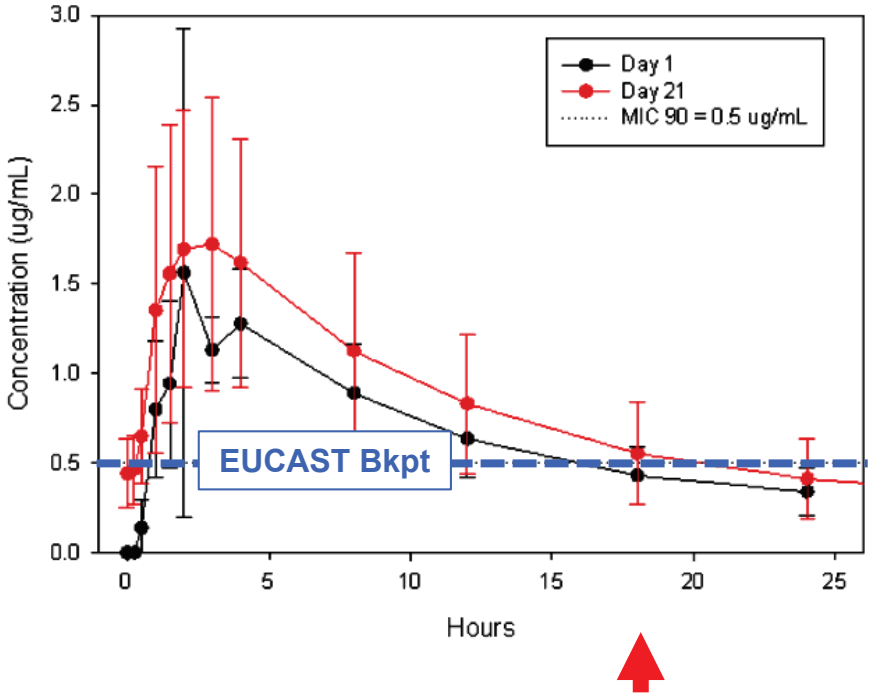
	Tedizolid Phosphate Half-Life	Tedizolid Phosphate Remaining after 2 Hours	Tedizolid Formed after 2 Hours[a]
	min	%	%
Mouse	28.8	4.1	90.7
Rat	77.0	29.6	76.7
Dog	28.3	3.4	80.5
Human	36.1	8.5	76.9

[a] percentage of the initial molar concentration of tedizolid phosphate.

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 x greater than linezolid
- longer initial presence at a concentration > the EU breakpoint

This allows for a once-a-day dosing

Muñoz et al. ECCMID 2010 P1594

Tedizolid: a fast development…

ORIGINAL CONTRIBUTION

Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections

The ESTABLISH-1 Randomized Trial

Philippe Prokocimer, MD
Carisa De Anda, PharmD
Edward Fang, MD
Purvi Mehra, 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.

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

Design, Setting, and Patients:

- Efficacy and Safety of
  - 6-day Oral Tedizolid (200 mg once-daily) *vs*
  - 10-day Oral Linezolid Therapy (600 mg twice daily)
- Intent-to-treat analysis from 667 adults (tedizolid: n=332; linezolid: n=335).

Tedizolid: a fast development…

ORIGINAL CONTRIBUTION

Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections

The ESTABLISH-1 Randomized Trial

TREATMENT OF ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS

Table 2. Clinical Response at Early and Late Time Points

Clinical Response	Tedizolid Phosphate (n = 332)	Linezolid (n = 335)	Absolute Treatment Difference (95% CI), %
At the 48- to 72-h assessment (ITT analysis set)			
Treatment responder, No. (%) [95% CI]	264 (79.5) [74.8 to 83.7]	266 (79.4) [74.7 to 83.6]	0.1 (−6.1 to 6.2)
Cellulitis/erysipelas, No./total (%)	101/135 (74.8)	100/139 (71.9)	
Major cutaneous abscess, No./total (%)	80/100 (80.0)	84/98 (85.7)	
Wound infection, No./total (%)	83/97 (85.6)	82/98 (83.7)	
Treatment nonresponder or indeterminate, No. (%)[a]	68 (20.5)	69 (20.6)	
Treatment nonresponder	27 (8.1)	35 (10.4)	
Indeterminate	41 (12.3)	34 (10.1)	
Missing lesion measurements	22 (6.6)	24 (7.2)	
Missing temperature data	37 (11.1)	32 (9.6)	

Tedizolid: a fast development…

ORIGINAL CONTRIBUTION

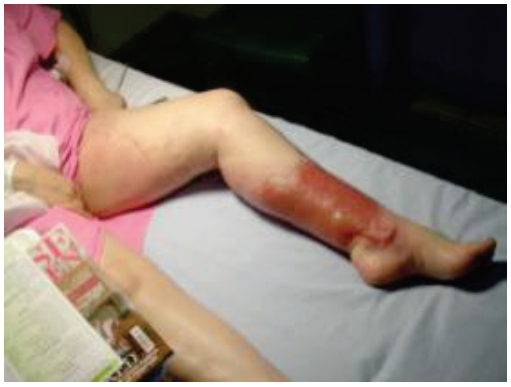
Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections

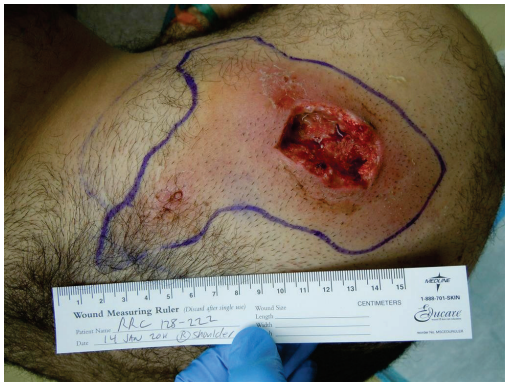
The ESTABLISH-1 Randomized Trial

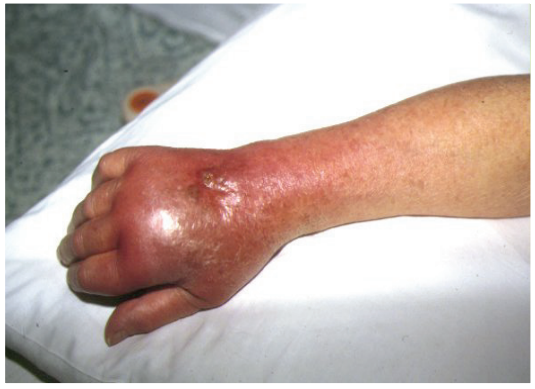
Table 2. Clinical Response at Early and Late Time Points

Clinical Response	Tedizolid Phosphate (n = 332)	Linezolid (n = 335)	Absolute Treatment Difference (95% CI), %
Sustained at the EOT assessment (ITT analysis set)			
Clinical success, No. (%) [95% CI]	230 (69.3) [64.0 to 74.2]	241 (71.9) [66.8 to 76.7]	−2.6 (−9.6 to 4.2)
Cellulitis/erysipelas, No./total (%)	85/133 (63.9)	84/135 (62.2)	
Major cutaneous abscess, No./total (%)	72/100 (72.0)	78/97 (80.4)	
Wound infection, No./total (%)	73/99 (73.7)	79/103 (76.7)	
Clinical treatment failure or indeterminate, No. (%)	102 (30.7)	94 (28.1)	
Clinical treatment failure	60 (18.1)	61 (18.2)	
Indeterminate	42 (12.7)	33 (9.9)	
Lost to follow-up	14 (4.2)	14 (4.2)	
Gram-negative infection	4 (1.2)	3 (0.9)	
Withdrew consent	6 (1.8)	2 (0.6)	
Indeterminate at the 48- to 72-h assessment	33 (9.9)	26 (7.8)	
Pregnancy	1 (0.3)	1 (0.3)	
Sustained at the EOT assessment (CE-EOT analysis set)	**(n = 273)**	**(n = 286)**	

US indications and dosages for tedizolid (SIVEXTRO®) [1]







- adults with **acute bacterial skin and skin structure infections** (ABSSSI) caused by **susceptible** Gram-positive isolates (*S. aureus* [including MRSA], *S. pyogenes*, *S. agalactiae*, *S. anginosus* Group, and *E. faecalis*).
- ➢ 200 mg once daily for 6 days (no adjustment for elderly, renal or hepatic insufficiency) IV or oral

[1] https://www.merck.com/product/usa/pi_circulars/s/sivextro/sivextro_pi.pdf

Pros and cons of tedizolid *vs* linezolid

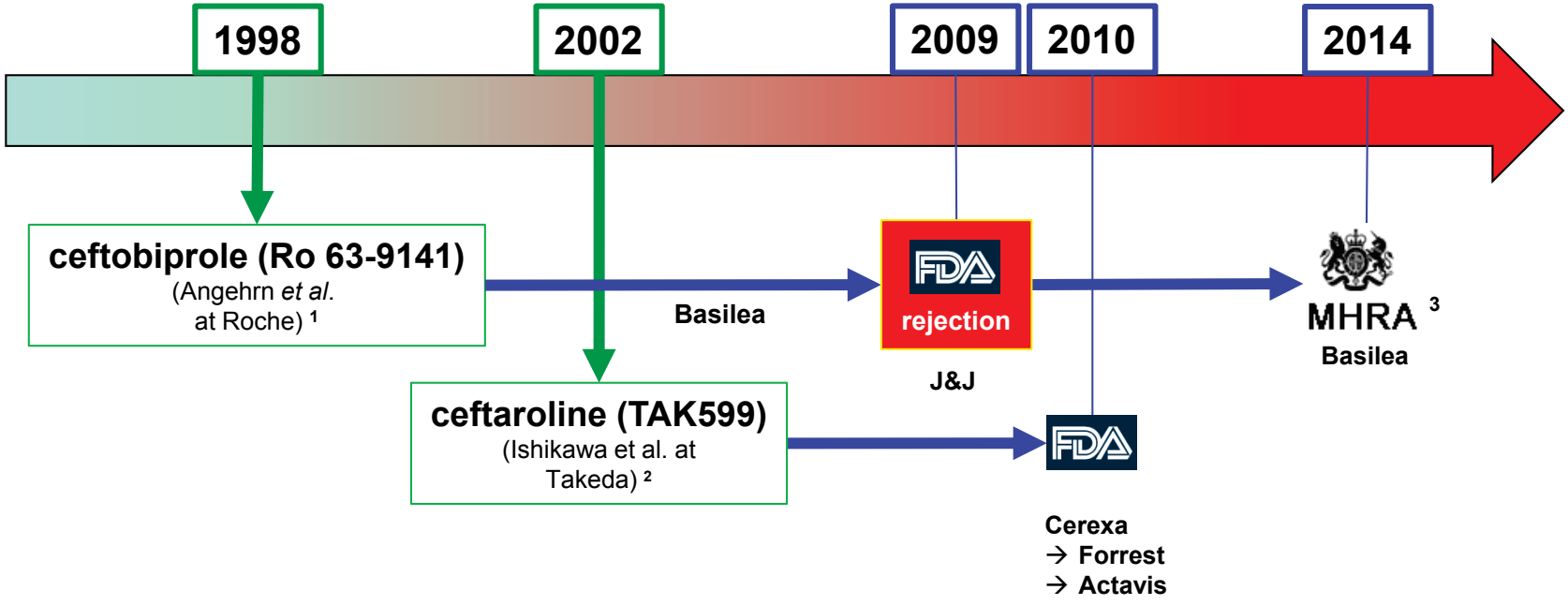
Pros

- Once daily dosing
- IV to oral switch totally effective and easy
- No serotoninergic syndrome (prodrug is tedizolid phosphate)
- no toxicity risk in renal insufficiency
- efficacious in 6 days (lower toxicity risk …)

Cons

- Limited indications (at present)
- Insufficient knowledge about toxicity risks (> 6 days)
- Price (but low clinical burden than vancomycin)

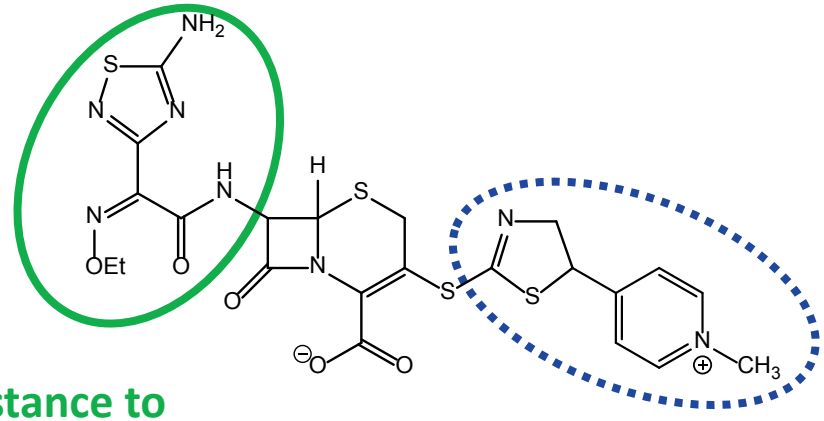
Ceftaroline - Ceftobiprole



[1] Angehrn et al. Rur. Pat. Appl. (1998), EP 849269 A1 19980624.
[2] Ishikawa et al. PCT Int. Appl. (2002), WO 2002014333 A1 Feb 21, 2002
[3] extension to 13 European countries and Canada (http://www.basilea.com/Portfolio/Ceftobiprole/)

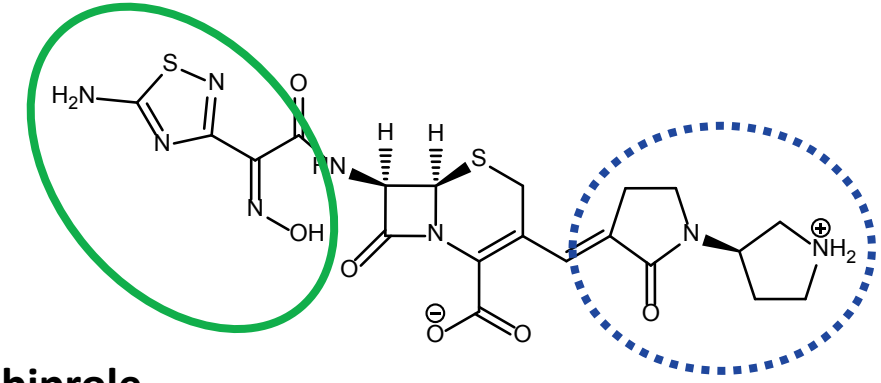
Ceftaroline and ceftobiprole

ceftaroline



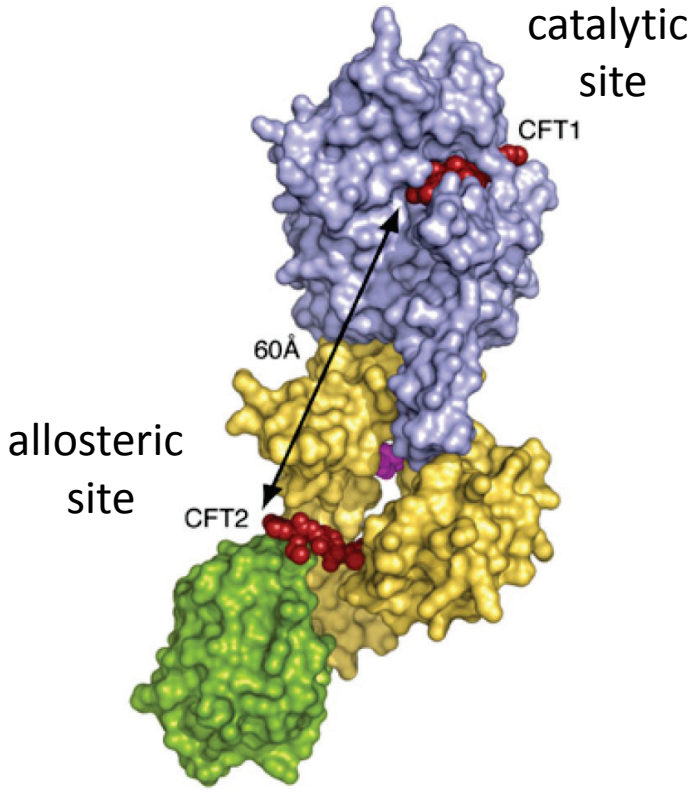
Resistance to β-lactamases

Binding to PBP2a



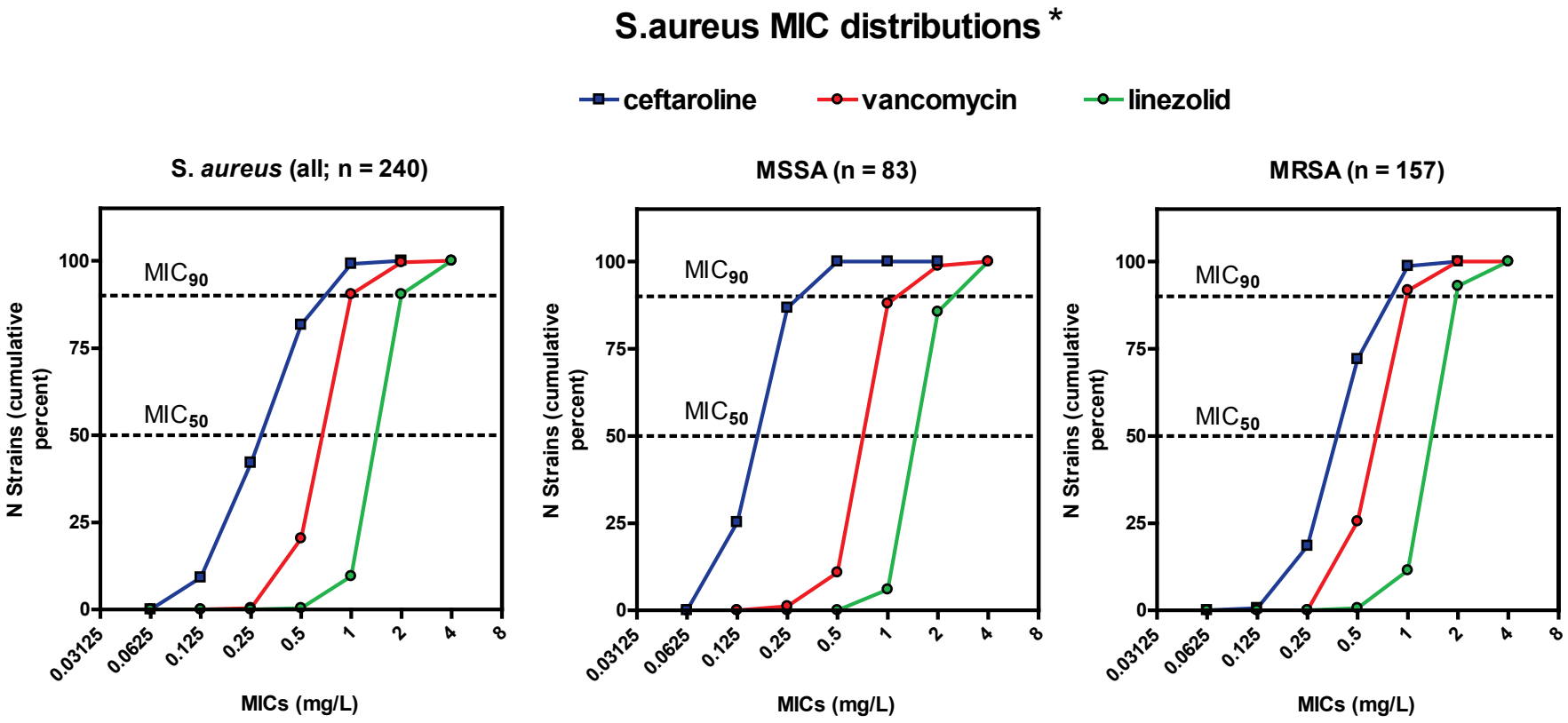
ceftobiprole

ceftaroline & PBP2a



- Van Bambeke at al. Infectious Diseases, 3d EditionChap. 130: Mechanisms of action, Elsevier/Mosby, 2010 Available on line at http://www.expertconsultbook.com/
- Otero et al, PNAS (2013) 110:16808–13

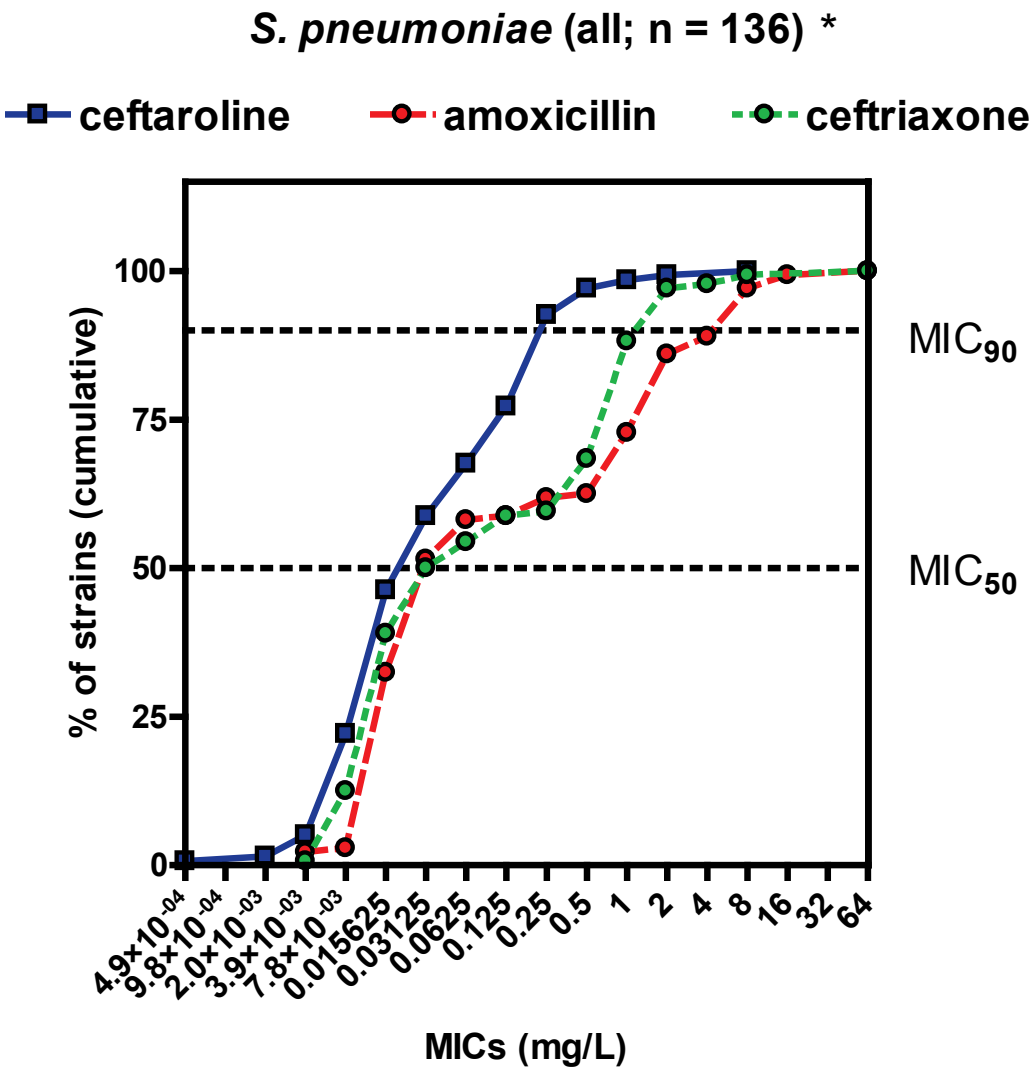
Ceftaroline and *S. aureus*



* isolates collected between 2011 and 2012 in Belgium from patients suffering of wound infections in 3 hospitals in Belgium (1 in South-East of Brussels; 1 in North of Brussels; 1 in Hainaut)

Tulkens et al. 26th ICC, 2013 and unpublished

Ceftaroline and *S. pneumoniae*



* isolates collected in Belgium between 2009 and 2012 obtained from patients with confirmed cases of CAP (clinical and radiological criteria) and seen at the Emergency Departement of 4 hospitals (1 in East-Flanders, 1 in North Brussels, 1 in South-East Brussels, 1 in Hainaut)

N.B. the high MICs of amoxicillin in this collection (with 11 % of the strains for which the MIC of amoxicillin is > 2 mg/L) is largely driven by recent isolates from patients who had suffered from episodes of COPD before having contracted a CAP.

Tulkens et al. 26th ICC, 2013 and unpublished

Ceftaroline: global pre-registration MICs (Gram +)

Table I. *In vitro* activity of ceftaroline and comparators against Gram-positive aerobic bacteria[29,30,36,37]

Bacteria, number of isolates	Ceftaroline			Ceftazidime		Ceftriaxone		Reference
	MIC_{50} (mg/L)	MIC_{90} (mg/L)	range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	
Staphylococcus aureus (MS), 1554	0.25	0.25	≤0.008–1	NA	NA	4	4	37
S. aureus (MR), 1237	1	1	0.25–2	NA	NA	32	>32	37
S. aureus (hVISA and VISA), 100	1	2	0.25–4	NA	NA	>32	>32	36
S. epidermidis (MS), 15	0.13	0.13	0.06–0.13	4	8	1	2	30
S. epidermidis (MR), 26	0.5	1	0.25–1	32	64	32	64	30
Enterococcus faecalis, 613	2	8	0.12 to >16	NA	NA	>32	>32	37
E. faecium (VAN-R), 26	>16	>16	4–16	>32	>32	>32	>32	29
Streptococcus pneumoniae (PS), 202	≤0.008	0.015	≤0.008–0.12	≤1	≤1	0.03	0.06	29
S. pneumoniae (PI), 103	0.015	0.06	≤0.008–0.5	2	8	0.12	0.5	29
S. pneumoniae (PR), 296	0.12	0.12	≤0.008–0.5	16	32	1	2	29
Viridans group streptococci (PS), 190	0.03	0.06	≤0.008–1	NA	NA	≤0.25	0.5	37
Viridans group streptococci (PR), 42	0.03	0.5	≤0.008–1	NA	NA	≤0.25	8	37
S. pyogenes (ERY-S), 91	≤0.008	≤0.008	≤0.008–0.03	≤1	≤1	≤0.015	0.03	29
S. agalactiae (ERY-S), 59	0.015	0.015	≤0.008–0.06	≤1	≤1	0.06	0.12	29
S. agalactiae (ERY-NS), 42	0.015	0.015	≤0.008–0.12	≤1	≤1	0.06	0.12	29

ERY-NS = erythromycin-nonsusceptible; **ERY-S** = erythromycin-susceptible; **hVISA** = hetero-resistant vancomycin-intermediate *S. aureus*; **MIC_{50}** = minimum inhibitory concentration (mg/L) of 50% of isolates; **MIC_{90}** = minimum inhibitory concentration of 90% of isolates; **MR** = meticillin-resistant; **MS** = meticillin-susceptible; **NA** = not available/assessed in study from which data for this pathogen is reported; **PI** = penicillin-intermediate; **PR** = penicillin-resistant; **PS** = penicillin-susceptible; **VAN-R** = vancomycin-resistant; **VISA** = vancomycin-intermediate *S. aureus*.

Ceftaroline: US breakpoints (FDA)

Table 6: Susceptibility Interpretive Criteria for Ceftaroline

Pathogen and Isolate Source	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
Staphylococcus aureus (includes methicillin-resistant isolates - skin isolates only) -See **NOTE** below	≤ 1	2	≥ 4	≥ 24	21-23	≤ 20
Streptococcus agalactiae[a] (skin isolates only)	≤ 0.5	—	—	≥ 26	—	—
Streptococcus pyogenes[a] (skin isolates only)	≤ 0.5	—	—	≥ 26	—	—
Streptococcus pneumoniae[a] (CABP isolates only)	≤ 0.5	—	—	≥ 26	—	—
Haemophilus influenzae[a] (CABP isolates only)	≤ 0. 5	—	—	≥ 30	—	—
Enterobacteriaceae[b] (CABP and skin isolates)	≤ 0.5	1	≥ 2	≥ 23	20-22	≤ 19

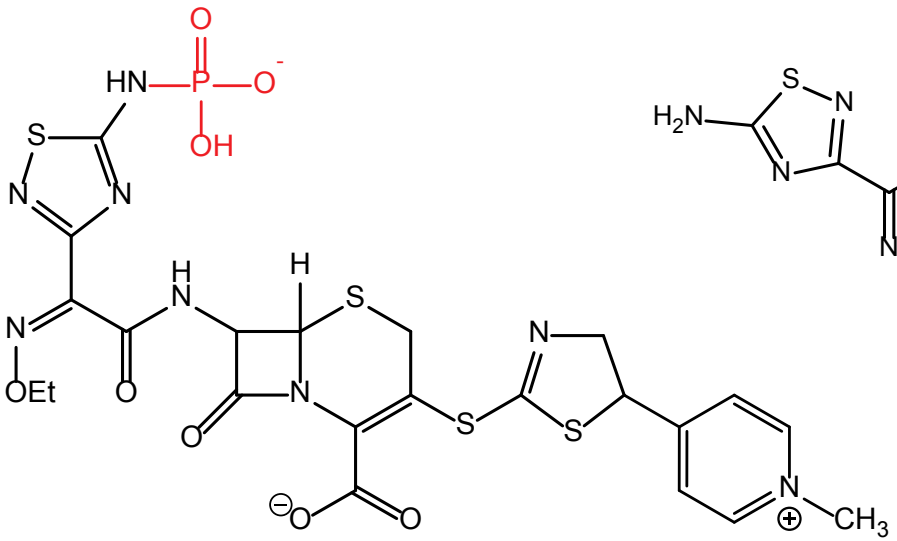
S = susceptible, I = intermediate, R = resistant

NOTE: Clinical efficacy of Teflaro to treat lower respiratory infections such as community-acquired bacterial pneumonia due to MRSA has not been studied in adequate and well controlled trials (See "Clinical Trials" section 14)

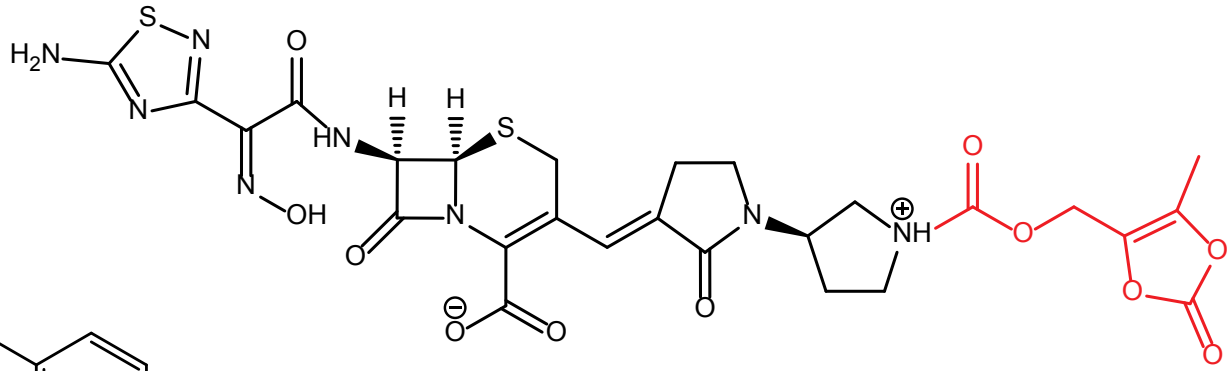
[a] The current absence of resistant isolates precludes defining any results other than "Susceptible." Isolates yielding MIC results other than "Susceptible" should be submitted to a reference laboratory for further testing.

[b] Clinical efficacy was shown for the following *Enterobacteriaceae: Escherichia coli, Klebsiella pneumoniae, and Klebsiella oxytoca.*

Ceftaroline and ceftobiprole clinical presentations: both are prodrugs (to improve solubility)



ceftaroline fosamil



ceftobiprole medocaril

Ceftaroline and ceftobiprole: indications and dosages

- **Ceftaroline** (TEFLARO®) in US [1]
  - adults with **acute bacterial skin and skin structure infections** (ABSSSI) caused by **susceptible** isolates (*S. aureus* [including MRSA], *S. pyogenes*, *S. agalactiae*, *E. coli*, *K. pneumoniae*, and *K. oxytoca*).
  - **community-acquired pneumonia** (CAP) caused by **susceptible** isolates (*S. pneumoniae* [including bacteremia], *S. aureus* (**MSSA only**), *H. influenzae*, *K. pneumoniae*, *K. oxytoca*, and *E. coli*
  - ➢ 600 mg q12 h by infusion over 5 to 60 min (cSSTI: 5 to 14 days; CAP: 5 to 7 days
    Reduced dosages based on CrCl (ml/min): > 30 to ≤ 50: 400 mg, 15 to ≤ 30: 300 mg, End-stage renal disease and hemodialysis: 200 mg

- **Ceftobiprole** (ZEVTERA®) in EU and Canada [2]
  - **Hospital-acquired pneumonia** (HAP), excluding ventilator-associated pneumonia (VAP) or **community-acquired pneumonia** (CAP)
  - ➢ 500 mg q8h by infusion over 2 h
    Reduced dosages based on CrCl (mL/min): 30 to < 50: 500 mg q12H, < 30: 250 mg q12h, End stage renal disease and hemodialysis: 250 mg q24h
    Patients with CCl > 150 mL/min: 500 mg infused over 4h

[1] http://pi.actavis.com/data_stream.asp?product_group=1915&p=pi&language=E
[2] https://www.medicines.org.uk/emc/medicine/29764 (decentralized registration procedure with UK as reference country).

Pros and cons of the new anti-MRSA cepahalosporins

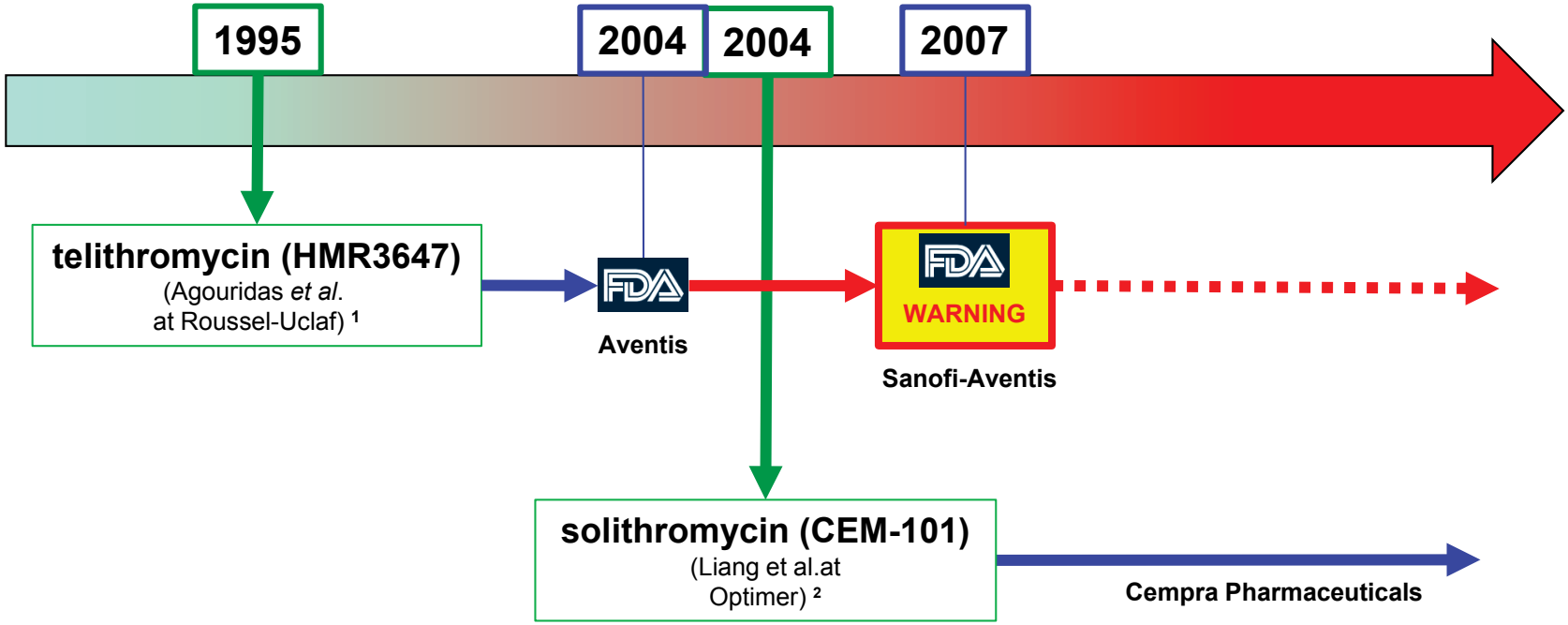
Pros

- Patient with MRSA with reduced susceptibility to vancomycin
  → VISA and hVISA strains -- **check ceftaroline/ceftobiprole MICs !**
  !!! check the indications or use off label (pneumonia !!!)
- Mixed infections: may cover Enterobacteriaceae (but susceptible to ESBLs !)
  → **check ceftaroline/ceftobiprole MICs**
- CAP in case of reduced susceptibility to amoxicillin/ceftriaxone

Cons

- Infusion only (no oral switch possible)
- Limited indications (at present)
- Insufficient knowledge about toxicity risks
- Price (but low clinical burden than vancomycin)

Solithromycin: the new telithromycin ?

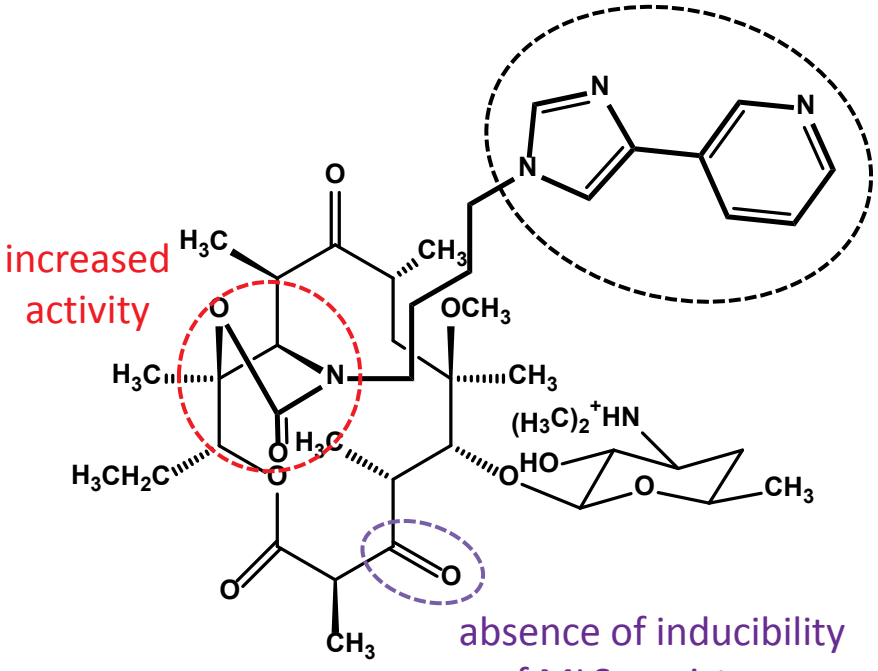


1 Agouridas et al. Eur. Pat. Appl. (1995), EP 680967 A1 19951108.
Agouridas et al. J. Med Chem 1998;41:4080-100
2 Liang et al. PCT Int. Appl. (2004), WO 2004080391 A2 20040923

See also: Van Bambeke. Annals of Medicine (2014) 46:512-29
(available at http://www.facm.ucl.ac.be/Full-texts-FACM/Vanbambeke-2014-2.pdf)
.

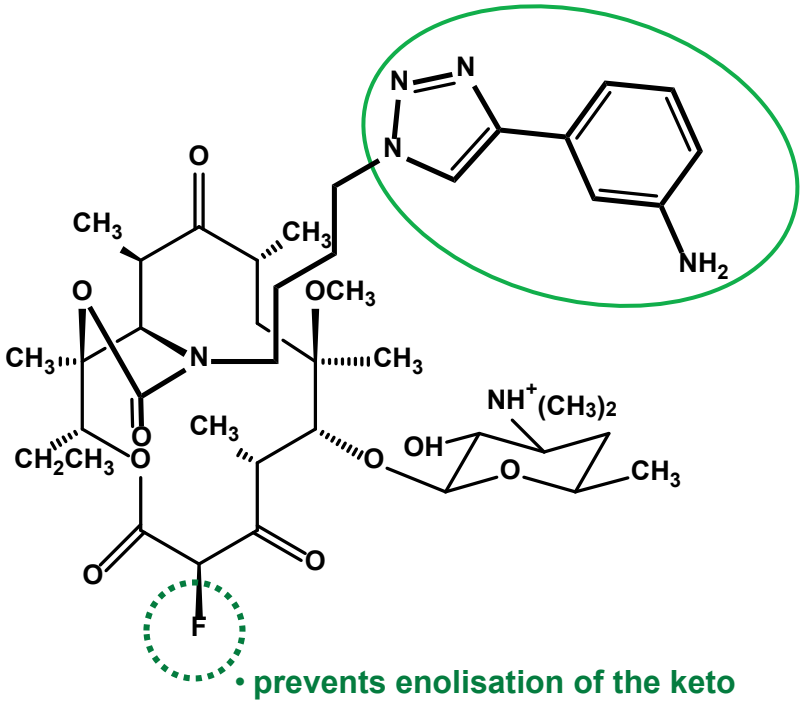
From telithromycin to solithromycin

- binding to ribosomal domain II
- poor recognition by pneumococci efflux pumps



telithromycin

lower interaction with nicotinic receptor



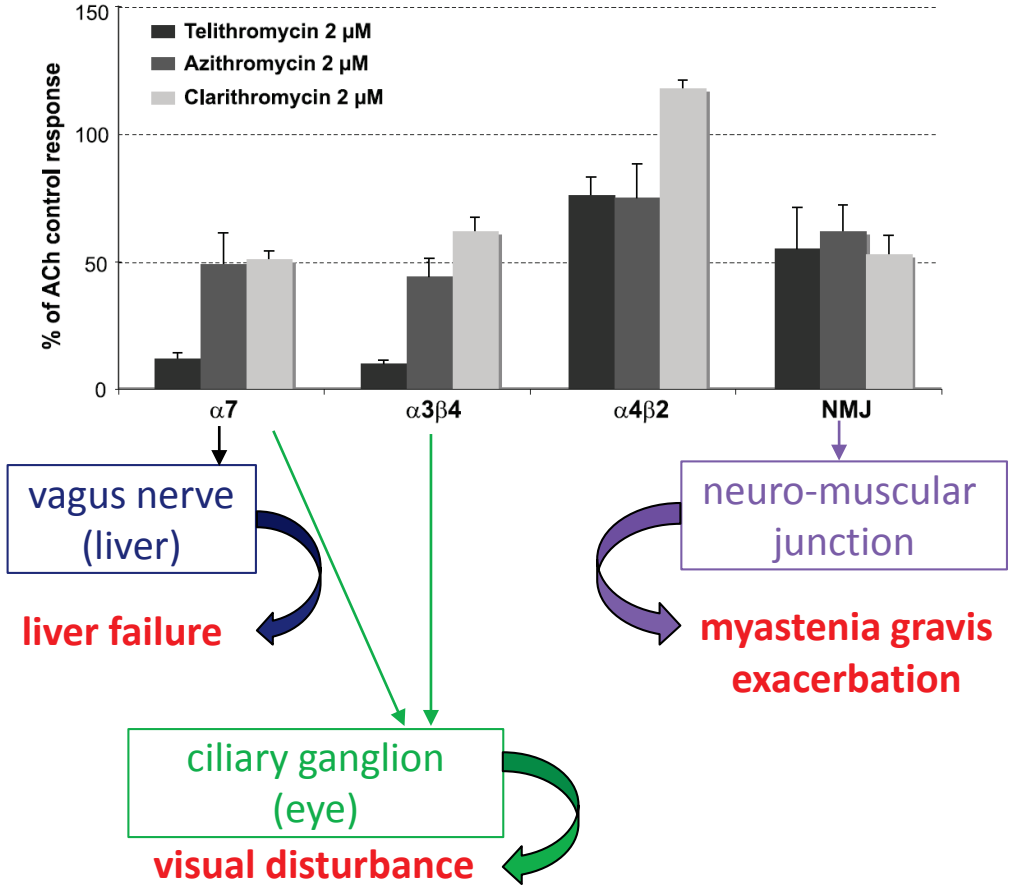
- **prevents enolisation of the keto group**
- **cooperates with the side-chain to overcome resistance**

solithromycin

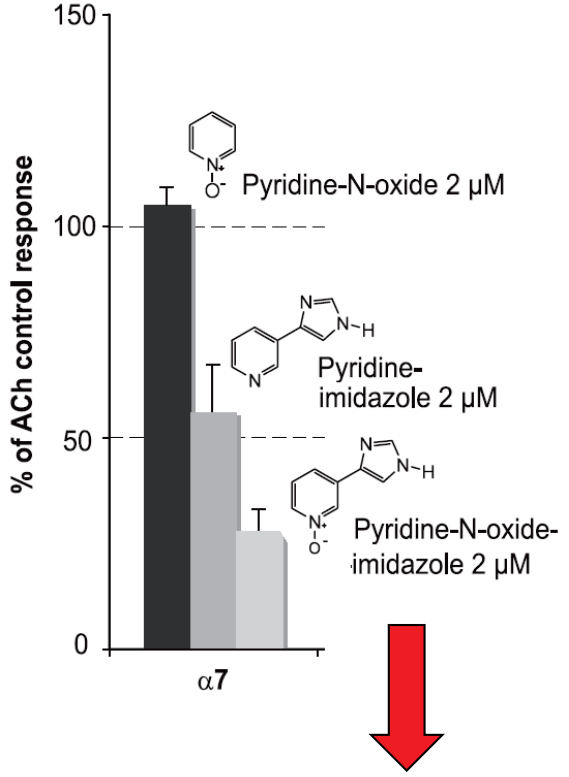
Modified from Van Bambeke, Ann. Med (2014) 46:512-29

telithromycin : structure-toxicity relationship

Inhibition of acetycholine nicotinic receptors



Role of telithromycin metabolites



Metabolites
NOT present for solithromycin

Adapted from Bertrand et al, AAC (2010) 54:5399-42

Solithromycin: first analysis of susceptibility of European *S. pneumoniae* (semi-random collection)

Isolates		MIC (mg/L)						
		SOL	PEN	AMX	CRO	MXF	LVX	CPT
A. all isolates (n)		423	426	426	418	425	424	425
MIC (mg/L)	**min**	0.0018	0.0002	0.0039	0.0039	0.0039	0.0078	0.0005
	geom. mean	0.0229	0.0481	0.0726	0.0609	0.2279	1.4470	0.0252
	90%	0.062	2	2	1	2	8	0.25
	max	1	64	64	8	128	128	8
B. NS or R [a] isolates (n)			116 [b]	80 [b]	60 [b]	65 [b]	57 [b]	19 [b]
MIC (mg/L)	**geom. mean**	0.0434 [c]	1.1542	2.5713	1.3360	3.7123	15.615	0.9642
	90%	0.25 [c]	4	8	2	16	32	2
correlation [d]	**alpha [e]**		0.19	0.06	0.01	0.31	0.33	-0.54
	R^2 [f]		0.03	0.002	0.00019	0.1	0.05	0.092
	prob. > F [g]		0.04	0.68	0.97	0.008	0.070	0.207

[a] MIC (mg/L) above EUCAST S breakpoint (PEN > 0.06; AMX > 0.5; CRO > 0.5; MXF > 0.5; LVX > 2; CPT > 0.25; see http://www.eucast.org; not breakpoint set yet for solithromycin

[b] isolates with NS or R phenotype to the corresponding antibiotic

[c] for strains with a NS or R phenotype to PEN

[d] correlations SOL (y) *vs*. each other antibiotic (x)

[e] from equation: SOL MIC = alpha x (comparator MIC) + b

[f] coefficient of determination

[g] p-value for "Lack of Fit" test.

SOL: solithromycin
PEN: penicillin G
AMX: amoxicillin
CRO ceftriaxone
MXF: moxifloxacin
LVX: levofloxacin
CPT: ceftaroline

Tulkens et al. ICCAC 2013 – Poster A1021

Solithromycin: second analysis of susceptibility of European *S. pneumoniae* *(collection enriched in strains with expected resistance to commonly used antistreptococcal antibiotics)*

	mg/L [a]								
	SOL	TEL	CLR	AZM	AMX	CRO	CPT	LVX	MXF
MIC_{50}	0.0156	0.0156	0.0625	0.125	0.0312	0.0312	0.0156	1	0.125
MIC_{90}	**0.0625**	0.125	**64**	**64**	2	1	0.25	**16**	**4**
	Susceptible / Resistant (%) [b]								
S		95.8 %	66.6 %	53.5 %	82.0%	86.3%	95.8%	88.4%	87.0%
R		2.9%	**29.8%**	**35.4%**	**5.0%**	0.8%	4.2%	**11.6%**	**13.0%**

[a] SOL: solithromycin; TEL: telithromycin, CLR: clarithromycin; AZM: azithromycin; AMX: amoxicillin; CRO: ceftriaxone; CPT: ceftaroline; LVX: levofloxacin; MXF: moxifloxacin

[b] EUCAST interpretive criteria (2014).

The elevated resistance levels for LVX and MXF were driven from the Belgian RTI (10.3 and 14.1%) and COPD (8.4 and 13.3%), and the German IPI (53.5 and 58.1%) collections vs only 3.0 and 0.6% for the Belgian CAP collection.

Tulkens et al. ECCMD 2015 – e-poster EV0153

Solithromycin: completed clinical trials

Study number & development Phase	Drugs and doses	Study title	Status
NCT01966055; Phase I	Solithromycin; dose not specified	Pharmacokinetics and Safety of Solithromycin Capsules in Adolescents	Completed (2014)
NCT01168713; Phase II	Oral solithromycin (800 mg QD day 1; 400 mg QD days 2-5) ; comparator: oral levofloxacin (750 mg QD days 1-5)	Efficacy and Safety Study of Oral CEM-101 Compared to Oral Levofloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia	Completed (2011)
NCT01591447; Phase II	Single dose solithromycin 1000 mg by oral route	Safety and Efficacy Study of Single-Dose Oral CEM-101 in Patients With Uncomplicated Urogenital Gonorrhea	Completed (2013)
NCT01968733; Phase III	Solithromycin (intravenous with the potential step-down to oral); comparator: moxifloxacin (intravenous with the potential step-down to oral); doses not specified	Efficacy and Safety Study of Intravenous to Oral Solithromycin (CEM-101) Compared to Intravenous to Oral Moxifloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia (SOLITAIRE-IV)	Completed (2015)
NCT01756339; Phase III	Solithromycin (800 mg orally on day 1 followed by 400 mg daily on days 2 through 5, followed by placebo on days 6 and 7); comparator: moxifloxacin (400 mg orally on Day 1 to 7)	Efficacy and Safety Study of Oral Solithromycin (CEM-101) Compared to Oral Moxifloxacin in Treatment of Patients With Community-Acquired Bacterial Pneumonia (SOLITAIRE-ORAL)	Completed (2014)

Pros and cons of solithromycin

Pros

- restores the position of macrolides / ketolides as potential first line **monotherapy in respiratory tract infections** (incl. activity against agents causing both typical and atypical pneumonia)
- **as effective as moxifloxacin** with potentially less toxicity risks
- **both IV and oral** forms and pediatric formulation (in development)
- active against *Gonococci* and a series of bioterrorism isolates [1]

Cons

- not yet available and will be registered with limited indications (at present)
- Insufficient knowledge about toxicity risks
- price (not yet defined)

[1] http://www.phe.gov/Preparedness/news/Pages/broad-spectrum-June2013.aspx

What shall I focus on ?

Drugs that are registered in Europe (* or will be soon) …

a) Lipoglycopeptides (*from vancomycin*)
   - telavancin (old but renewed…)
   - dalbavancin
   - oritavancin

b) Oxazolidinones (*from linezolid*)
   - tedizolid

c) cephalosporines anti-MRSA (*from ceftazidime*)
   - ceftaroline
   - ceftobiprole

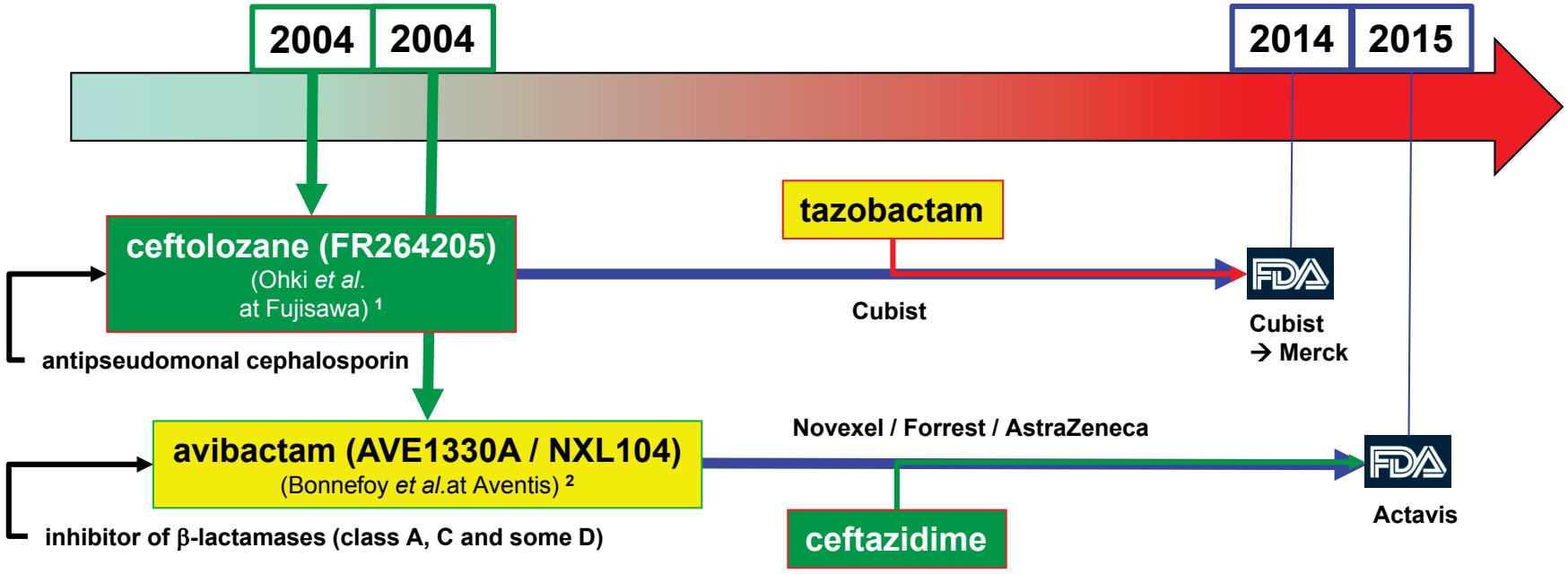
d) Ketolides (*from telithromycine*)
   - solithromycin *

anti Gram (+)

e) cephalosporins x β-lactamase inhibitors
   - ceftozolane x tazobactam
   - ceftzidime x avibactam *

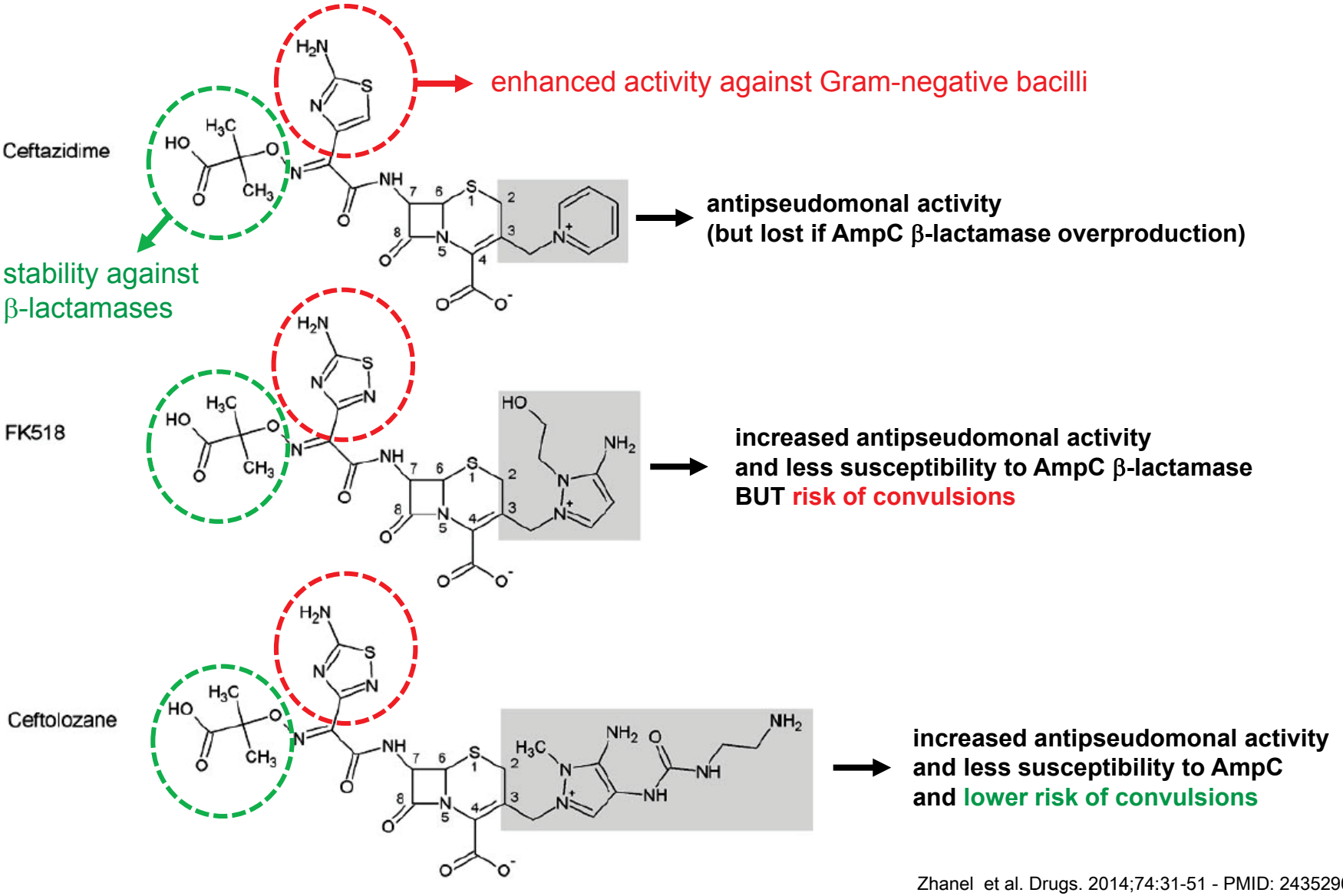
anti Gram (-)

Ceftolozane (+tazobactam) **– Avibactam** (+ ceftazidime)**: the new Graal ?**



[1] Ohki *et al*. PCT Int. Appl. (2004), WO 2004039814 A1 2 Liang et al. PCT Int. Appl. (2004), WO 2004080391 A2 20040923
[2] Bonnefoy *et al.* J. Antimicrob. Chemother. (2004) 54 (2): 410-417

ceftolozane: the origins…



Zhanel et al. Drugs. 2014;74:31-51 - PMID: 24352909.

Table 1 In vitro activities of ceftolozane/tazobactam[a] and comparators against Gram-negative and Gram-positive aerobes

Organism	Ceftolozane			Ceftolozane/tazobactam[a]		
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
Gram-negative aerobes						
Acinetobacter baumannii	–[b]	–	–	0.5	2	≤0.12 to 16
Acinetobacter spp.	8	>32	≤0.12 to ≥32	8	>32	≤0.12 to ≥32
Burkholderia cepacia	4	32	≤0.25 to >256	–	–	–
Citrobacter spp. (all)	0.5	16	≤0.12 to ≥32	0.25	8	≤0.12 to ≥32
Ceftazidime-resistant[c]	32	>32	1 to >32	16	>16	0.25 to >16
Enterobacter cloacae	0.25	32	≤0.12 to ≥32	0.25	8	≤0.12 to ≥32
Enterobacter spp.	0.5	16	–	0.25	8	≤0.03 to ≥32
Ceftazidime-resistant[c]/non-susceptible	>32	>32	4 to >32	8	32	0.25 to >32
Escherichia coli (all)	0.12	0.5	0.12 to >64	0.12	0.5	≤0.12 to >32
Ceftazidime resistant[c]	>32	>32	1 to >32	1	16	≤0.12 to >16
ESBL producers	64	>64	0.25 to >64	0.5	4	≤0.12 to >32
Haemophilus influenzae	0.12	0.25	≤0.12 to 1	≤0.12	0.25	≤0.12 to 1
Klebsiella oxytoca	–	–	–	≤0.12	0.5	≤0.12 to 2
Klebsiella pneumoniae (all)	0.25	16	≤0.12 to >64	0.25	8	≤0.12 to ≥32
Ceftazidime-resistant[c]	>32	>32	4 to >32	4	>16	≤0.12 to >16
ESBL producers	32	>64	2 to >64	0.5	64	≤0.12 to >64
KPC producers	>32	>32	32 to >32	>16	>16	16 to >16
Klebsiella spp. (all)	0.25	>32	–	0.25	4	0.12 to >32
ESBL producers	>32	>32	–	2	>32	0.12 to >32
Moraxella catarrhalis	≤0.12	0.5	–	–	–	–
Proteus mirabilis (all)	0.25	0.5	≤0.12 to 16	0.25	0.5	≤0.12 to 16
ESBL producers	8	>32	≤0.25 to >32	1	8	0.25 to >16
Proteus spp., indole-positive	–	–	–	0.25	1	0.12 to ≥32
Ceftazidime-resistant[c]	>32	>32	4 to >32	2	>16	0.25 to >16
Pseudomonas aeruginosa (all)	0.5	2	≤0.12 to ≥128	0.5	2	≤0.12 to >128
Serratia marcescens	0.5	1	0.25 to ≥32	0.5	1	≤0.12 to ≥32
Serratia spp.	0.5	1	–	0.5	1	0.12 to ≥32
Stenotrophomonas maltophilia	–	–	–	16	>64	0.5 to >64

ceftozolane tazobactam

this will be an antibiotic for **documented therapy**

Zhanel et al. Drugs. 2014;74:31-51 - PMID: 24352909.

Ceftozolane-tazobactam (ZERBAXA®): **US indications and dosages**

- Adults with the following infections caused by **designated susceptible microorganisms**:

  – Complicated Intra-abdominal Infections (with metronidazole):
  Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus, and Streptococcus salivarius.

  – Complicated Urinary Tract Infections, including Pyelonephritis:
  Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and Pseudomonas aeruginosa.

- 1.5 g (1 g + 0.5 g) q8h infused over 1 h

  Reduced doses for CrCl (ml/min): 30 to 50: 750 mg (500+250), 15 to 29: 375 mg (250+125 mg), End-stage renal disease (ESRD) on hemodialysis (HD): single loading dose 750 mg (500+/250) and 150 mg (100+50) q8h, hemodialysis days: dose after completion of dialysis

https://www.merck.com/product/usa/pi_circulars/z/zerbaxa/zerbaxa_pi.pdf

Ceftozolane-tazobactam (ZERBAXA®): what is "susceptible" ?

FDA breakpoints

Table 7: Susceptibility Interpretive Criteria for Ceftolozane/Tazobactam

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
Enterobacteriaceae	≤2/4	4/4	≥8/4	---	---	---
Pseudomonas aeruginosa	≤4/4	8/4	≥16/4	≥21	17-20	≤16
Streptococcus anginosus *Streptococcus constellatus and* *Streptococcus salivarius*	≤8/4	16/4	≥32/4	---	---	---
B. fragilis	≤8/4	16/4	≥32/4	---	---	---

S = susceptible, I = intermediate, R = resistant

Ceftolozane/tazobactam susceptibility testing is performed with a fixed 4 µg/mL concentration of tazobactam.

https://www.merck.com/product/usa/pi_circulars/z/zerbaxa/zerbaxa_pi.pdf

Ceftazidime - avibactam

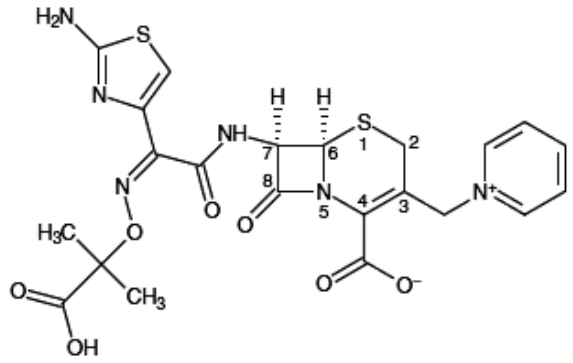


Fig. 1 Chemical structure of ceftazidime

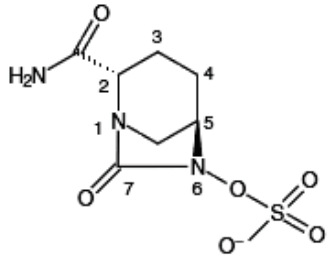


Fig. 2 Chemical structure of avibactam

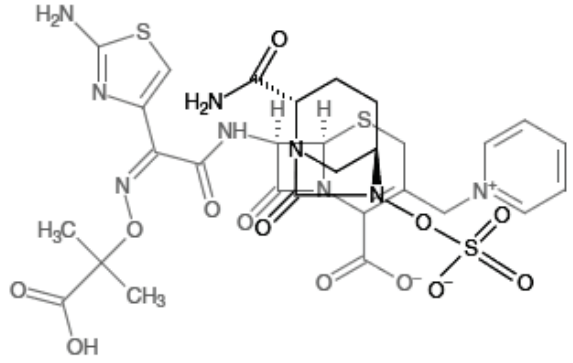


Fig. 3 Structural comparison of avibactam to ceftazidime

Table 1 Half maximal inhibitory concentration values for avibactam and comparator β-lactamase inhibitors determined after 5 min of incubation with different β-lactamases

	β-lactamase inhibitor IC_{50} (nM)			Reference
	Avibactam	Clavulanic acid	Tazobactam	
Class A				
TEM-1	8	130	40	[42]
TEM-1	8	58	32	[41]
SHV-4	1.5	5	120	[79]
SHV-4	3	4	55	[41]
KPC-2	38	6,500	80,000	[82]
KPC-2	37.5 ± 2.6	6,500 ± 400	9,200 ± 4,100	[78]
KPC-2	170	>100,000	50,000	[41]
CTX-M-15	4.5 ± 0.9	12.5 ± 2.8	5.8 ± 2.7	[78]
CTX-M-15	5	12	6	[34]
CTX-M-15	5	12	6	[41]
Class C				
P99	80	1×10^6	5,000	[42]
P99	100	>100,000	1,300	[41]
AmpC	128	>100,000	4,600	[41]

IC_{50} Half maximal inhibitory concentration

Zhanel et al. Drugs. 2013;73:159-77 -- PMID: 23371303.

Table 2 In vitro activity[a] of ceftazidime-avibactam and comparators against Gram-negative aerobes [47–66]

Gram negative aerobe	Ceftazidime			Ceftazidime-avibactam[a]			Ceftazidime-avibactam MIC_{90} reduction (fold)
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	
Citrobacter spp.	0.25	>32	NA	0.12	0.5	≤0.06–4	>64
Ceftazidime non-susceptible	32	>32	NA	0.25	1	≤0.06–4	>32
Enterobacter aerogenes	≤0.5	>32	≤0.25–>32	0.25	0.5	≤0.06–2	>64
Enterobacter cloacae	0.5	>32	≤0.25–>32	0.25	1	≤0.06–2	>32
Enterobacter spp.	0.25	>32	NA	0.25	1	≤0.03–>32	>32
Ceftazidime-resistant[b]	32	>32	NA	0.5	2	0.06–>32	>16
AmpC producing + porin loss	256	256	64–256	1	1	0.25–1	256
Escherichia coli	0.25	2	≤0.03–>32	0.12	0.25	≤0.03–2	8
ESBL producing	16	32	0.5–>64	0.12	0.25	<0.008–2	128
AmpC hyper-producing	16	64	0.12–>64	0.12	0.5	≤0.004–4	128
ESBL producing and AmpC hyper-producing	32	>64	2–>64	0.12	0.12	0.015–0.12	>512
Klebsiella oxytoca	≤0.25	0.5	≤0.25–>64	0.12	0.5	≤0.06–1	1
Klebsiella pneumoniae	≤0.25	1	≤0.5–>32	0.12	0.5	≤0.06–2	2
ESBL producing	64	>64	0.12–256	0.5	1	0.06–2	>64
OXA-48 carbapenemase-producing	256	512	≤0.12–512	0.25	0.5	<0.008–1	1024
KPC-producing	≥512	≥512	32–≥512	0.25	1	≤0.06–1	≥512
ESBL-producing plus porin loss	256	512	126–512	1	1	0.5–2	512
Klebsiella spp.	0.12	32	NA	0.12	0.5	≤0.03–32	64
ESBL	>32	>32	NA	0.5	2	≤0.03–32	>16
Carbapenem non-susceptible[c]	>32	>32	NA	0.5	2	≤0.03–32	>16
Serratia marcescens	0.12	2	≤0.25–16	0.25	0.5	≤0.06–>8	4
Serratia spp.	0.25	0.5	N	0.25	0.5	0.06–8	1
Pseudomonas aeruginosa	4	32	≤0.25–256	2	8	≤0.06–>128	4
MDR[d]			NA	8	32	≤1–>128	NA
AmpC-derepressed	64	>128	8–>128	4	8	≤1–64	>16
Intrinsic MexA/OprM	4	8	≤1–16	4	8	≤1–16	1

potentially very useful if documented

Zhanel et al. Drugs. 2013;73:159-77 -- PMID: 23371303.

Ceftazidime-avibactam in cystic fibrosis (*P. aeruginosa*)

J Antimicrob Chemother 2015
doi:10.1093/jac/dku551
Advance Access publication 14 January 2015

Avibactam confers susceptibility to a large proportion of ceftazidime-resistant *Pseudomonas aeruginosa* isolates recovered from cystic fibrosis patients

Hussein Chalhoub[1], Michael Tunney[2], J. Stuart Elborn[2], Anne Vergison[3]†, Olivier Denis[4], Patrick Plésiat[5], Barbara C. Kahl[6], Françoise Van Bambeke[1] and Paul M. Tulkens[1]*

[1]Pharmacologie cellulaire et moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium; [2]CF & Airways Microbiology Research Group, Queen's University Belfast, Belfast, UK; [3]Unité des maladies infectieuses, Hôpital Universitaire des Enfants Reine Fabiola, Brussels, Belgium; [4]Laboratoire de microbiologie, Hôpital Erasme, Brussels, Belgium; [5]Laboratoire de bactériologie, Hôpital Jean Minjoz, Besançon, France; [6]Medical Microbiology, University Hospital Münster, Münster, Germany

Avibactam is active against most Ambler class A (including ESBLs and Klebsiella pneumoniae carbapenemases), class C and class D β-lactamases (serine enzymes)
.
It is NOT active against class B (metallo-enzyme)

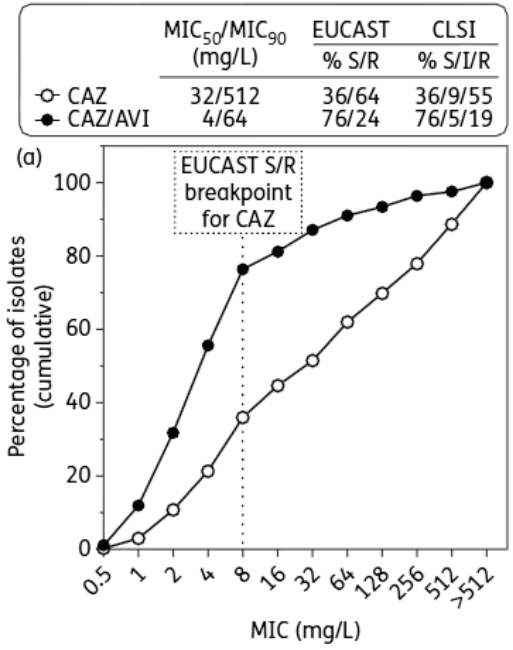
Ceftazidime-avibactam in cystic fibrosis (*P. aeruginosa*)

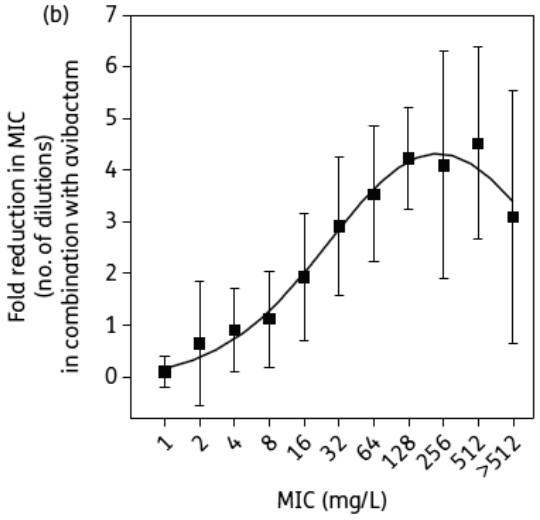
J Antimicrob Chemother 2015
doi:10.1093/jac/dku551
Advance Access publication 14 January 2015

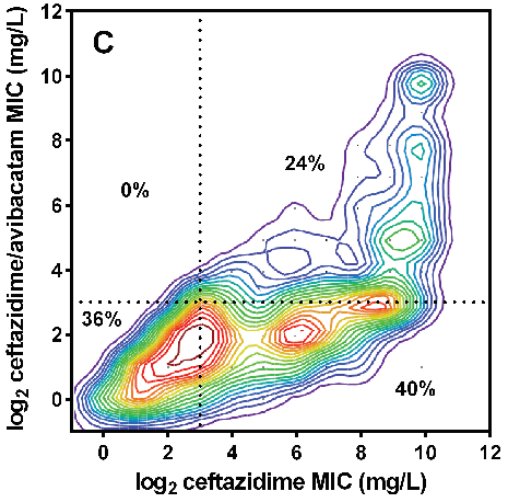
Avibactam confers susceptibility to a large proportion of ceftazidime-resistant *Pseudomonas aeruginosa* isolates recovered from cystic fibrosis patients

Hussein Chalhoub[1], Michael Tunney[2], J. Stuart Elbo Anne Vergison[3]†, Olivier Denis[4], Patrick Plésiat[5], Barbara C. Kahl[6], Françoise Van Bambeke[1] and Paul M. Tulkens[1]*

[1]Pharmacologie cellulaire et moléculaire, Louvain Drug Rese Institute, Université catholique de Louvain, Brussels, Belgium; Airways Microbiology Research Group, Queen's University Be Belfast, UK; [3]Unité des maladies infectieuses, Hôpital Univer des Enfants Reine Fabiola, Brussels, Belgium; [4]Laboratoire de microbiologie, Hôpital Erasme, Brussels, Belgium; [5]Laboratoi bactériologie, Hôpital Jean Minjoz, Besançon, France; [6]Medic Microbiology, University Hospital Münster, Münster, Germany







Avibactam is active against most Ambler class A (including ESBLs and Klebsiella pneumoniae carbapenemases), class C and some class D β-lactamases (serine enzymes)
.
It is NOT active against class B (metallo-enzyme)

Cefazidime-avibactam US indications and dosages

Indications

- **Complicated Intra-Abdominal Infections (cIAI)** in combination with metronidazole for the following susceptible microorganisms:
  Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Enterobacter cloacae, Klebsiella oxytoca, and *Pseudomonas aeruginosa*

- **Complicated Urinary Tract Infections (cUTI), including Pyelonephritis** for the following susceptible microorganisms:
  Escherichia coli, Klebsiella pneumoniae, Citrobacter koseri, Enterobacter aerogenes, Enterobacter cloacae, Citrobacter freundii, Proteus spp., and *Pseudomonas aeruginosa*

As only limited clinical safety and efficacy data for AVYCAZ are currently available, reserve AVYCAZ for use in patients who have limited or no alternative treatment options

Dosage: 2.5 g (2+0.5) q8h infused over 2 h

Reduced dosages for CrCl (ml/min): 31 to 50: 1.25 g (1 + 0.25) q8h, 16 to 30: 0.94 g (0.75+0.19) q12h, 6 to 15: 0.94 g (0.75+0.19) q24 h, ≤ 5: 0.94 g (0.75+0.19) q48 h

Pros and cons of the new cephalosporins-β-lactamase inhibitor combinations

Pros

- May help to (transiently ?) tackle with **β-lactamase-related resistance in Gram-negative bacteria**
- Safety profile and clinical uses are well known for ceftazidime and for tazobactam

Cons

- **you need to call your microbiologist for identification and MIC determinations (and trust her/him)**
- the safety profiles of ceftozolane and of avibactam are still uncertain (lack of clinical experience [fast approval])
- Price (but these may be the only options beyond colistin…)

Antibiotic pipeline: did you change your mind ?

- We now have at least 6-7 new molecules that partialy meet our needs for fighting resistant bacteria !
- These molecules have existed for at least 10 years (and may not be totally new…) but their development and registration has been unlocked thanks to the financial stimulations and easier filing processes.
- There is actually a much large number of molecules in clinical development [1] and even more at preclinical level.

- The real question is how we should approve and use them so as to protect them…

[1] http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development

But are you ready to pay ?

- Three simple figures:
  - the new antibiotics mentioned in this lecture will cost anywhere between **600 and 3,000 US$ / treatment** ….
  - new anti-hepatitis C drugs will cost around **30,000 US$ / treatment**
  - anticancer drugs may cost much more … (**10,000 to > 50,000 US$/QALY**)

We must reinvent the **economy** of the antibiotics:
How finding and developing them …
without selling them (too much)

please, give ideas…

Can Medellin help ?

This was presented as a
"major improvement (and brilliant idea) for urban transport"
at the Belgian Prime Time News
on November 27, 2015

What about the future ?

Back-up

And what about the EMA ?

Circumstances in which only limited clinical data can be generated

- organisms with specific types and/or patterns of multi-resistance currently uncommon or rare
- few patients that can be enrolled in commonly sought indications.

Addendum to the note for guidance on evaluation of medicinal products indicated for the treatment of bacterial infections (CPMP/EWP/558/95 Rev 2) to address indication-specific clinical data – http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500129443

And what about the EMA ?

Circumstances in which only limited clinical data can be generated

- organisms with specific types and/or patterns of multi-resistance currently uncommon or rare
- few patients that can be enrolled in commonly sought indications.

Acceptable approaches

- strong prediction of efficacy in the intended use(s) from PK/PD analyses
- limit to one randomized and active controlled study in a specific type of infection where resistant organisms are frequent
- evidence of efficacy through non-controlled studies in situations where resistance is very problematic *(retrospective comparison)*
- use of flexible (adaptive) study design

Addendum to the note for guidance on evaluation of medicinal products indicated for the treatment of bacterial infections (CPMP/EWP/558/95 Rev 2) to address indication-specific clinical data – http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500129443

What EMA has in store for drug developpers…

- **A test agent** expected or shown to be **clinically active against multi-resistant Gram-negative pathogens** could be indicated for studied infections **without qualification by pathogen**.
- Details of the actual organisms treated would be reflected in the "Pharmacodynamic" section of the SmPC along with mention of the evidence supporting activity (specific multi-resistant organisms).
- **A pathogen-specific indication is a possibility**.
- The label could include **a restriction to use when other commonly used agents are not suitable for the individual patient.**

Addendum to the note for guidance on evaluation of medicinal products indicated for the treatment of bacterial infections (CPMP/EWP/558/95 Rev 2) to address indication-specific clinical data – http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500129443

Tedizolid

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry
ELSEVIER
Bioorganic & Medicinal Chemistry 12 (2004) 5909–5915

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 Choi[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

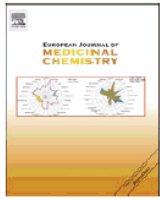
European Journal of Medicinal Chemistry 46 (2011) 1027–1039

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

ELSEVIER



1178x506

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

Ceftozolane-tazobactam EU indications and dosages

- Complicated intra-abdominal infections, acute pyelonephritis, Complicated urinary tract infections

Susceptibility testing breakpoints

Minimum inhibitory concentration breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

	Minimum Inhibitory Concentrations (mg/L)	
Pathogen	**Susceptible**	**Resistant**
Enterobacteriaceae	≤ 1	> 1
P. aeruginosa	≤ 4	> 4

- 1.5 g (1 g + 0.5 g) q8h infused over 1 h

Reduced doses for CrCl (ml/min): 30 to 50: 750 mg (500+250), 15 to 29: 375 mg (250+125 mg), End-stage renal disease (ESRD) on hemodialysis (HD): single loading dose 750 mg (500+/250) and 150 mg (100+50) q8h, hemodialysis days: dose after completion of dialysis

Antibiotic pipeline: can we do better ?

- Equivalence to current options in comparative clinical trials

  ⇨ This will raise issues for reimbursement,
  especially against the generics of the comparators
  used in these studies

  ⇨ Need to design superiority trials and
  to focus pricing and reimbursement
  for documented cases of infection by resistant organisms

Non-inferiority vs superiority trials ?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

NON-INFERIORITY if NO evidence of spontaneous resolution rate (more effective than placebo)

Indications (and delta):

- Community-acquired pneumonia (-10%; more in PORT scores of IV-V)
- Hospital-acquired pneumonia and ventilator-associated pneumonia (less than ≤ -12.5%)
- Skin and soft tissue infections (-10%)
- Intra-abdominal infections (-12.5%)
- Urinary tract infections (-10 %)

→ DRUG/comparator trial

SUPERIORITY if spontaneous resolution (placebo effective)

- Acute bacterial maxillary sinusitis
- Acute bacterial exacerbations of chronic bronchitis
- Acute otitis media
- Superficial skin infections (such as impetigo and minor wounds)
- Inhaled antibacterial agents (excl. CF)

→ Placebo/ DRUG/comparator trial

LIMITED TRIALS

- Rare MDR organisms
- Few patients

→ DRUG non comparative trial

Non-inferiority vs superiority trials ?

White Paper: Recommendations on the Conduct of Superiority and Organism-Specific Clinical Trials of Antibacterial Agents for the Treatment of Infections Caused by Drug-Resistant Bacterial Pathogens

Clinical Infectious Diseases 2012;55(8):1031–46

Infectious Diseases Society of America (IDSA)[a]

IDSA PUBLIC POLICY