PERSPECTIVES EN ANTIBIOTHÉRAPIE

PR M.DUPON

SERVICE DE MALADIES INFECTIEUSES ET TROPICALES

HÔPITAL PELLEGRIN . BORDEAUX

CHU Hôpitaux de Bordeaux

JARCA

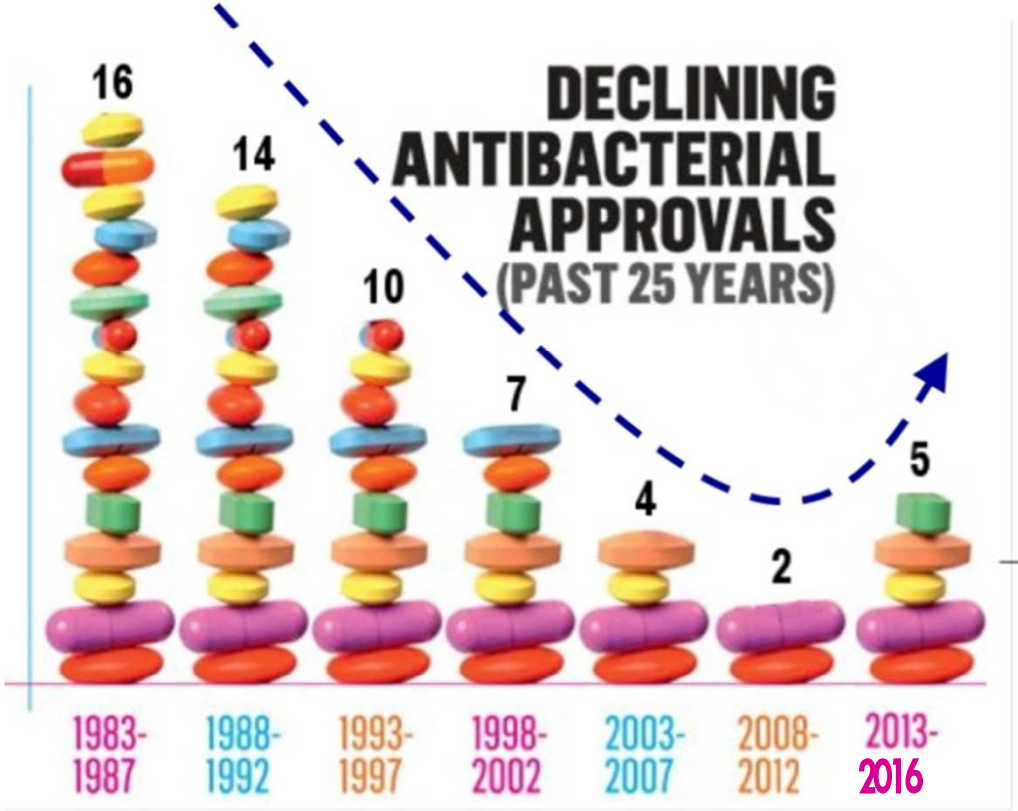
Actualités en réanimation

Journée du 9 décembre 2016

UNIVERSITÉ BORDEAUX

New antibiotics: where are we ?

Approvals by FDA/EMA – systemic antibiotics



Des 61 nouveaux ATB approuvés entre 1980 et 2009, 26 (43 %) ont été retirés en raison de toxicité ou absence de marché, vs un taux de retrait de 13 % pour les autres catégories thérapeutiques *(Outterson et al., 2013)*

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

- telavancin

Nouveaux antibiotiques : où en sommes-nous ?

- Les bonnes nouvelles
  - IDSA's 10 X '20
  - FDA-GAIN Act (2012)
    - QIDP – qualified infectious disease product
      - Fast track
      - Priority review
      - Longer period of exclusivity (>5 years)
  - European Innovative Medicines Initiative
    - Increase academic-industrial collaboration (COMBACTE)
    - New Drugs 4 Bad Bugs (ND4BB)

Développement d'essais limités, sans aveugle, sur populations particulières (I.Rén), bactéries MR, évaluant l'innocuité, définissant la dose optimale, en conditions réelles

- Mais des études de non-infériorité avec des bornes de ± 20% et des AMM restrictives (« niches »):
  - Peau, tissus mous (cSSSI, ABSSI)
  - Poumons (PAC, PN, PAVM) restreint à SARM (HAP,CAP)
  - Urinaires (cUTI)
  - Abdominales (cIAI)
- et des SMR insuffisants ou des ASMR V

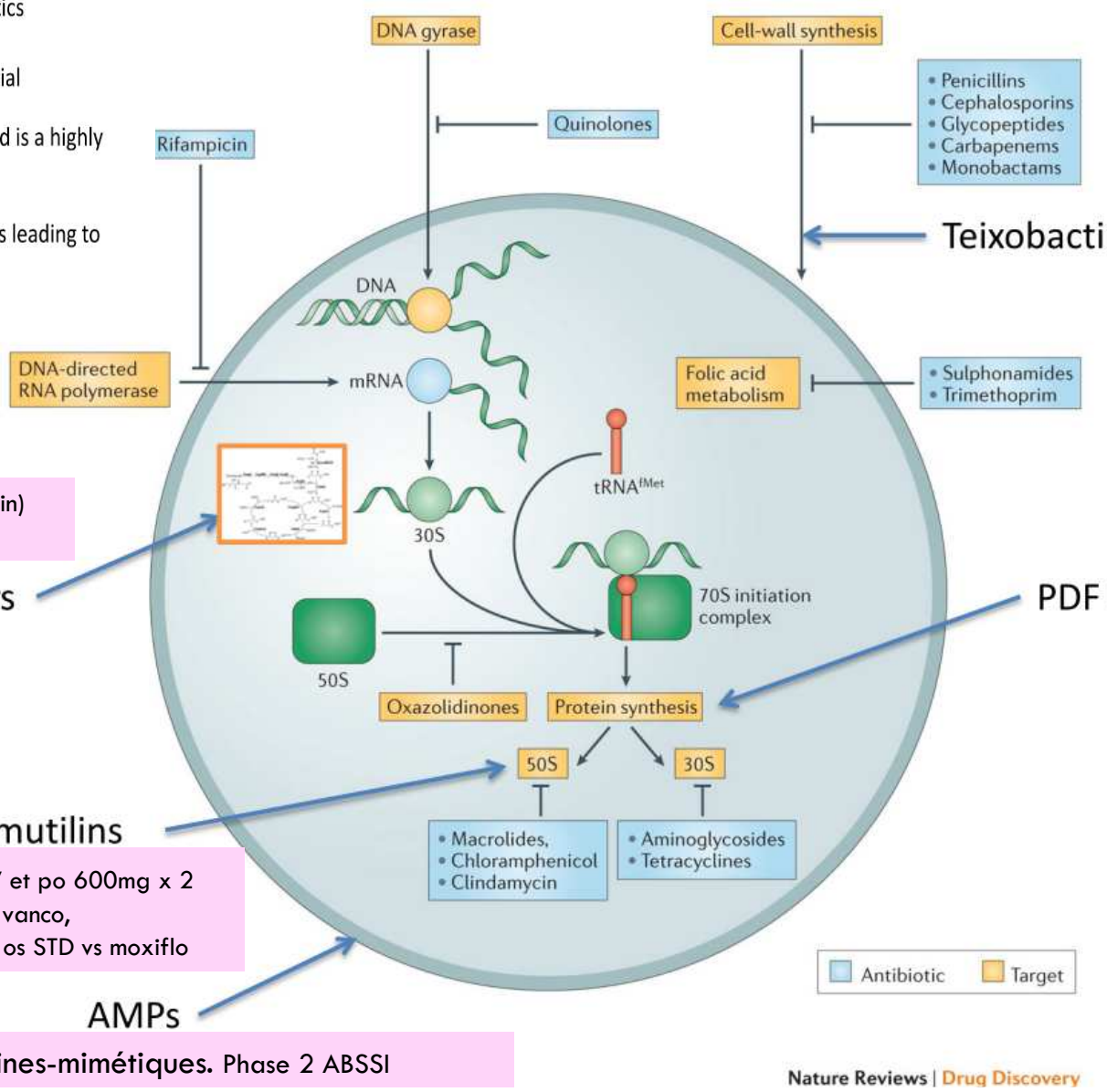
ANTI GRAM +

Nouvelles classes thérapeutiques

Novel Mechanisms & Agents

Gram <0, pas de résistance croisée

1. Fatty acid synthesis inhibitors
   - FabI – Enoyl-acyl carrier protein (ACP) reductase
2. Membrane-acting agents (Defensins)
   - Antimicrobial peptides (AMPs) and mimetics
3. PDF Inhibitors
   - Peptide deformylase – an essential bacterial metalloenzyme in peptide synthesis
   - An essential role in protein maturation and is a highly conserved target
4. Pleuromutilins
   - Selective binding of prokaryotic ribosomes leading to protein synthesis inhibition



Inhibiteur enoyl –(acyl-carrier-protein) reductase

Debio phase 2

FabI Inhibitors

PDF Inhibitors

Pleuromutilins

Lefamuline 150mg x 2/j IV et po 600mg x 2
ABSSI phase 2 vs vanco,
phase 3 en cours CABP, HAP, os STD vs moxiflo

AMPs

Brilacidine =défensines-mimétiques. Phase 2 ABSSI

ANTI GRAM +

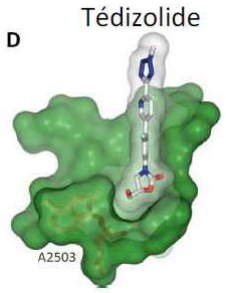
Dérivés de classes ATB existantes

ATB anti Gram >0 (Ad)

Molécule DCI laboratoires	classe	voie posologie	statut FDA	statut EMA	statut France
Dalbavancine Xydalba®–Durata Dalvance®-Allergan	lipo-glycopeptide	i.v. 1000 mg J1, puis 500 mg J8 ou 1500 mg 1 dose	05/2014 ABSSSI Ad marketed	AMM 02/2015 et 2016 marketed	En cours
Oritavancine Orbactiv® The Medicines Co	lipo-glycopeptide	i.v. 1200mg 1 dose	08/2014 ABSSSI marketed	AMM 03/2015	SMR important ASMR V
Télavancine Vibativ® Theravance (USA) Novex pharma	lipo-glycopeptide	10 mg/kg/dose i.v. x1/24h pour 7 à 21j	ABSSSI (09/2009) et HABP en alternative (06/2013) marketed	AMM 09/2011 HABP dont PAVM SARM (3ème intention)	06/2015 SMR insuffisant et néphrotoxicité (dossier retiré)
Tedizolide phosphate* Sivextro® Cubist	oxazolidinone	200 mg p.o./i.v. /j pour 6j	FDA 06/2014 ABSSSI Moins d'effets IIaires / LNZ	AMM 03/2015	11/2015 SMR important ASMR V commercialisé
Solithromycine* Cempra	fluorokétolide	400 mg/j,IV puis p.o., 7j	Phase 3 (CABP-GC)		
Iclaprim* Motif Bio PLC	diaminopyrimidine inhibiteur dihydrofolate reductase	0,8 mg/kg x2/j	Phase 3 vs vanco (HABP-ABSSSI REVIVE trial) Essai pédiatrie		

ABSSSI = IBAPTM infections bactériennes aigues peau et tissus mous
CABP/HABP/VABP = pneumopathies bactériennes communautaires/ nosocomiales/associées à la ventilation

Tedizolide (Sivextro®) Merck commercialisé France 2005



- IV/oral 200 mg/j (avec ou sans nourriture) Pro-drogue microbiologiquement inactive, convertie *in vivo* en forme active, le tedizolide, par phosphatases sanguines et tissulaires
- Spectre anti-Gram + (actif sur *E.faecalis et faecium* VancoS) avec CMI plus basses/linézolide et amélioration du profil de resistance : maintien de l'activité sur souches avec gene cfr
- Bactériostatique; ½ vie 12h (vs ~ 6h); liaison Prot (80% vs 30%)
- Pas d'interaction CP450; peu d'interaction sérotoninergique Moins d'effets II^{aires}; pas de toxicité hématologique (**mais ttt court dans essais** – en moyenne 6j) ni neuropathie . Nausées (8%), céphalées (6%), diarrhée (4%)
- Efficacité non démontrée infections sévères, neutropéniques
- AMM France 03/2015 IBPTM Ad SARM (SMR important; ASMR V)

diffusion pulmonaire +++

	Liquide broncho-alvéolaire			
	2 heures	4 heures	12 heures	24 heures
Fluide alvéolaire (µg/mL)	9.05 (3.83)	4.45 (2.18)	5.62 (1.99)	1.33 (0.59)
Macrophages alvéolaires (µg/mL)	3.67 (1.02)	4.38 (2.18)	1.42 (0.63)	1.04 (0.52)
Plasma (conc totale)(µg/mL)	2.01 (0.55)	1.51 (0.33)	0.946 (0.31)	0.398 (0.17)
Plasma (conc libre) (µg/mL)	0.213 (0.058)	0.159 (0.035)	0.100 (0.033)	0.042 (0.018)

Perspectives

- Essai pnp nosocomiale en cours (7j vs 10j Linézolide)
- Essai pédiatrie
- Tolérance long terme
- Efficacité mycobactéries (MDR)
- Efficacité anaérobies Gram + (C. difficile)
- Os ?

Lipoglycopeptides: pharmacokinetics

parameter	VAN	ORI	TLV	TEC	DAL
Dosage	15 mg/kg	1200 mg	10 mg/kg	6 mg/kg	1000 mg
Cmax (mg/L)	20-50	138	93	43	287
AUC (mg.h/L)	260	1110 (24h) 2800 (tot)	668	600	3185 (24h) 23443 (tot)
(%) prot. binding	55	85	95	88-94	99
T ½ (h)	1 (β) 3-9 (γ)	14 (β) 245 (γ)	8	10 (β) 168 (γ)	346 (γ)

single dose treatment

once-a-week dose treatment (1 à 2 doses)

*Jauregui LE et al. Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. Clin Infect Dis **2005**; 41:1407–15*

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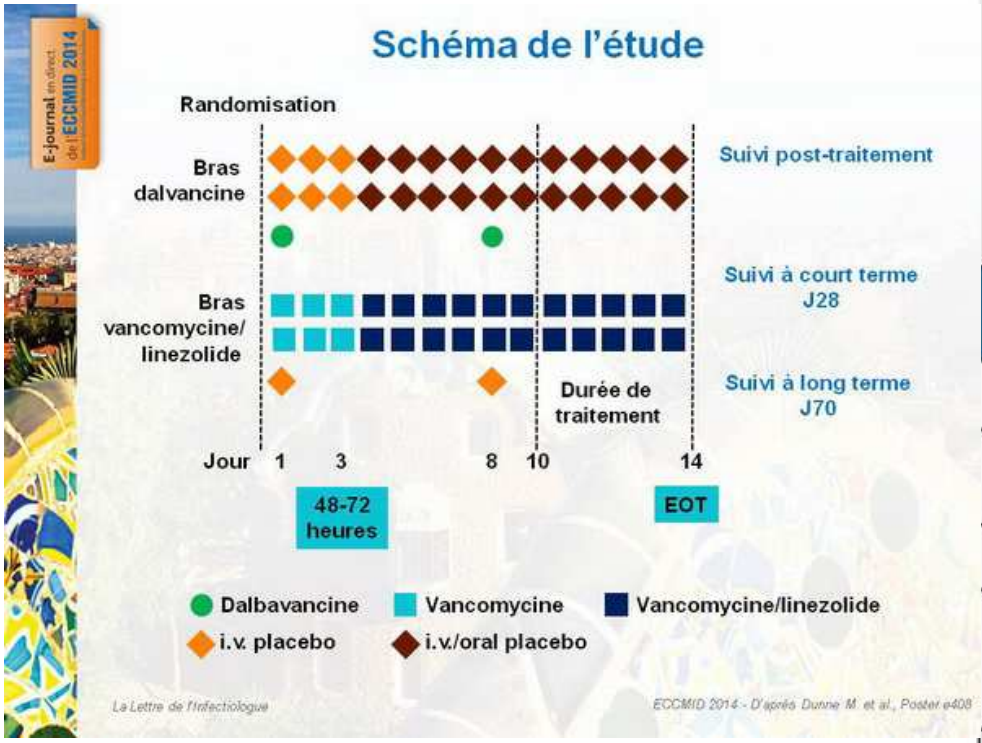
Dalbavancine (Zydalba®)



- Phase 3 study, DISCOVER 1 and 2, pooled analysis of 1,312 **ABSSSI** patients[2]
- IV dose of dalbavancin (DAL) days 1 and 8 or IV VAN for ≥3 days and option to switch to oral LIN

	Early Clinical Response, %[a,b]		Clinical Cure, %[e,f]	
	DAL	V/L	DAL	V/L
Wound infection	78.2	78.6	86.7	88.6
Cellulitis	79.4	77.1	90.7	91.7
Major cutaneous abscess	81.6	86.1	94.0	95.7
Fewer AEs reported with DAL than V/L				

[a] At 48-72 h after first infusion. [b] Defined as cessation of spread, absence of fever, no rescue antibiotics at 48-72 h; ITT analysis. [d] At 7-14 d after EoT. [c] In patients with ≥ 1 pathogen [e] Defined as clinical response at EoT. [f] Assessed in subgroup of patients with monomicrobial infection in microbiologic per-protocol population.

Randomisée, double aveugle, non-infériorité

Boucher HW, et al. Once-weekly dalbavancin versus daily conventional therapy for skin infection. N Engl J Med **2014**; 370:2169–2179.

1 injection de 1500mg est suffisante

AMM européenne 06/16

Clinical Infectious Diseases 2016;62(5):545 – 51
MAJOR ARTICLE

A Randomized Clinical Trial of Single-Dose Versus Weekly Dalbavancin for Treatment of Acute Bacterial Skin and Skin Structure Infection

Michael W. Dunne,[1] Sailaja Puttagunta,[1] Philip Giordano,[2] Dainis Krievins,[3] Michael Zelasky,[1] and James Baldassarre[4]

- The primary endpoint was a ≥20% reduction in the area of erythema at 48–72 hours. Clinical evaluation at D14 and D28)
- A single 1500-mg infusion of dalbavancin is noninferior to a 2-dose regimen (1000mg followed by 500mg), has similar safety profile.

TABLE 4 Dalbavancin tissue concentrations (safety population)

	Dalbavancin concn (mean [SD]; no. of samples) at hours (days) postdose that samples were collected:					
Tissue	12 (0.5)	24 (1)	72 (3)	168 (7)	240 (10)	336 (14)
Plasma (μg/ml)[a]	85.3 (18.9); 31	ND[b]	ND	ND	ND	15.3 (4.1); 31
Synovium (μg/g)[c]	25.0 (0); 3	17.9 (7.8); 3	19.5 (4.9); 3	19.2 (8.9); 4	25.0 (0); 2	15.9 (7.9); 3
Synovial fluid (μg/ml)[c]	22.9; 1	27.4 (10.8); 4	19.2 (4.9); 3	11.6 (3.3); 2	13.9 (1.0); 3	6.2 (1.7); 2
Bone (μg/g)	6.3 (3.1); 5	5.0 (3.5); 5	4.6 (3.8); 5	3.8 (2.7); 5	3.7 (2.2); 5	4.1 (1.6); 5
Skin (μg/g)[c]	19.4 (7.9); 2	12.5 (6.5); 3	13.8 (1.4); 2	15.7 (1.0); 2	21.6; 1	13.8 (2.1); 2

Bonne pénétration synovial et intra-osseuse
Ratio/plasma 13% (fixation Prot plasma : 93%)

AAC
2015.59:1849–1855.

Extended-Duration Dosing and Distribution of Dalbavancin into Bone and Articular Tissue

Michael W. Dunne,[a] Sailaja Puttagunta,[a] Craig R. Sprenger,[a,b] Chris Rubino,[b] Scott Van Wart,[b] James Baldassarre[a]

Bonne pénétration tissu pulmonaire (ratio ELF/Plas libre : 36%)
Intérêt pneumopathie à S. aureus et S. pneumoniae avec une injection

Dunne et al intra pulmonary concentrations of dalbavancin in healthy adults after a single 1500 mg infusion P1198 ECCMID 04/2016

ORITAVANCINE Orbactiv® The Medicines Co

- Phase 3 study, SOLO 1[1] of 954 **ABSSSI** patients
- Evaluating IV dose of oritavancin (ORI) or vancomycin (VAN) for 7-10 days

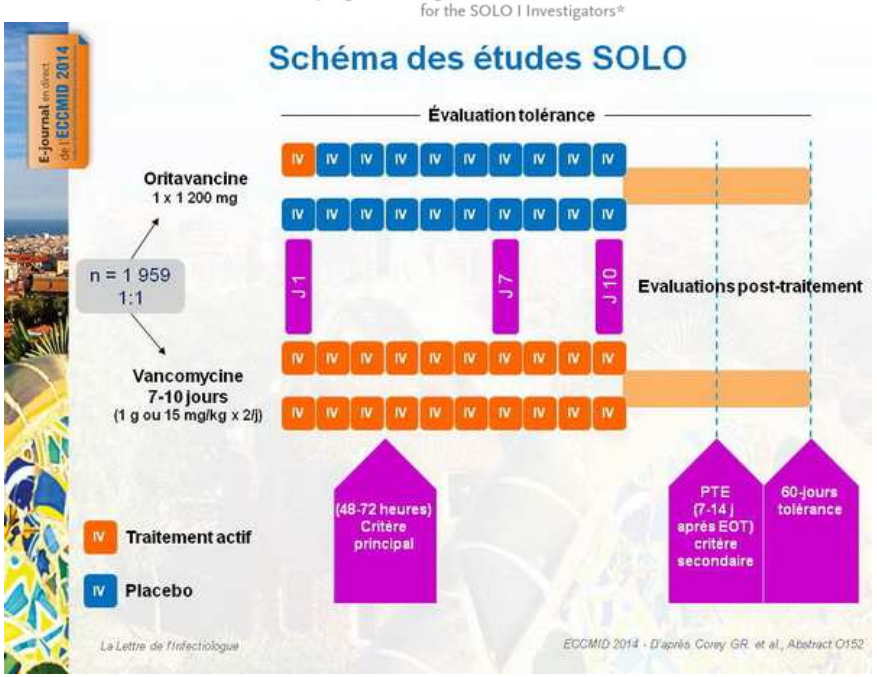
	Early Clinical Response, %[a,b]		Clinical Cure, %[c,d]	
	ORI	VAN	ORI	VAN
Wound infection	85.9	87.6	82.3	79.9
Cellulitis	81.1	75.5	82.2	87.8
Major cutaneous abscess	82.1	78.0	76.1	77.9
Similar safety profile				

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*



[a] At 48-72 h after first infusion. [b] Defined as cessation of spread, absence of fever, no rescue antibiotics at 48-72 h; ITT analysis. [d] At 7-14 d after EoT. [c] In patients with ≥ 1 pathogen [e] Defined as clinical response at EoT.
[f] Assessed in subgroup of patients with monomicrobial infection in microbiologic per-protocol population.

Randomisée, double aveugle, non-infériorité 10%

CMI in vitro basses <lipoglycopeptides

PeerVoice

Activity (MIC_{90} in mg/L) of telavancin, dalbavancin and oritavancin against the main gram-positive cocci (from Refs. [5–7])

Microorganism	VCM	TLV[a]	ORV[a]	DLB[a]
Methicillin susceptible *S. aureus*	1	0.5	0.06	0.06
Methicillin resistant *S. aureus*	1	0.25	0.06	0.06
Methicillin susceptible coagulase-negative staphylococci	2	0.5	0.06	0.06
Methicillin resistant coagulase-negative staphylococci	2	0.5	0.06	0.12
Vancomycin susceptible *E. faecalis*	2	1	0.03	0.06
Vancomycin susceptible *E. faecium*	1	0.25	≤0.008	0.12
Vancomicina resistant *E. faecium* (Van A)	>16	8	0.12	>4
Vancomicina resistant *E. faecium* (Van B)	>16	2	≤0.008	>1
S. pneumoniae	0.5	0.03	≤0.008	0.03

VCM, vancomycin; TLV, telavancin; DLB, dalbavancin; ORV, oritavancin.

[a] For staphylococci, EUCAST breakpoints for telavancin, oritavancin (only for *S. aureus*) and dalbavancin are: $S \leq 0.125$ mg/L and $R > 0.125$ mg/L. There are no breakpoints for enterococci.

Current Opinion in Pharmacology 2015, 24:45–51

Oritavancine (Orbactiv®)

THE MEDICINES COMPANY FRANCE SAS

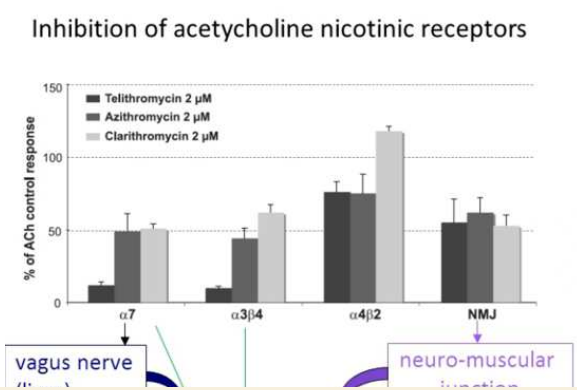
COMMISSION DE LA TRANSPARENCE
Avis
18 novembre 2015

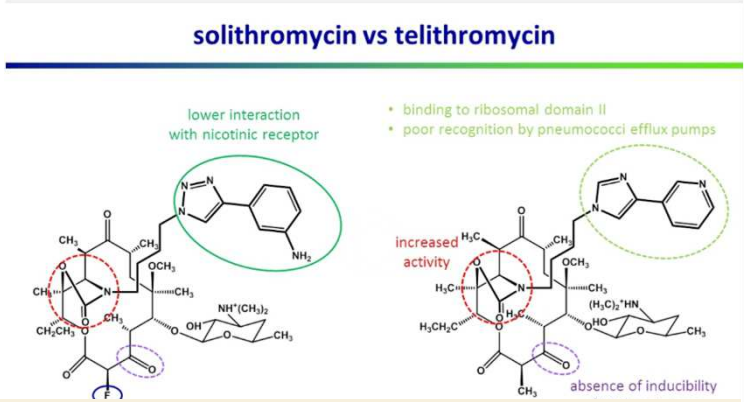
- **SMR important** dans le traitement des IBAPTM uniquement chez les adultes ayant des infections d'un certain degré de gravité, pour les lesquelles une étiologie staphylococcique est prouvée ou suspectée (infections suppuratives) et que la résistance à la méticilline est prouvée ou fortement suspectée.
- n'apporte pas d'amélioration du service médical rendu (**ASMR V**) par rapport à la vancomycine dans la prise en charge des IBAPTM chez Ad
- Compte tenu des caractéristiques du produit (**longue demi-vie**) et des **incertitudes actuelles sur l'efficacité clinique et la tolérance** en cas d'infections cutanées sévères et/ou dues à des bactéries MR, **la décision thérapeutique doit être prise avec l'aide d'un référent antibiotique**

Télavancine (Vibativ®) Astellas

- EMA pneumonies nosocomiales (PN), y compris pneumonies acquises sous ventilation mécanique (PAVM), connues ou suspectées d'être à SARM
- FDA AMM 08/14 infections compliquées peau et tissus mous, pneumonie nosocomiale VAP (SAMS,SARM) 7 à 21 j
- Commission transparence :ttt PN chez l'Ad. y compris (PCAM), connues ou suspectées d'être à SARM; dans les situations où l'absence d'alternatives adaptées est connue ou suspectée. **05/15 SMR insuffisant**
- 10 mg/kg IV/j en 1 dose sur 1h (si obèse dose idem aminoside)
- Si IR CrCl 30-50 mL/min 7.5 mg/kg /24 h. CrCl 30-10 mL/min 10 mg/kg /48 h
- Pas d'ajustement si Ins hépatique légère à modéré
- Effets secondaires :
  - rash, nausées++, dysgeusie++, vomissements diarrhée, céphalées,
  - Interaction avec test de coagulation
  - Augmentation QTc
  - **Néphrotoxicité** (augmentation crétinine reversible); contient cyclodextrine qui s'accumule si Ins rénale
- Grossesse catégorie C (CI)

Solithromycine = nouveau fluorokétolide (Cempra)





Essais de phase 3 :

* SOLITAIRE-ORAL 10/2015: *Barrera et al. Lancet ID April 2016,16, 421-30*; non-inférieur, pas de diférence dans les effets secondaires (hépatiques, digestifs, CV)

* SOLITAIRE-IV:; phase 3 IV J1 to oral J2 –J7;PAC modéré à sévère Port II à IV; 863 pts, randomisée, double-aveugle, vs moxifloxacine, 400 mg/j,IV puis p.o., 7j. Réponse non inférieure à 72h et 5 à 10j après la fin du ttt. *Fine T Clin Inf Dis 2016;63(8):1007–16*

Plus d'effet adverses au site de perfusion 31,3% solithro vs 5,4% moxiflo et d'atteintes hépatiques (>3N) 12,2 vs 4,3% (moxiflo plus d'augmentation du QT)

* SOLITAIRE- U : on going. Open-Label, Randomized, Multi-Center Study to Evaluate the Efficacy and Safety of a Single Dose of Oral Solithromycin Compared to Single-Dose Intramuscular Ceftriaxone Plus Single-Dose Oral Azithromycin in the Treatment of Male and Female Patients With Uncomplicated Urogenital Gonorrhea With or Without Concomitant Chlamydia

- essais enfant CABP

AMM FDA demandée 2016

POUR

Iclaprim Motif Bio plc

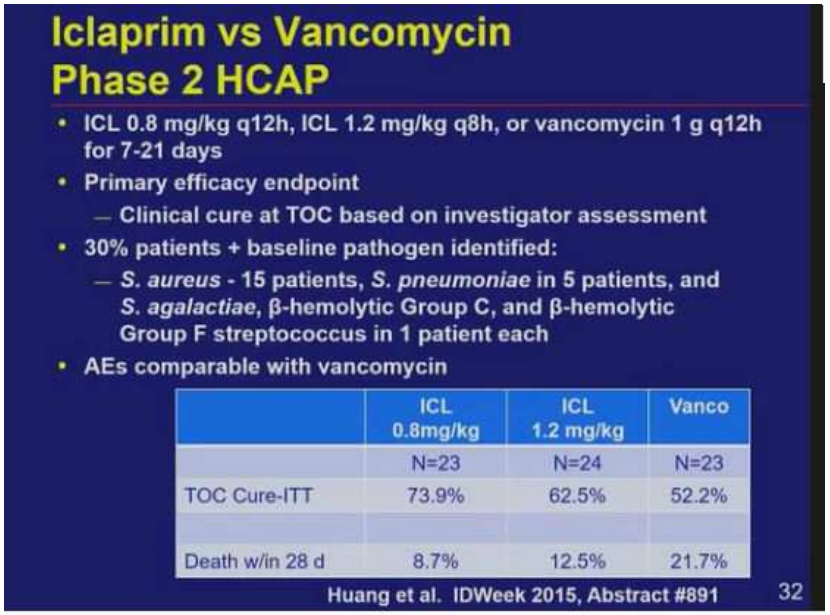
- Diaminopyrimidine : Inhibiteur dihydrofolate reductase
- IV et po
- Actif contre bactéries Gram >0 : MSSA, MRSA, *S. pneumoniae*, S.groupe A
- Essai phase 2 HCAP

Table 1: Iclaprim MIC50/90; Range of Gram Positive Isolates

Pathogen (MIC50/90; range mg/L)	N	ICL	TMP	TMP/SMX	VAN	LIN	DAP
S. aureus	1,178	0.06/0.12; 0.015->8	1/2; 0.25->64	0.06/0.12; 0.03->8	1/1; 0.25-2	1/1; <=0.12-2	0.25/0.5; <=0.06-2
MRSA	582	0.06/0.12; 0.015->8	1/8; 0.25->64	0.06/0.25; 0.03->8	1/1; 0.25-2	1/1; <=0.12-2	0.25/0.5; <=0.06-2
MSSA	596	0.06/0.12; 0.015->8	1/2; 0.25->64	0.06/0.06; 0.03->8	1/1; 0.5-2	1/1; <=0.25-2	0.25/0.5; <=0.12-2
β-hemolytic streptococci	199	0.06/0.25; 0.008->8	1/2; 0.12->64	0.12/0.25; 0.03->8	0.25/0.5; 0.25-1	1/1; 0.5-1	0.12/0.25; <=0.06-0.5
S. pneumoniae	259	0.06/2; 0.015->8	2/64; 0.25->64	0.25/8; 0.12->8	0.25/0.5; <=0.12-0.5	1/1; <=0.12-2	0.12/0.25; <=0.06-0.5
Total	1636						

TMP: Trimethoprim; SMX: Sulfamethoxale; VAN: Vancomycin; LIN: Linozolid; DAP: Daptomycin

D. Huang. Idweek poster 16836.



- À venir : essai REVIVE phase 3 ABSSSIs vs vanco 15mg/kg x 2/j
- Gram <0 (HABP)

ANTI GRAM +/-

Dérivés de classes ATB existantes

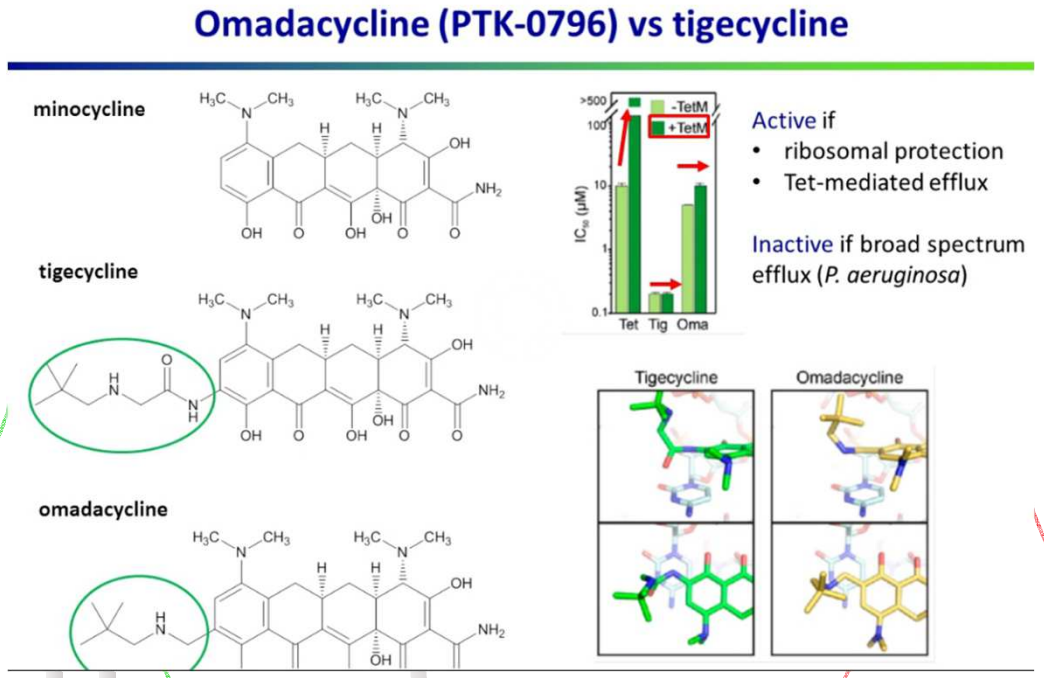
ATB anti Gram >0 et Gram <0 (Ad)

Molécule DCI laboratoires	classe	voie posologie	statut FDA	statut EMA	statut France
Omadacyline* Paratek	tétracycline	IV/po	Phase 3 (CAP. ABSSSI, cUTI)		
Eravacyline* Tetraphase Pharmaceuticals Inc	tétracycline	IV/po	Phase 3 (cIAI, cUTI)		
Delafloxacine * Melinta	fluoroquinolone	IV/po	Phase 3 (ABSSSI, CAP, GC)		

ABSSSI = IBAPTM infections bactériennes aigues peau et tissus mous
CABP/HABP/VABP = pneumopathies bactériennes communautaires/ nosocomiales/associées à la ventilation
cUTI infections urinaires compliquées; cIAI infections intra-abdominales compliquées
GC infections uro-génitales (gonorrhée, chlamydiose)

Omadacycline = nouvelle tétracycline

Paratek Pharmaceuticals, Inc.



- Spectre large = monothérapie
- Distribution tissulaire importante
- Actif sur bactéries G+ (pnc péniR, CTXR, FQR, macroR, tétraR; SARM), G- (entérobactéries -E. coli-EBLSE; *H. influenzae*), atypiques, anaérobies *(C.difficile)*
- Administration 1 fois/j; ½ vie17h
- IV 200mg puis 100mg/j/ po
- Phase 3 IBPTM vs linézolide et en cours PAC vs moxifloxacine

POUR

- Spectre large = sélection résistance
- Inactif P.aeruginosa
- Bactériostatique
- CI grossesse, enfant
- Données de tolérance à confirmer

CONTRE

Omadacycline vs linézolide IBPTM

Phase 2 and a truncated Phase 3 study pooled (100mg IV then 300 or 200 mg po)
± aztréonam (phase 2) or moxifloxacin (phase 3) . Non infériority margin : 10%

Figure 1. Clinical Success Across Different Patient Populations

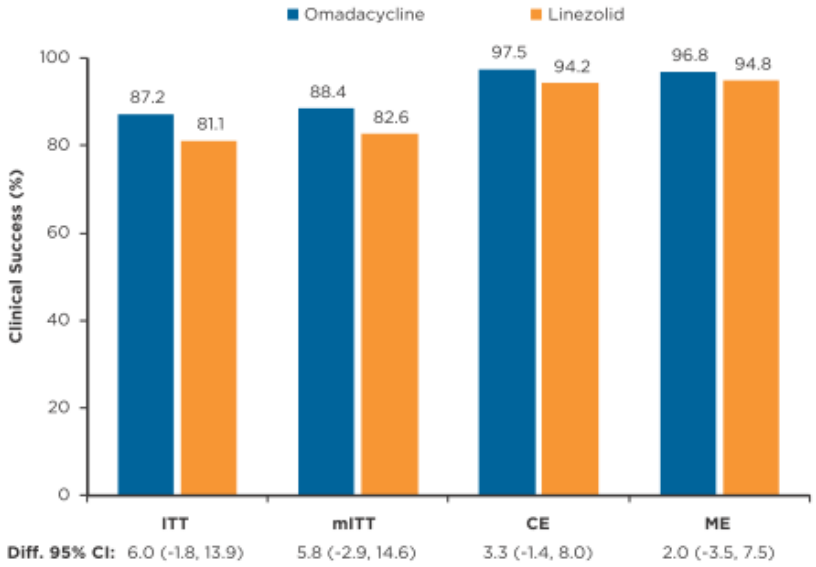
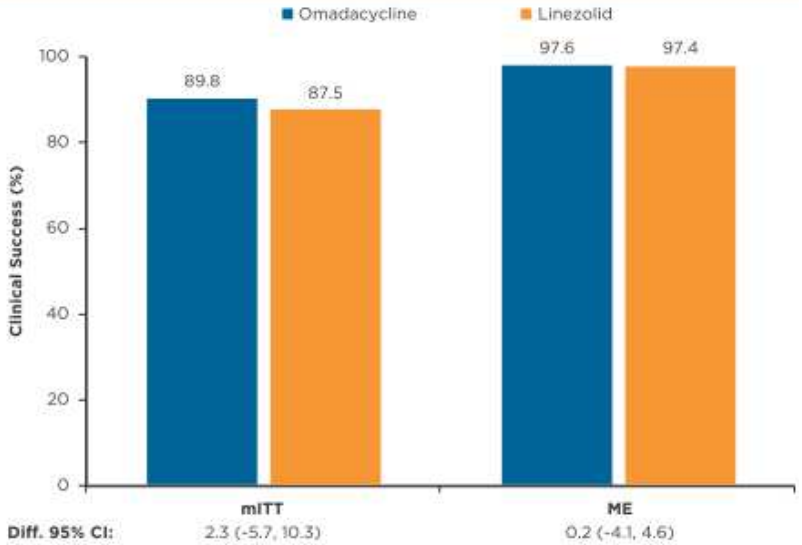


Figure 2. Microbiological Success in MITT and Microbiologically Evaluable Patients

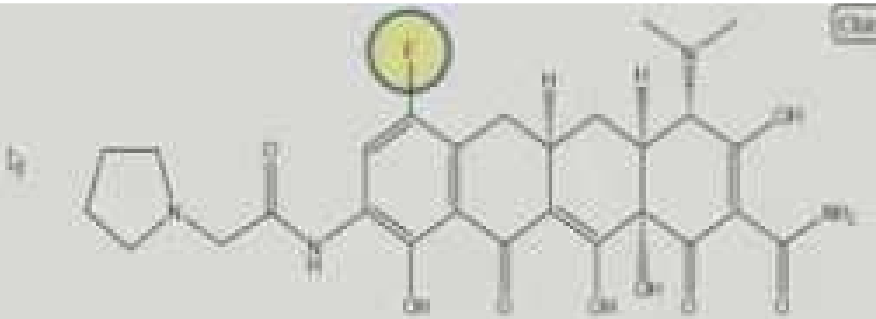


S. Ken Tanaka A Pooled Analysis of Two Randomized Multicenter, Evaluator-Blind Studies Comparing the Safety and Efficacy of Omadacycline and Linezolid for the Treatment of Complicated Skin and Skin Structure Infections. ECCMID 2016 poster1326

Table 5. Treatment-Emergent Adverse Events Occurring in at Least 3% of Patients in Either Treatment Group

	Number (% of Patients)	
	Omadacycline N=179	Linezolid N=180
Nausea	31 (17.3)	27 (15.0)
Headache	23 (12.9)	14 (7.8)
Vomiting	11 (6.2)	15 (8.3)
Diarrhea	6 (3.4)	19 (10.6)
Dizziness	11 (6.2)	11 (6.1)
Alanine aminotransferase increased	5 (2.8)	11 (6.1)
Creatine phosphokinase increased	10 (5.6)	3 (1.7)
Fatigue	8 (4.5)	5 (2.8)
Insomnia	4 (2.2)	8 (4.4)
Rash	6 (3.4)	6 (3.3)
Aspartate aminotransferase increased	4 (2.2)	7 (3.9)
Decreased appetite	2 (1.1)	6 (3.3)

Eravacycline



Pathogen	Eravacycline	Tigecycline	Meropenem	Pip/Tazo
K. pneumoniae	0.5 / 1	1 / 2	0.03 / 0.03	4 / 32
Carb NS	0.5 / 2	1 / 2	> 8 / > 16	> 64 / > 128
Acinetobacter baumannii	0.5 / 1	0.5 / 4	0.5 / 2	≤ 1 / 64
MDR	0.5 / 2	0.5 / 8	> 8 / > 16	> 64 / > 128

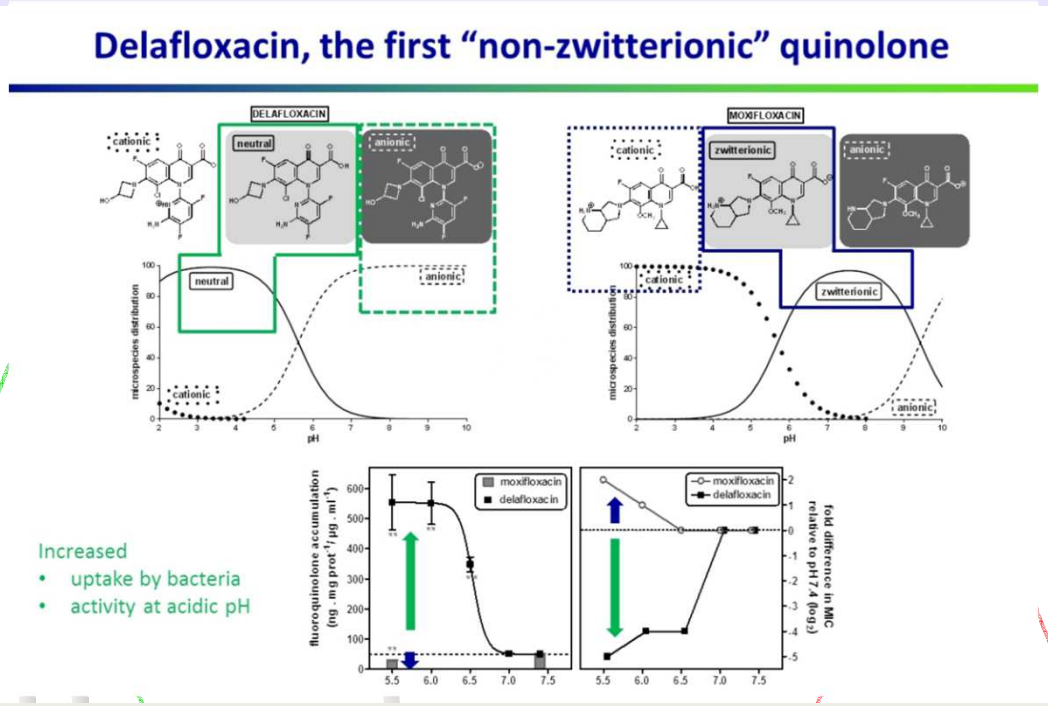
- Overall ~ 2-fold more potent than tigecycline
- Also potent anti- gram+, -anaerobe activity Spectre large
- Orally bioavailable (but new formulation in development)
- Phase 3 trials:
  - cIAI (vs. ertapenem): met NI endpoint; 2nd trial vs. meropenem planned
  - cUTI (vs. IV/PO levofloxacin): Failed to meet NI in primary endpoint
- Dose: Eravacycline 1mg/kg IV q 12h

Eravacycline = nouvelle tétracycline TetraphasePharmaceuticals

- Dec 14. **IGNITE 1** randomisée, multicentrique, en double-aveugle, non-infériorité (marge 10 %), visant à évaluer l'efficacité et l'innocuité de l'eravacycline 1 mg/kg IV toutes les 12 h (puis 1,5 mg/kg /24h), comparée à l' ertapénème 1 g IV toutes les 24 heures, dans le traitement d' **infection intraabdominale compliquée** (n = 536). Le critère d'évaluation principal était la réponse clinique lors de la visite (TOC) de test-de-cure dans la population de patients intention de traiter (microbiological-ITT). Eravacycline a montré une non-infériorité statistique de réponse clinique lors de la visite (TOC) de test-de-cure [95 % CI:-7.1% ; 5,5 %]

- Sept 15. **IGNITE 2** phase III, randomisée, multicentrique, en double-aveugle, non-infériorité (marge 10 %). 908 patients patients atteints **d'infection urinaire compliquée**, ont reçu éravacycline 1,5 mg/kg IV puis 250 mg ou 200 mg x 2/j vs lévofloxacine 750 mg/j 7j débutant par 3 j de ttt IV suivis d'une forme orale si la clinique le permettait. Le taux de guérison dans les six à huit jours après le traitement obtenu avec l'éravacycline ne s'est pas avéré équivalent (non inférieur) à la lévofloxacine pour les pts avec relai oral précoce.

Delafloxacine = nouvelle fluoroquinolone



Etude PROCEED 2015 phase 3 ABSSSI, randomisée, en double aveugle : **délafloxacine (300 mg IV x 2/j) vs association vancomycine + aztréonam** chez 660 patients (avec cyclodextrine modifiée pour améliorer la solubilité et la stabilité) résultats identiques sur réduction de l'érythème associé à la lésion à 48 h à 72 h et résolution clinique à J14 (plus efficace chez 240 obèses avec >30 kg/m2)

À l'avenir, MELINTA prévoit études cliniques pour la pneumonie bactérienne nosocomiale (HABP), les infections urinaires compliquées (cUTI) et infections intra-abdominales compliquées (CIAI).

POUR

CONTRE

ANTI GRAM -

Dérivés de classes ATB existantes

ATB anti Gram <0 (Ad)

Molécule DCI laboratoires	classe	voie poso.	statut FDA	statut EMA	statut France
Ceftozolane-tazobactam **Zerbaxa®** Astra Zeneca	C3G + inh. β-lactamase	IV 1/0,5g x 3/j	Phase 3 (CAP. ABSSSI, cUTI) marketed	AMM EMA 7/2015 commercialisé	SMR important ASMR V 07/16 commercialisé cIAI, cUTI (PN)
Ceftazidime-avibactam **Zavicefta®** Astra Zeneca	C3G + inh. β-lactamase	IV 2/0,5g x 3/j	Phase 3 (cIAI, cUTI) marketed	07/2016 AMM (cIAI,cUTI,HABP R aer;Gram<0)	ATU nominative Évaluation en cours
Imipenem/ cilastatin + relebactam - MK-7655 Merck & Co. Inc	carbapénem + inh. β-lactamase	IV	Phase 3 (cIAI, cUTI, HABP, VABP)		
Carbavance (meropenem + Vaborbactam – RPX 7009) Rempex Pharmaceuticals Inc.	carbapénem + inh. β-lactamase	IV	Phase 3 (cIAI, cUTI, HABP, VABP, febrile neutropenia)		
Plazomicin Achaogen Inc.	aminoglycoside	IV	Phase 3 Bloodstream infections and HABP penem-R Enterobacter		
S-649266 cefiderocol Shionogi Inc.	céphalosporine	IV	Phase 3 (cIAI, HABP, VABP, bloodstream infections)		

ABSSSI = IBAPTM infections bactériennes aigues peau et tissus mous
CABP/HABP/VABP = pneumopathies bactériennes communautaires/ nosocomiales/associées à la ventilation
cUTI infections urinaires compliquées; cIAI infections intra-abdominales compliquées; GC infections uro-génitales (gonorrhée, chlamydiose)

Table 1. β-Lactamases (Ambler Classification).

Type	Ambler Molecular Class	Characteristics	Examples of Enzymes
Narrow-spectrum β-lactamases[12,18,19]	A	Hydrolyze penicillin; produced primarily by *Enterobacteriaceae*	Staphylococcal penicillinase, TEM-1, TEM-2, SHV-1
Extended-spectrum β-lactamases[20]	A	Hydrolyze narrow and extended-spectrum β-lactam antibiotics	SHV-2, CTX-M-15, PER-1, VEB-1
Serine carbapenemases[20]	A	Hydrolyze carbapenems	KPC-1, IMI-1, SME-1
Metallo-β-lactamases[21,22]	B	Hydrolyze carbapenems	VIM-1, IMP-1, NDM-1
Cephalosporinases[10,23,24]	C	Hydrolyze cephamycins and some oxyimino β-lactams; inducible; chromosomally mediated	AmpC, P99, ACT-1, CMY-2, FOX-1, MIR-1
OXA-type enzymes[25-27]	D	Hydrolyze oxacillin, oxyimino β-lactams, and carbapenems; produced by *Pseudomonas aeruginosa* and *Acinetobacter baumannii*	OXA enzymes

Table 2. β-Lactamase Inhibitor Combinations.

Inhibitor	Spectrum	Combination Antibiotics
Clavulanic acid[28-30]	Class A narrow spectrum	Amoxicillin
	Class A ESBLs	Ticarcillin
Tazobactam[6,39]	Class A narrow spectrum	Piperacillin
	Class A ESBLs	Ceftolozane
	Some class C enzymes	
Sulbactam[19,35,37]	Class A narrow spectrum	Ampicillin
	Class A ESBLs	Piperacillin
		Cefoperazone
Avibactam[46-48]	Class A narrow spectrum	Ceftaroline
	Class A ESBLs	Ceftazidime
	Class A carbapenemases	Aztreonam
	Some class C and class D enzymes	
MK-7655[75,76]	Class A narrow spectrum	Imipenem
relebactam	Class A ESBLs	
	Class A carbapenemases	
	Some class C enzymes	
RPX7009[83,84,85]	Class A narrow spectrum	Biapenem
varbobactam	Class A ESBLs	
	Class A carbapenemases	
	Some class C enzymes	

Abbreviation: ESBL, extended-spectrum β-lactamase.

Lucasti C, et al. Multicenter, double-blind, randomized, phase II trial to assess the safety and efficacy of ceftolozane-tazobactam plus metronidazole compared with meropenem in adult patients with complicated intra-abdominal infections. Antimicrob Agents Chemother. 2014;58(9):5350

Ceftozolane-tazobactam (Zerbaxa®)

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

Figure 1: Chemical structure of ceftolozane sulfate

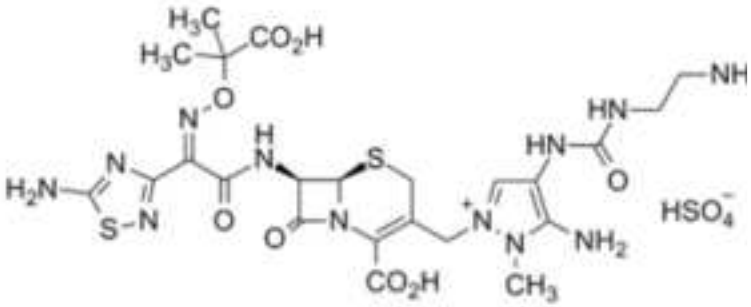
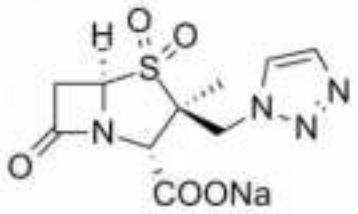


Figure 2: Chemical structure of tazobactam sodiu



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

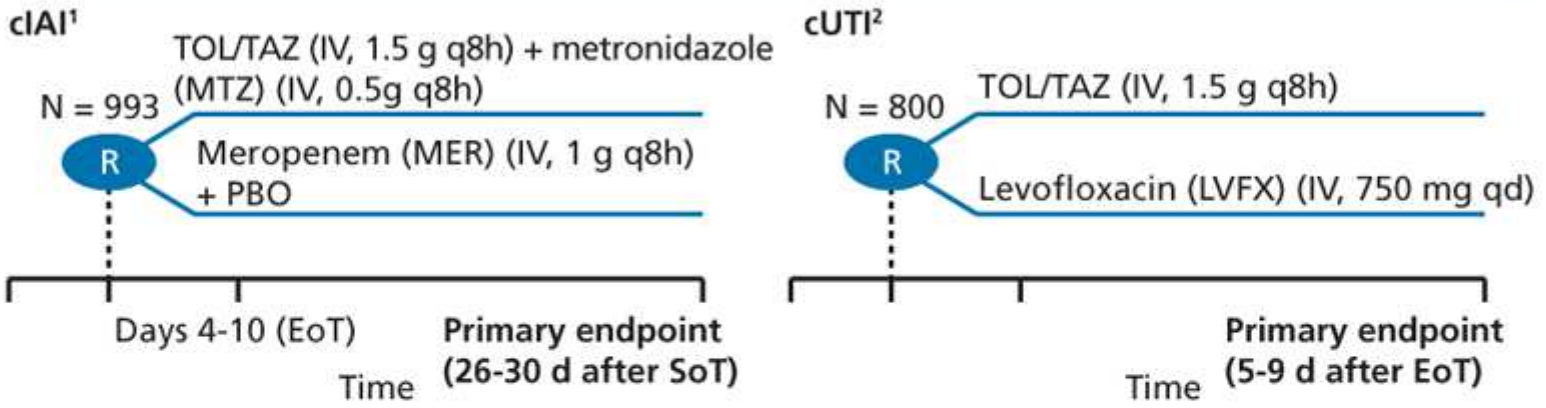
Approved FDA 19 dec 2014

AMM EMA 7/15, commercialisé France 2016, SMR important, ASMR V

Infections intra abdominales compliquées; Infections urinaires compliquées (pyélonéphrites) sur documentation bactériologique dans les infections à EBLSE ou à *P. aeruginosa* sensibles

Wagenlehner FM et al.. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). Lancet 2015 16;385:1949-56.

Gram-Negative Therapeutics: New Data on Ceftolozane/ Tazobactam (TOL/TAZ) for Complicated IAI or UTI



Microbiologically evaluable patients		TOL/TAZ + MTZ, %	MER + PBO, %
Microbiologic eradication	Gram(–) AE	96.3	95.4
	Gram(–) ANA	98.2	97.8
	Gram(+) AE	92.9	94.6
	Gram(+) ANA	100	93.9
Clinical cure		**94.2**	**94.7**

Microbiologically evaluable patients	TOL/TAZ, %	LVFX, %
Microbiological eradication (ME)	84.7[a]	75.1
Clinical cure (CC)	95.9	93.2
ME + CC	**83.3**	**75.4**

Bold = primary endpoint

[a] For 1 patient, the outcome differed depending on US vs EU definitions of ME and was not included in analysis.

SolomkinJ. et al.Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI)
Clin Infect Dis. 2015 15; 60(10): 1462–71

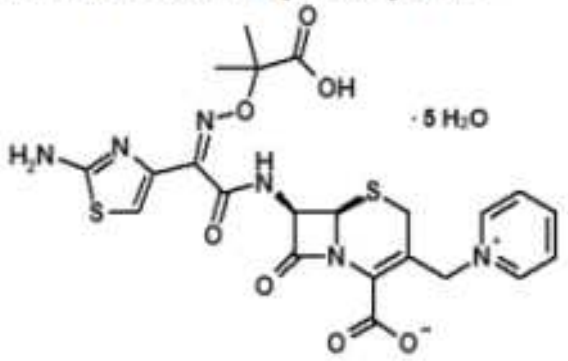
Ceftazidime-avibactam (Avycaz ®)

ATU n Astra-Zeneca **Zavicefta®**

- Microbiological Spectrum: **Gram negatives only**
  - *Pseudomonas aeruginosa*
  - Most ESBLs
  - Some carbapenemases
    - KPCs, OXAs, no NDMs

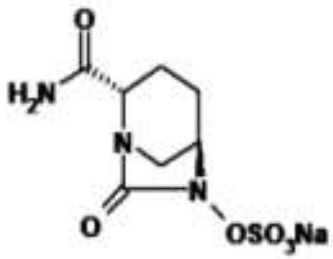
Approved FDA 25 Feb 2015

Chemical structure of ceftazidime pentahydrate



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

Chemical structure of avibactam sodium



EMA 07/2016 AMM
(cIAI,cUTI,HABP, infections à aérobies Gram<0 R)

Ceftazidime-avibactam (Avycaz ®)

Design

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

Results

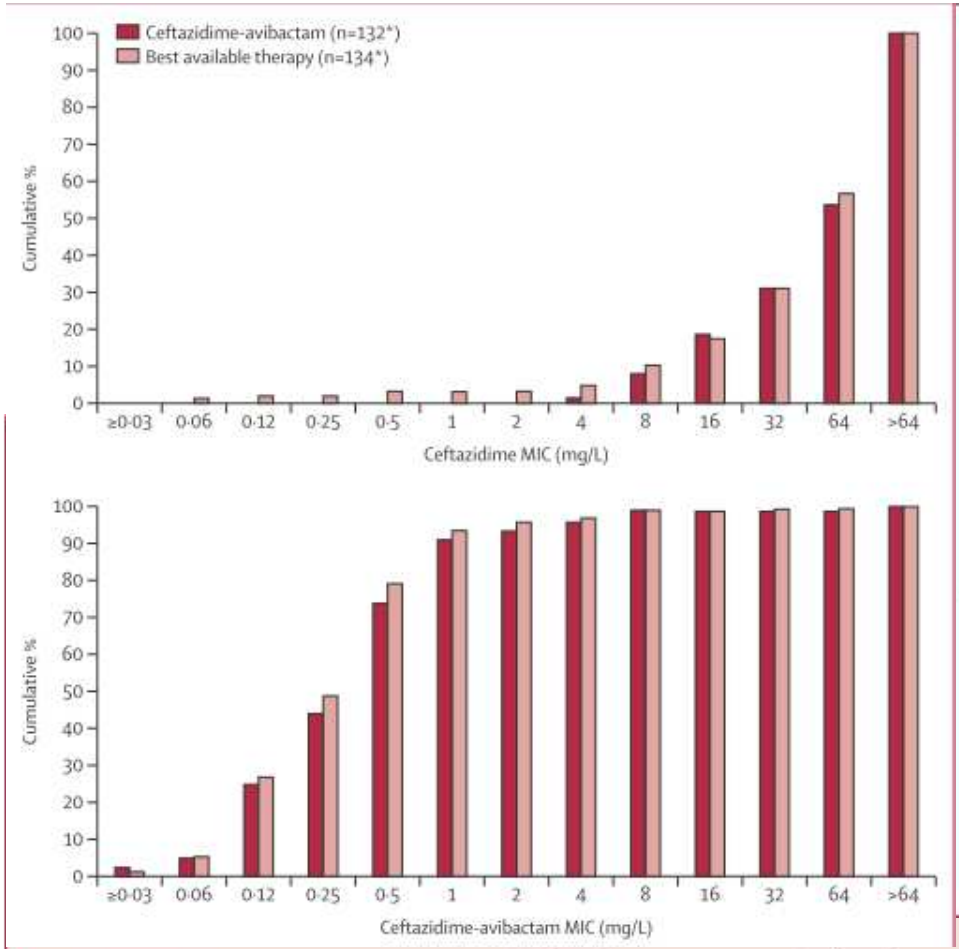
- Similar overall rates of efficacy, adverse events, and mortality
- patients with moderate renal impairment (estimated creatinine clearance : [30-50 mL/minute] had lower cure rates in the ceftazidime /avibactam plus metronidazole arm (45%) vs the meropenem arm (74%). This may have been secondary to an observed delay in dose readjustment back to full dosing in patients with recoveryof renal function

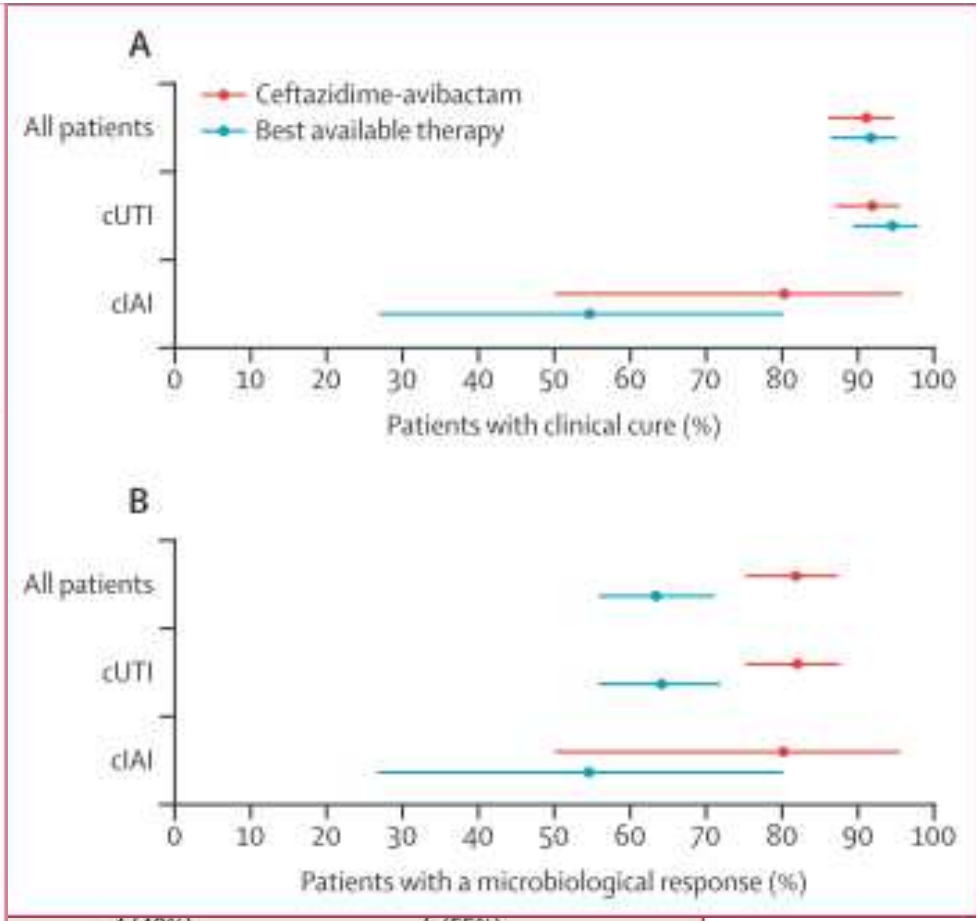
Vazquez JA,et al. Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. Curr Med Res Opin. 2012; 28:1921-31. [PubMed 23145859]

Mazuski J.E. Efficacy and Safety of Ceftazidime-Avibactam Plus Metronidazole Vs Meropenem in the Ttt of Complicated Intra-abdominal Infection: Results From a Randomized, Controlled, Double-Blind,Phase 3 Program.*Clin Infect Dis. 2016 March on line*

Carmeli Y et al. Lancet Infect Dis April 20, 2016 Published Online

Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and P. aeruginosa complicated urinary tract or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study



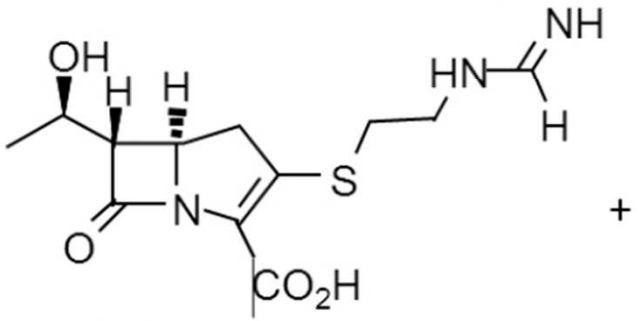


			4 (40%)	6 (55%)
Klebsiella pneumoniae	55 (38%)	65 (47%)	5 (50%)	3 (27%)
Enterobacter cloacae	8 (6%)	6 (4%)	3 (30%)	1 (9%)
Pseudomonas aeruginosa	14 (10%)	5 (4%)	1 (10%)	1 (9%)
Other identified pathogens‖	12 (8%)	10 (7%)	5 (50%)	8 (73%)

Imipenem / MK-7655 (relabactam)

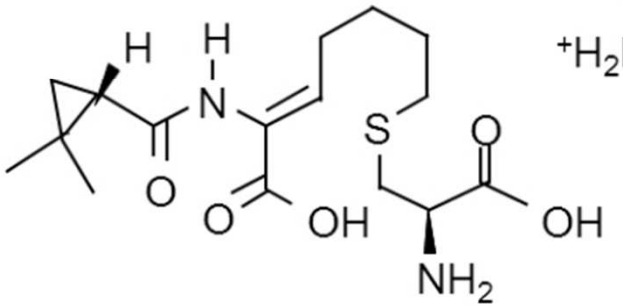
- Combination of imipenem-cilastatin and a BLI
- *In vitro* activity against *P. aeruginosa* and many ESBL producers, including carbapenem-resistant strains but not metallo-carbapenemases
- Limited activity against *A. baumannii*
- 2 separate Phase II studies of 2 doses (125 or 250 mg) of MK-7655 + imipenem-cilastatin vs imipenem-cilastatin alone for treatment of cUTI or cIAI initiated in early 2012

Résultats ICAAC 2015 351 pts randomisée, double aveugle: non infériorité (95 vs 98%)

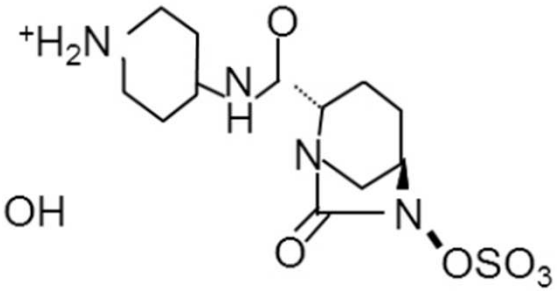


Imipenem

+



Cilastatin



MK-7655

Phase 3 en cours :

- imipenem/cilastatin/relebactam vs colistimethate sodium with imipenem/cilastatin for the treatment of imipenem-resistant bacterial infection cUTI, cIAI, HAP, VAP
- imipenem/cilastatin/relebactam vs piperacillin/tazobactam inh HAP, VAP

CARBAVANCE

Meropenem-Vaborbactam (formerly RPX7009)

Castanheira et al, ICAAC 2015

Pathogen	MER-VAB (8 µg/ml)	Ceftazidime	Meropenem	Pip/Tazo
Antibiotic MIC_{50} / MIC_{90} (2014 US Bloodstream Isolates)				
E. coli	≤0.015 / ≤0.015	0.25 /16	≤0.015 / ≤ 0.03	2 / 8
K. pneumoniae	0.03 / 0.03	0.12 / 32	0.03 / 0.06	4 / 32
ESBL pheno	≤0.015 / 0.12	16 / >32	≤0.03 / 16	8 / > 64
CRE	0.06 / 1	>32 / >32	32 / > 32	>64 / > 64

- PK properties of meropenem & vaborbactam well-matched in plasma, ELF (Wenzler, AAC 2015)
- MICs vs. *Pseudomonas aeruginosa*, *Acinetobacter spp* same as meropenem (higher MP dose/prolonged infusion covers MICs of 4-8 ug/ml)

TANGO 1 : Phase 3, randomized, double-blind, double dummy trial in cUTI, including AP. M-V (2g/2g via a 3 h infusion) or P-T (4g/0.5g via a 30 min infusion) every 8h. After ≥15 doses, pts could be switched to oral levofloxacin

Overall success occurred in 189 (98.4%) of 192 randomized to M-V and 171 (94.0%) of 182 in the P-T group (95% CI of difference: 0.7, 9.1) at the EOIVT (primary endpoint)

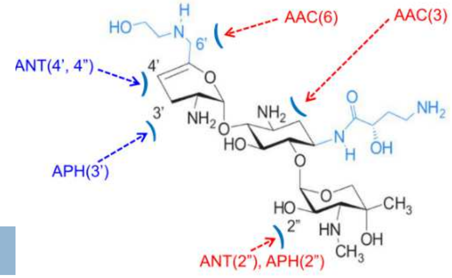
AEs were reported in 39.0% pts receiving M-V vs 35.5% on P-T, the majority being mild or moderate in severity

ID week 2016 Late breaker 7. J. Loutit

TANGO 2 Phase 3, multi-center, randomized, open-label study of CARBAVANCE (meropenem-vaborbactam) versus "best available therapy" in subjects with selected serious infections due to CRE. Approximately 150 study subjects with cUTI, nosocomial pneumonia and/or bacteremia will be randomly assigned (2:1) to CARBAVANCE or "best available therapy" for up to 14 days.

Plazomicin : aminoglycoside

(Achaogen Inc.)



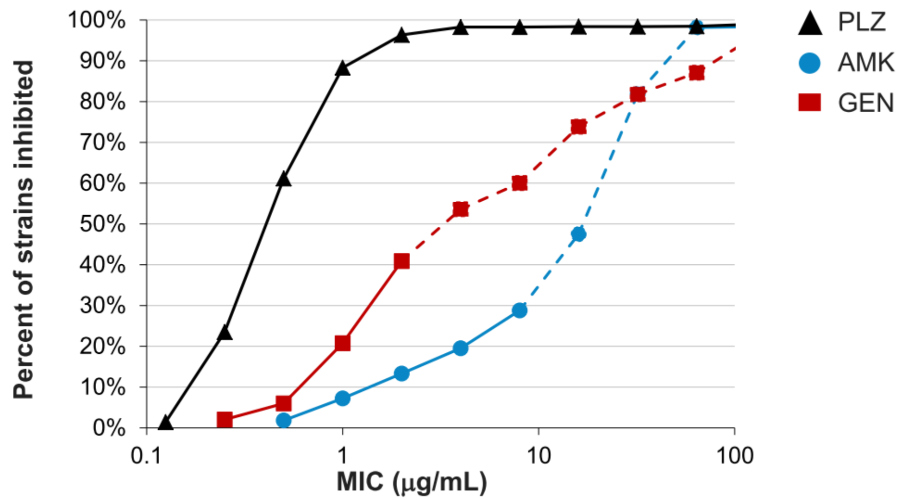
- Actif contre souches genta et tobra R; Active contre les enzymes hydrolysant les AMG sauf AAC2', fa, ile et 12o (++*Providencia*) et RNAmeyhylase
- Actif contre AmpC, BLSE, KPC (sauf *Proteus*). Inactif contre NDM
- Actif contre S. aureus and S. coagulase-neg
- Activité limitée contre *Acinetobacter, S. pneumoniae, Enterococcus sp.*

- Demi-vie de 4 heures
- Elimination rénale 87%
- Phase II dans UTI, vs levofloxacine : idem
- Moins ou pas de néphrotoxicité, cochléotoxicité
- À venir : études de phase 3 (résultats 2017)
  - CAP/HAP
  - Bactériémies, CAB
  - Association avec méropénem ou tigécycline; colistine + méropénem ou tigécycline
  - PK/PD; 15mg/kg/j

Pathogen	Plazomicin	Amikacin	Meropenem	Pip/Tazo
K. pneumoniae	0.25 / 0.5	≤1 / ≤1	≤0.03 / 0.06	2 / 4
MDR	1 / 2	32 / >32	>8 / >8	>64 / >64
E. coli	0.5 / 1	2 / 4	≤0.03 / ≤0.03	≤1 / 4
Ps. aeruginosa	4 / 16	4 / 8	0.5 / 4	4 / 32
MDR	8 / 32	4 / 32	4 / 32	64 / 256

Walktyl. AAC 2014;58:2554. Haider AAC 2016;60:5208; Galani J Infect 2012;24:191

Plazomicin and Comparator Activity vs. 983 Clinical CRE Isolates



N=983 Enterobacteriaceae isolates with an MIC ≥4 µg/mL for any type 2 carbapenem; dashed line indicates non-susceptible via EUCAST breakpoints

Recyclage , ATB vintage :

- Témocilline (Négaban®)
- Triméthoprime (TMP)

(Alprim, Delprim ®), AMM en révision