

**Foreword****EUCAST**

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is organised by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the European Centre for Disease Prevention and Control (ECDC), and the active national antimicrobial breakpoint committees in Europe. EUCAST was established by ESCMID in 1997, was restructured in 2001-2002 and has been in operation in its current form since 2002. The current remit of EUCAST is to harmonise clinical breakpoints for existing drugs in Europe, to determine clinical breakpoints for new drugs, to set epidemiological cut-off values (ECOFFs), to revise breakpoints as required, to develop and harmonise methodology for antimicrobial susceptibility testing, to develop a website with MIC and zone diameter distributions of antimicrobial agents for a wide range of organisms and to liaise with European governmental agencies and European networks involved with antimicrobial resistance and resistance surveillance.

Information on EUCAST and EUCAST breakpoints is available on the EUCAST website at <http://www.EUCAST.org>.

**EUCAST rationale documents**

EUCAST rationale documents summarise the information on which the EUCAST clinical breakpoints are based.

**Availability of EUCAST document**

All EUCAST documents are freely available from the EUCAST website at <http://www.EUCAST.org>.

**Citation of EUCAST documents**

This rationale document should be cited as: "European Committee on Antimicrobial Susceptibility Testing. **Temocillin**: Rationale for the clinical breakpoints, version 1,0, year. <http://www.eucast.org>.

## Introduction

Temocillin is a beta-lactam agent based on a penam core and a derivative of ticarcillin. The 6-methoxy and the other side chains confer an unusual spectrum for a penam, including relative resistance to a range of beta-lactamases and no useful activity against gram-positive microorganisms, most non-fermentative gram-negative bacteria and most of the common anaerobic pathogens (Jules and Neu, 1982; van Landuyt et al., 1982). Its activity is affected by changes in penicillin binding proteins, notably PBP3 (of *Escherichia coli*), which is the main drug target (Labia et al., 1984). Temocillin MICs are affected to some extent by extended-spectrum beta-lactamases (ESBLs), especially the CTX-M type (Giske, 2015), and also AmpC beta-lactamases. The agent resists the action of KPC carbapenemases to some extent, but not other types of carbapenemase (metallo-enzymes, OXA carbapenemases) (Giske, 2015, Alexandre and Fantin, 2018). Temocillin appears active against strains of *Neisseria gonorrhoeae* harbouring a range of resistance mechanisms (Ghathian et al., 2016).

Temocillin can only be administered parenterally. It is licensed in a limited number of European countries (currently UK, Belgium, Luxembourg, France and Germany), where it is used principally in the empirical treatment of pyelonephritis, as well as complicated UTI and more serious infections caused by *Enterobacterales* that produce extended-spectrum and AmpC type beta-lactamases.

### References:

- Jules K, Neu HC. Antibacterial activity and beta-lactamase stability of temocillin Antimicrob Agents Chemother. 1982 Sep;22(3):453-60
- Van Landuyt HW, Pyckavet M, Lambert A, Boelaert J. In vitro activity of temocillin (BRL 17421), a novel beta-lactam antibiotic. Antimicrob Agents Chemother. 1982;22(4):535-40
- Livermore DM, Tulkens PM. Temocillin revived. J Antimicrob Chemother. 2009;63(2):243-5
- Labia R, Baron P, Masson JM, Hill G, Cole M. Affinity of temocillin for Escherichia coli K-12 penicillin-binding proteins. Antimicrob Agents Chemother. 1984;26(3):335-8
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- Alexandre K, Fantin B. Pharmacokinetics and Pharmacodynamics of Temocillin. Clin Pharmacokinet. 2018;57(3):287-296.
- Ghathian K, Calum H, Gyssens IC, Frimodt-Møller N. Temocillin in vitro activity against recent clinical isolates of *Neisseria gonorrhoeae* compared with penicillin, ceftriaxone and ciprofloxacin. J Antimicrob Chemother. 2016;71(4):1122-3

## 1. Dosage

	<b>BSAC (UK)</b>	<b>CA-SFM (France)</b>	<b>German NAC</b>
Most common dose	2g x 2	2g x 2	2g x 2
Maximum dose schedule	2g x 3	2g x 3	2g x 3
Available formulations	iv	iv	iv

## 2. MIC distributions<sup>1</sup> and epidemiological cut-off (ECOFF) values (mg/L)

MIC distributions and ECOFFs can be found at <https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=init>

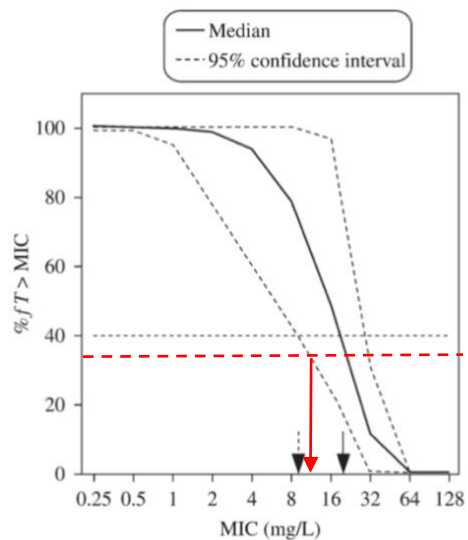
3. Breakpoints prior to harmonisation (mg/L) S <sub>≤</sub> / R <sub>&gt;</sub>							
	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA	CLSI
<b>General breakpoints</b>							
<b>Species-related breakpoints</b>							
<i>Enterobacterales</i>	8 / 8 (systemic) 32 / 32 (uUTI)	8 / 8					
<i>Pseudomonas</i> spp.							
<i>Acinetobacter</i> spp.							
<i>Staphylococcus</i> spp.							
<i>Streptococcus</i> spp.							
<i>Streptococcus pneumoniae</i>							
<i>Enterococcus</i> spp.							
<i>Haemophilus influenzae</i>							
<i>Moraxella catarrhalis</i>							
<i>Corynebacterium</i> spp.							
<i>Neisseria meningitidis</i>							
<i>Neisseria gonorrhoeae</i>							
<i>Pasteurella multocida</i>							
Anaerobes, Gram-positive							
Anaerobes, Gram-negative							
<i>Campylobacter</i> spp.							
<i>Helicobacter pylori</i>							

<b>4. Pharmacokinetics</b>				
Dosage (mg)	500 (Healthy volunteers)	1000 (Healthy volunteers)	2000 (Healthy volunteers)	2000 (ICU patients)
C <sub>max</sub> (mg/L)	77.9	160.8	236.1	147 +/- 12
C <sub>min</sub> (mg/L)				
Total body clearance (L/h)	18.5	19.6	29.8	40.7
T <sub>1/2</sub> (h), mean (range)	5.2	5.0	5.0	4.3 +/- 0.3
AUC <sub>0-∞</sub> (mg.h/L)	344.1	573.3	784.5	1856 +/- 282 (0-24h)
Fraction unbound (%)	15		37	23.7
Volume of distribution (L/kg)	0.15	0.17	0.24	14.3 L
Comments	<ul style="list-style-type: none"> <li>• Two values are given where references differ. Cells are left empty when data are not readily available.</li> <li>• Protein binding is concentration-dependent.</li> </ul>			
References	<ul style="list-style-type: none"> <li>• Alexandre K, Fantin B. Pharmacokinetics and Pharmacodynamics of Temocillin. Clin Pharmacokinet. 2018;57(3):287-296.</li> <li>• Hampel B, Feike M, Koeppe P, Lode H. Pharmacokinetics of temocillin in volunteers. Drugs. 1985;29(Suppl 5):99-102</li> <li>• De Jongh R, Hens R, Basma V, Mouton JW, Tulkens PM, Carryn S. Continuous versus intermittent infusion of temocillin, a directed spectrum penicillin for intensive care patients with nosocomial pneumonia: stability, compatibility, population pharmacokinetic studies and breakpoint selection. J Antimicrob Chemother. 2008; 61:382-8.</li> </ul>			

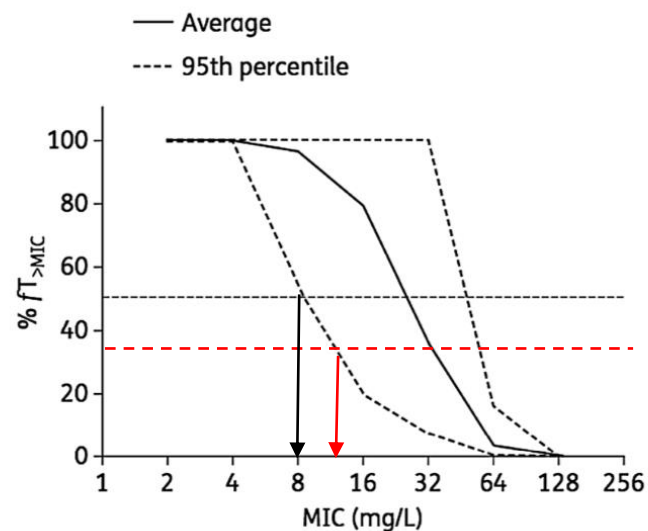
5. Pharmacodynamics				
Dose		2g 12-hourly equivalent (Soubirou et al., 2015)		
$f\%T>MIC$ for bacteriostasis	40-50%	35-41%		
$f\%T>MIC$ for 2 log reduction				
$f\%T>MIC$ from clinical data				
Comments	<ul style="list-style-type: none"> <li>• Temocillin has not been subjected to detailed analysis of its pharmacodynamics. There are no in vitro model data and only non-conventional animal model studies. The first estimate for the bacteriostatic target is presumed, based on comparison with other penicillins.</li> <li>• There are data from two studies using a murine model of acute pyelonephritis (Soubirou et al., 2015; Alexandre et al, 2019). Isolates with ESBLs were studied and efficacy established using humanised dosing equivalent to 2g 12-hourly showing microbial eradication from the kidneys in strains with an MIC of 8 mg/L and eradication in 43% of mice in strains with an MIC of 16 mg/L.</li> </ul>			
References	<ul style="list-style-type: none"> <li>• Alexandre K, Fantin B. Pharmacokinetics and Pharmacodynamics of Temocillin. Clin Pharmacokinet. 2018;57(3):287-296</li> <li>• De Jongh R, Hens R, Basma V, Mouton JW, Tulkens PM, Carryn S. Continuous versus intermittent infusion of temocillin, a directed spectrum penicillin for intensive care patients with nosocomial pneumonia: stability, compatibility, population pharmacokinetic studies and breakpoint selection. J Antimicrob Chemother. 2008; 61:382–8</li> <li>• Alexandre K, Chau F, Guérin F, Massias L, Lefort A, Cattoir V, et al. Activity of temocillin in a lethal murine model of infection of intra-abdominal origin due to KPC-producing <i>Escherichia coli</i>. J Antimicrob Chemother. 2016; 71:1899–904</li> <li>• Soubirou JF, Rossi B, Couffignal C, Ruppé E, Chau F, Massias L, Lepeule R, Mentre F, Fantin B. Activity of temocillin in a murine model of urinary tract infection due to <i>Escherichia coli</i> producing or not producing the ESBL CTX-M-15. J Antimicrob Chemother. 2015;70(5):1466-72.</li> <li>• Alexandre K, Soares A, Chau F, Fantin B, Caron F, Etienne M. Temocillin breakpoints in pyelonephritis: evaluation in a murine model due to ESBL-producing <i>Escherichia coli</i> clinical isolates. J Antimicrob Chemother. 2019 74(5) 2019: 1323–1326.</li> </ul>			

## 6. Monte Carlo simulations and Pk/Pd breakpoints

Temocillin 2g x 2 (De Jongh et al., JAC 2016)



Temocillin 2g x 3 (Laterre et al., JAC 2016)



MIC (mg/L)	<i>fT</i> >MIC (in %) of free temocillin (2 g) given		
	q24 h	q12 h	q8 h
0.50	100.00	100.00	100.00
1.00	87.50	100.00	100.00
2.00	70.60	100.00	100.00
4.00	53.70	100.00	100.00
8.00	36.70	79.70	100.00
16.00	19.40	45.10	80.30
32.00	1.60	9.50	26.90
64.00	0.00	0.00	0.00

**References**

- Alexandre K, Fantin B. Pharmacokinetics and Pharmacodynamics of Temocillin. Clin Pharmacokinet. 2018;57(3):287-296
- Alexandre K, Chau F, Guérin F, Massias L, Lefort A, Cattoir V, et al. Activity of temocillin in a lethal murine model of infection of intra-abdominal origin due to KPC-producing *Escherichia coli*. J Antimicrob Chemother. 2016; 71:1899–904
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- Laterre P-F, Wittebole X, Van de Velde S, Muller AE, Mouton JW, Carryn S, et al. Temocillin (6 g daily) in critically ill patients: continuous infusion versus three times daily administration. J Antimicrob Chemother. 2015; 70:891–8.
- Muller A, Mouton J. Monte Carlo simulation based on PK data from healthy volunteers (Beecham). EUMEDICA data on file.

## 7. Clinical data

Most of the clinical data on temocillin were generated in the 1980s when the agent was initially developed. Temocillin has been trialled in surgical patients, 'severe' infections, biliary sepsis, respiratory infections (Drugs supplement 1985) and pyelonephritis in children (Verboven et al., 1987). Recent published experience is more limited, and largely anecdotal (Barton et al., 2008; Gupta et al., 2009) or about use in combination with other active agents (Habayeb et al., 2015).

A study in the UK of temocillin efficacy demonstrated the inadequacy of doses of less than 2g twice daily for therapy of infections caused by ESBL- or AmpC-producing *Enterobacterales*: successful outcome in 67% for the lower doses versus 97% for 2g twice daily (Balakrishnan et al., 2011). Regimens with more than 4g per day were not used in this study.

### References

- Alexandre K, Fantin B. Pharmacokinetics and Pharmacodynamics of Temocillin. Clin Pharmacokinet. 2018;57(3):287-296
- Drugs. 1985;29 Suppl 5: 1-243 (Temocillin)
- Verboven M, Lauwers S, Pintens H. Temocillin in the treatment of pyelonephritis in children. Drugs Exp Clin Res. 1987;13(3):171-3.
- Barton E , Flanagan P, Hill S. Spinal infection caused by ESBL-producing *Klebsiella pneumoniae* treated with temocillin. J Infect. 2008;57(4):347-9.
- Gupta ND, Smith RE, Balakrishnan I. Clinical efficacy of temocillin. J Antimicrob Chemother. 2009 Aug;64(2):431-3.
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- Balakrishnan I, Awad-El-Kariem FM, Aali A, Kumari P, Mulla R, Tan B, Brudney D, Ladenheim D, Ghazy A, Khan I, Virgincar N, Iyer S, Carryn S, Van de Velde S. Temocillin use in England: clinical and microbiological efficacies in infections caused by extended-spectrum and/or derepressed AmpC  $\beta$ -lactamase-producing Enterobacteriaceae. J Antimicrob Chemother. 2011;66(11):2628-31.

<b>8. Clinical breakpoints</b>	
Non-species-related breakpoints	Insufficient evidence (IE)
Species-related breakpoints	<i>Enterobacterales: E. coli, Klebsiella spp. (except K. aerogenes), P. mirabilis</i> only S ≤0.001, R >16 mg/L The R-breakpoint is the same as the ECOFF for most target species. The wild-type population has been placed in the I-group to reflect that high exposure is needed to cover the entire wild-type (1 – 16 mg/L) of relevant organisms.
Species without breakpoints	All other species
Clinical qualifications	Species-related breakpoints apply to isolates from patients with complicated and more severe urinary tract infections including urosepsis, but excluding severe sepsis and septic shock. There are insufficient data to recommend breakpoints and dosing regimens for pneumonia or other invasive infections
Dosage	Breakpoints apply to high-exposure dosing regimen of 2 g x 3 iv.
Additional comment	Data from mouse non-severe pyelonephritis model supports a breakpoint of R >16 mg/L, but only with a dosing regimen of 2 g x 3. Some countries have used a lower “R” breakpoint (mostly 8 mg/L). This will split the wild type of primarily <i>E. coli</i> , the most important target for temocillin therapy. Using a target %fT>MIC of 35%, satisfactory target attainment rates can only be achieved in systemic infections using doses of 2 g every 8 hours, i.e. doses above those currently licensed.  High urinary concentrations may permit the use of lower-exposure dosing regimens such as 2g every 12 hours for lower urinary tract infections complicated by comorbidities or caused by species resistant to other drug classes.

## 9. Temocillin - EUCAST clinical MIC breakpoints

These are listed at <http://www.eucast.org>.

## 10. Exceptions noted for individual national committees

None