

Rationale for EUCAST clinical breakpoints

| | | |
|------------------------|--------------------|-------------------------|
| Agent | Nitroxoline | |
| Current version | 1.0 | 11 November 2016 |
| Previous versions | | |
| | | |

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 (microbiological) breakpoints, to revise breakpoints as required, to 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 documents

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

Citation of EUCAST documents

The copyright of all documents and data published on the EUCAST website remains with EUCAST. All are freely available for re-use if reference to the EUCAST website is given and documents and data are not resold. Any secondary publication of the data must be referenced with the declaration that "These data have (or this document has) been produced in part under ECDC service contracts, is made available at no cost by EUCAST and can be accessed freely on the EUCAST website www.eucast.org. EUCAST recommendations are frequently updated and the latest versions are available at www.eucast.org."

This rationale document should be cited as: "European Committee on Antimicrobial Susceptibility Testing. Nitroxoline: Rationale for the clinical breakpoints, version 1.0 2016, <http://www.eucast.org>."

1. Introduction

Nitroxoline (5-nitro-8-hydroxyquinoline) is an oral agent which is different from any other antimicrobial drug class. The mechanism of action is believed to be chelation of divalent cations required for activity of bacterial RNA polymerase.

The antimicrobial spectrum of nitroxoline covers *Escherichia coli* and some other uropathogens. *Pseudomonas* spp. are resistant.

There are some resistant isolates but the mechanisms of resistance have not yet been determined.

Nitroxoline has marketing authorisation for prophylaxis and treatment of acute and recurrent UTI in Germany, Bulgaria, Croatia, Poland, Romania, Bosnia-Herzegovina and Montenegro.

2. Dosage

| | |
|------------------------|-----------|
| Standard dose schedule | 250mg x 3 |
| Maximum dose schedule | 250mg x 3 |
| Available formulations | oral |

3. MIC distributions and epidemiological cut-off (ECOFF) values (mg/L)

| Organism | 0.06 | 0.125 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | 128 | 256 | ECOFF |
|-------------------------------------|------|-------|------|-----|----|-----|-----|-----|-----|----|----|-----|-----|-------|
| <i>Escherichia coli</i> | 1 | 1 | 0 | 0 | 32 | 464 | 462 | 551 | 115 | 1 | 1 | 0 | 0 | 16 |
| <i>Citrobacter</i> spp. | 0 | 0 | 0 | 0 | 0 | 2 | 4 | 41 | 11 | 2 | 0 | 0 | 0 | ND |
| <i>Klebsiella oxytoca</i> | 0 | 0 | 0 | 0 | 0 | 1 | 21 | 10 | 1 | 0 | 0 | 0 | 0 | ND |
| <i>Klebsiella pneumoniae</i> | 0 | 0 | 0 | 0 | 1 | 13 | 46 | 29 | 4 | 4 | 0 | 0 | 0 | ND |
| <i>Klebsiella</i> spp. | 0 | 0 | 0 | 0 | 2 | 1 | 8 | 57 | 58 | 17 | 3 | 0 | 0 | ND |
| <i>Morganella morganii</i> | 0 | 0 | 0 | 0 | 0 | 3 | 14 | 45 | 17 | 0 | 0 | 0 | 0 | ND |
| <i>Proteus mirabilis</i> | 0 | 0 | 0 | 0 | 2 | 12 | 99 | 221 | 42 | 1 | 1 | 0 | 0 | ND |
| <i>Proteus vulgaris</i> | 0 | 0 | 0 | 0 | 0 | 2 | 36 | 61 | 18 | 0 | 0 | 0 | 0 | ND |
| <i>Proteus</i> spp. indole-positive | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 13 | 11 | 1 | 1 | 0 | 0 | ND |
| <i>Serratia</i> spp. | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 55 | 11 | 0 | 0 | 0 | ND |
| <i>Enterobacter cloacae</i> | 0 | 0 | 0 | 0 | 1 | 1 | 4 | 27 | 4 | 0 | 0 | 0 | 0 | ND |
| <i>Enterobacter</i> spp. | 0 | 0 | 0 | 0 | 0 | 2 | 12 | 25 | 49 | 8 | 1 | 0 | 0 | ND |
| <i>Acinetobacter</i> spp. | 0 | 0 | 0 | 3 | 6 | 28 | 29 | 6 | 0 | 1 | 1 | 0 | 0 | ND |
| <i>Pseudomonas aeruginosa</i> | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 26 | 18 | 27 | 5 | 0 | ND |
| <i>Pseudomonas</i> spp. | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 27 | 57 | 23 | 3 | ND |
| <i>Staphylococcus aureus</i> | 0 | 0 | 0 | 0 | 17 | 39 | 29 | 130 | 1 | 0 | 0 | 0 | 0 | ND |
| <i>Staphylococcus epidermidis</i> | 0 | 0 | 0 | 0 | 0 | 1 | 36 | 113 | 21 | 0 | 0 | 0 | 0 | ND |
| <i>Staphylococcus saprophyticus</i> | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 30 | 0 | 1 | 0 | 0 | 0 | ND |
| Coagulase-negative staphylococci | 0 | 0 | 0 | 1 | 10 | 35 | 9 | 8 | 2 | 0 | 0 | 0 | 0 | ND |
| <i>Enterococcus faecalis</i> | 0 | 0 | 0 | 0 | 0 | 3 | 20 | 124 | 158 | 46 | 6 | 0 | 0 | ND |
| <i>Enterococcus faecium</i> | 0 | 0 | 0 | 0 | 0 | 1 | 8 | 42 | 0 | 0 | 0 | 0 | 0 | ND |

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple sources and time periods. The distributions are used to define the epidemiological cut-off values (ECOFF) and give an indication of the MICs for organisms with acquired resistance mechanisms. They should not be used to infer resistance rates. The MIC distributions at the underlined numbers are distorted by truncation of some aggregated distributions. When there is insufficient evidence or when the species has not been identified to species level the ECOFF has not been determined (ND). The ECOFF is not affected by the presence of resistance mechanisms; so distributions composed entirely of isolates with specific resistance mechanisms or mixtures of isolates with and without resistance mechanisms have the same ECOFF as the population of the same species with no resistance mechanisms.

4. Breakpoints prior to harmonisation (mg/L) S≤ / R>

| | BSAC | CA-SFM | SWAB | NAC-Germany | NWGA | SRGA | CLSI |
|-------------------------------------|------|--------|------|----------------------------|------|------|------|
| General breakpoints | | | | | | | |
| Species-related breakpoints | | | | | | | |
| Enterobacteriaceae | | | | 16 /16 <i>E. coli</i> only | | | |
| <i>Pseudomonas</i> spp. | | | | | | | |
| <i>Stenotrophomonas maltophilia</i> | | | | | | | |
| <i>Acinetobacter</i> spp. | | | | | | | |
| <i>Staphylococcus</i> spp. | | | | | | | |
| <i>Enterococcus</i> spp. | | | | | | | |
| Streptococcus groups A,B,C,G | | | | | | | |
| <i>Streptococcus pneumoniae</i> | | | | | | | |
| Viridans group streptococci | | | | | | | |
| <i>Haemophilus influenzae</i> | | | | | | | |
| <i>Moraxella catarrhalis</i> | | | | | | | |
| <i>Neisseria gonorrhoeae</i> | | | | | | | |
| <i>Neisseria meningitidis</i> | | | | | | | |
| Anaerobes, Gram-positive | | | | | | | |
| <i>Clostridium difficile</i> | | | | | | | |
| Anaerobes, Gram-negative | | | | | | | |
| Anaerobes, Gram-positive | | | | | | | |
| <i>Helicobacter pylori</i> | | | | | | | |
| <i>Listeria monocytogenes</i> | | | | | | | |
| <i>Pasteurella multocida</i> | | | | | | | |
| <i>Campylobacter</i> spp. | | | | | | | |
| <i>Corynebacterium</i> spp. | | | | | | | |
| <i>Aerococcus</i> spp. | | | | | | | |
| <i>Kingella kingae</i> | | | | | | | |

| 5. Pharmacokinetics | | | | |
|----------------------------------|---|--|--|--|
| Dosage (mg) | 250 mg oral Mean Value (SD) | | | |
| Cmax (mg/L) | 6.1-7.8 | | | |
| Cmin (mg/L) | | | | |
| Total body clearance (L/h) | | | | |
| T ½ (h), mean (range) | 2.0 | | | |
| AUC24h (mg.h/L) | | | | |
| AUC _{0-12h,ss} (mg.h/L) | | | | |
| AUC _∞ (mg.h/L) | | | | |
| Fraction unbound (%) | | | | |
| Volume of distribution (L/kg) | | | | |
| Comments | <ul style="list-style-type: none"> • Cells are left empty when data are not available. • Concentrations (mg/L) in urine following a dose of 200 mg in one study (Bergogne-Berezin <i>et al</i>) were 46±5 at 0-1 h, 216±137 at 1-2h, 187±134 at 2-3h, 220±131 at 3-4h, 105±83 at 4-6h, 84±71 at 6-8h, 59.5±34 at 8-10h. | | | |
| References | <ul style="list-style-type: none"> • Bergogne-Berezin E <i>et al</i>, <i>Pathol Biol (Paris)</i> 1987; 35: 873-8 | | | |

6. Pharmacodynamics

| | | | | |
|-----------------------------|---|--|--|--|
| Animal data | | | | |
| | | | | |
| f%T>MIC for bacteriostasis | | | | |
| f%T>MIC for 1 log reduction | | | | |
| f%T>MIC for 2 log reduction | | | | |
| Clinical Data | | | | |
| Comments | • Cells are left empty when data are not available. | | | |
| References | | | | |

7. Monte Carlo simulations and PK-PD breakpoints

No data

8. Clinical data

In a meta-analysis, published data from 26 uncontrolled studies were analysed (Naber KG *et al. BMC Infect Dis* 2014; 14:628-643). Studies included 1206 patients (947 adults and 259 children), two controlled studies (including 148 patients, 100 adults and 48 children) and one post-marketing observational study comprised of 9,800 patients with uncomplicated and complicated UTI. Nitroxoline was mainly administered for treatment of uncomplicated and complicated UTI as well as for prophylaxis of recurrent UTI, with daily dosages mostly between 300 and 900 mg. The treatment duration varied between three and 10 days depending on the indication. Success rates varied from 66-100%, with most in the 70-90% range.

A total of 466 female patients with acute uncomplicated or recurrent cystitis were included in four unpublished prospective open randomized studies reported in the Naber meta-analysis. Of these, 234 received 250 mg of nitroxoline orally three times daily and 232 either 960 mg of cotrimoxazole three times daily (n=178) or 400 mg norfloxacin twice daily (n=54) for 5-10 days. More than 90% of the patients treated with nitroxoline showed eradication of bacteriuria and met the statistical requirement of a 10% non-inferiority margin in eradication rates compared with the controls in all three evaluation sets. The clinical efficacy (reduction of symptoms, global assessment by patient and physician) was similar between the two treatment groups.

Data relating MIC to outcome are not available.

9. Clinical breakpoints

| | | | | |
|------------------------------|--|-------------------------------|-------------|--|
| PK-PD breakpoints | There is insufficient evidence to set PK-PD breakpoints. Clinical breakpoints are based on pharmacokinetic data, microbiological data and clinical experience. | | | |
| Species-related breakpoints | Organism group | MIC breakpoints (mg/L) | | Notes |
| | | S ≤ | R > | |
| | Enterobacteriaceae | 16 | 16 | 1. The breakpoints relate to <i>E. coli</i> from uncomplicated urinary tract infection only. |
| | <i>Pseudomonas</i> spp. | - | - | 2. These organisms were considered poor targets for therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints. |
| | <i>Stenotrophomonas maltophilia</i> | - | - | See note 2. |
| | <i>Acinetobacter</i> spp. | - | - | See note 2. |
| | <i>Staphylococcus</i> spp. | IE | IE | 4. The breakpoints relate to <i>S. saprophyticus</i> from uncomplicated urinary tract infection only. |
| | <i>Enterococcus</i> spp. | IE | IE | 5. The breakpoints relate to uncomplicated urinary tract infection only. |
| | Streptococcus groups A,B,C,G | - | - | See note 2. |
| | <i>Streptococcus pneumoniae</i> | - | - | See note 2. |
| | Viridans group streptococci | - | - | See note 3. There is insufficient evidence that the species in question is a good target for therapy with the agent. |
| | <i>Haemophilus influenzae</i> | - | - | See note 2. |
| | <i>Moraxella catarrhalis</i> | - | - | See note 2. |
| | <i>Neisseria gonorrhoeae</i> | - | - | See note 2. |
| | <i>Neisseria meningitidis</i> | - | - | See note 2. |
| | Anaerobes, Gram-positive | - | - | See note 2. |
| | <i>Clostridium difficile</i> | - | - | See note 2. |
| | Anaerobes, Gram-negative | - | - | See note 2. |
| | <i>Helicobacter pylori</i> | - | - | See note 2. |
| | <i>Listeria monocytogenes</i> | - | - | See note 2. |
| <i>Pasteurella multocida</i> | - | - | See note 2. | |
| <i>Campylobacter</i> spp. | - | - | See note 2. | |
| <i>Corynebacterium</i> spp. | - | - | See note 2. | |
| <i>Aerococcus</i> spp. | - | - | See note 2. | |
| <i>Kingella kingae</i> | - | - | See note 2. | |
| Clinical qualifications | The breakpoints relate to uncomplicated urinary tract infection only. | | | |
| Dosage | 250mg orally every 8 h. | | | |
| Additional comment | | | | |

| |
|--|
| 10. Exceptions noted for individual national committees |
|--|

| |
|-------|
| None. |
|-------|