N | A | K

Nationales Antibiotika-Sensitivitätstest-Komitee

Nitroxoline	Rationale for the NAK clinical breakpoints, version 1.1	3rd December 2014

Foreword

NAK
The German Antimicrobial Susceptibility Testing Committee (NAK - Nationales Antibiotika-Sensitivitätstest -Komitee; German NAC) was founded the 14th of June, 2012. Major objectives are I) to establish EUCAST breakpoints and technical aspects of in vitro antimicrobial susceptibility testing in German laboratories, II) to adapt EUCAST breakpoint to local requirements, and (III) to evaluate breakpoints for antimicrobial agents that have not yet been considered by EUCAST.
The organizational structure largely follows that of EUCAST. The General Committee comprising representatives of national scientific societies and organizations in the fields of infectious diseases and patient safety decides on recommendations proposed by the Steering Committee. The Steering Committee currently consists of 15 experts having a background in clinical microbiology, infectious diseases or regulatory affairs. Both boards will meet at least once a year. Industry has an observational status only.

Information on NAK is available on the NAK website at http://www.nak-deutschland.org.

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

Availability of NAK document
All NAK documents are freely available from the NAK website at http://www.nak-deutschland.org.

Citation of NAK documents
This rationale document should be cited as: “NAK - Nationales Antibiotika-Sensitivitätstest -Komitee. Nitroxoline: Rationale for the clinical breakpoints, version 1.0, 2014.

1. Introduction

Nitroxoline (5-nitro-8-hydroxyquinoline) is an oral antibiotic which is different from any other antimicrobial drug class.

The mechanism of action is believed to be chelation of divalent cations required for bacterial RNA polymerase[1].

Its antimicrobial spectrum covers *Escherichia coli* and other uropathogens. *Pseudomonas* spp. are resistant.

The mechanisms of resistance have not been described yet.

Nitroxoline has been shown to be equally active against fully susceptible and multidrug resistant (MDR) *E. coli* isolates, including those resistant to amoxicillin, amoxicillin-clavulanate, cefuroxime, third-generation cephalosporins (cefixime and cefpodoxime), ciprofloxacin, and cotrimoxazole.[2]

Nitroxoline has obtained marketing authorization for prophylaxis and treatment of acute and recurrent UTI in Germany and some other European countries.

[1] Fraser RS, Creanor J. Rapid and selective inhibition of RNA synthesis in yeast by 8-hydroxyquinoline. Eur. J. Biochem. 1974; 46: 67-73.
[2] Kresken M, Körber-Irrgang B. Antimicrob Agents Chemother. 2014; 58: 7019-20

2. Dosage

	BSAC	CA-SFM[1]	CRG	NAK Germany[2]	NWGA	SRGA
Most common dose schedule		200 mg oral x 3[1]		250 mg oral x 3		
Maximum dose schedule		200 mg oral x 3[1]		250 mg oral x 3		
Available formulations		oral[1]		oral		

[1] According to information of the French regulatory authority (ANSM) the last nitroxoline product lost the marketing authorization in 2006.
[2] Nitroxoline at a dosage of 250 mg oral x 3 has also received a marketing authorization in Bulgaria, Croatia, Poland and Romania as well as in some non-EU member states like Bosnia-Herzegovina and Montenegro.

3. MIC distributions[1] and epidemiological cut-off (ECOFF) values (mg/L)

Organism	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Escherichia coli - Kresken	0	0	0	0	0	0	0	0	0	21	286	190	2	0	0	0	0	0	0	
Escherichia coli - Marre	0	0	0	0	0	0	0	0	0	1	8	77	50	2	0	0	0	0	0	
Escherichia coli - Opferkuch	0	0	0	0	0	0	0	0	0	0	12	117	463	112	0	0	0	0	0	
Escherichia coli - Pfister	0	0	0	0	0	1	1	0	0	5	158	74	12	1	0	1	0	0	0	
Escherichia coli - Jacobs	0	0	0	0	0	0	0	0	0	5	0	4	24	0	1	0	0	0	0	
Escherichia coli	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**0**	**0**	**32**	**464**	**462**	**551**	**115**	**1**	**1**	**0**	**0**	**0**	**16**
Citrobacter spp - Opferkuch	0	0	0	0	0	0	0	0	0	0	2	4	41	11	2	0	0	0	0	
***Citrobacter* spp.**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2**	**4**	**41**	**11**	**2**	**0**	**0**	**0**	**0**	**ND**
Klebsiella oxytoca - Marre	0	0	0	0	0	0	0	0	0	0	0	1	2	0	0	0	0	0	0	
Klebsiella oxytoca - Pfister	0	0	0	0	0	0	0	0	0	0	1	20	8	1	0	0	0	0	0	
Klebsiella oxytoca	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**21**	**10**	**1**	**0**	**0**	**0**	**0**	**0**	**ND**
Klebsiella pneumoniae - Kresken	0	0	0	0	0	0	0	0	0	0	4	17	9	0	0	0	0	0	0	
Klebsiella pneumoniae - Marre	0	0	0	0	0	0	0	0	0	0	0	4	10	1	2	0	0	0	0	
Klebsiella pneumoniae - Pfister	0	0	0	0	0	0	0	0	0	1	9	25	10	3	2	0	0	0	0	
Klebsiella pneumoniae	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**13**	**46**	**29**	**4**	**4**	**0**	**0**	**0**	**0**	**16**
Klebsiella spp - Opferkuch	0	0	0	0	0	0	0	0	0	0	0	6	52	47	5	2	0	0	0	
Klebsiella spp – Jacobs	0	0	0	0	0	0	0	0	0	2	1	2	5	11	12	1	0	0	0	
***Klebsiella* spp.**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2**	**1**	**8**	**57**	**58**	**17**	**3**	**0**	**0**	**0**	**ND**
Morganella morganii – Kresken	0	0	0	0	0	0	0	0	0	0	3	13	14	9	0	0	0	0	0	
Morganella morganii - Opferkuch	0	0	0	0	0	0	0	0	0	0	0	1	31	8	0	0	0	0	0	
Morganella morganii	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**14**	**45**	**17**	**0**	**0**	**0**	**0**	**0**	**ND**
Proteus mirabilis - Kresken	0	0	0	0	0	0	0	0	0	0	0	34	67	0	0	0	0	0	0	
Proteus mirabilis - Marre	0	0	0	0	0	0	0	0	0	0	0	1	3	2	0	0	0	0	0	
Proteus mirabilis - Opferkuch	0	0	0	0	0	0	0	0	0	0	0	37	90	31	1	0	0	0	0	
Proteus mirabilis - Pfister	0	0	0	0	0	0	0	0	0	1	12	26	57	3	0	1	0	0	0	
Proteus mirabilis - Jacobs	0	0	0	0	0	0	0	0	0	1	0	1	4	6						
Proteus mirabilis	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2**	**12**	**99**	**221**	**42**	**1**	**1**	**0**	**0**	**0**	**16**

3. MIC distributions[1] and epidemiological cut-off (ECOFF) values (mg/L)

Organism	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Proteus vulgaris – Kresken	0	0	0	0	0	0	0	0	0	0	0	20	30	9	0	0	0	0	0	
Proteus vulgaris - Opferkuch	0	0	0	0	0	0	0	0	0	0	0	11	30	9	0	0	0	0	0	
Proteus vulgaris - Pfister	0	0	0	0	0	0	0	0	0	0	2	5	1	0	0	0	0	0	0	
Proteus vulgaris	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2**	**36**	**61**	**18**	**0**	**0**	**0**	**0**	**0**	**ND**
Proteus spp. indole-positive - Jacobs	0	0	0	0	0	0	0	0	0	0	2	1	13	11	1	1	0	0	0	
***Proteus* spp. indole-positive - Jacobs**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2**	**1**	**13**	**11**	**1**	**1**	**0**	**0**	**0**	**ND**
Serratia spp - Opferkuch	0	0	0	0	0	0	0	0	0	0	0	0	3	55	11	0	0	0	0	
***Serratia* spp.**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**55**	**11**	**0**	**0**	**0**	**0**	**ND**
Enterobacter cloacae - Pfister	0	0	0	0	0	0	0	0	0	1	1	4	27	4	0	0	0	0	0	
Enterobacter cloacae	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**4**	**27**	**4**	**0**	**0**	**0**	**0**	**0**	**ND**
Enterobacter spp - Marre	0	0	0	0	0	0	0	0	0	0	0	1	4	0	0	0	0	0	0	
Enterobacter spp - Opferkuch	0	0	0	0	0	0	0	0	0	0	0	7	18	49	6	1	0	0	0	
Enterobacter spp - Pfister	0	0	0	0	0	0	0	0	0	0	2	3	2	0	0	0	0	0	0	
Enterobacter spp - Jacobs	0	0	0	0	0	0	0	0	0	0	0	1	1	0	2	0	0	0	0	
***Enterobacter* spp.**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2**	**12**	**25**	**49**	**8**	**1**	**0**	**0**	**0**	**ND**
Other Enterobacteriaceae - Pfister	0	0	0	0	0	0	0	0	0	0	3	9	6	14	1	0	0	0	0	
Other Enterobacteriaceae	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**9**	**6**	**14**	**1**	**0**	**0**	**0**	**0**	**ND**
Acinetobacter spp - Opferkuch	0	0	0	0	0	0	0	0	1	0	21	29	6	0	1	1	0	0	0	
Acinetobacter spp - Pfister	0	0	0	0	0	0	0	0	2	6	7	0	0	0	0	0	0	0	0	
***Acinetobacter* spp.**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**6**	**28**	**29**	**6**	**0**	**1**	**1**	**0**	**0**	**0**	**ND**
Pseudomonas aeruginosa - Marre	0	0	0	0	0	0	0	0	0	0	0	0	0	2	5	2	1	0	0	
Pseudomonas aeruginosa - Pfister	0	0	0	0	0	0	0	0	0	0	0	1	1	7	11	13	4	0	0	
Pseudomonas aeruginosa - Jacobs	0	0	0	0	0	0	0	0	0	0	0	0	0	17	2	12	0	0	0	
Pseudomonas aeruginosa	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**26**	**18**	**27**	**5**	**0**	**0**	**ND**
Pseudomonas spp - Opferkuch	0	0	0	0	0	0	0	0	0	0	0	0	0	0	27	57	23	3	0	
***Pseudomonas* spp.**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**27**	**57**	**23**	**3**	**0**	**ND**
Staphylococcus aureus - Marre	0	0	0	0	0	0	0	0	0	0	0	6	1	0	0	0	0	0	0	

3. MIC distributions[1] and epidemiological cut-off (ECOFF) values (mg/L)

Staphylococcus aureus - Opferkuch	0	0	0	0	0	0	0	0	0	0	1	18	102	0	0	0	0	0	0	
Staphylococcus aureus - Pfister	0	0	0	0	0	0	0	0	0	16	38	3	3	1	0	0	0	0	0	
Organism	**0.002**	**0.004**	**0.008**	**0.016**	**0.032**	**0.064**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**	**256**	**512**	**ECOFF**
Staphylococcus aureus - Jacobs	0	0	0	0	0	0	0	0	0	1	0	2	24	0	0	0	0	0	0	
Staphylococcus aureus	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**17**	**39**	**29**	**130**	**1**	**0**	**0**	**0**	**0**	**0**	**ND**
Staphylococcus epidermidis - Opferkuch	0	0	0	0	0	0	0	0	0	0	1	36	106	15	0	0	0	0	0	
Staphylococcus epidermidis - Jacobs	0	0	0	0	0	0	0	0	0	0	0	0	7	6	0	0	0	0	0	
Staphylococcus epidermidis	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**36**	**113**	**21**	**0**	**0**	**0**	**0**	**0**	**ND**
CNS - Marre	0	0	0	0	0	0	0	0	0	0	0	1	3	1	0	0	0	0	0	
CNS - Pfister	0	0	0	0	0	0	0	0	1	10	35	8	5	1	0	0	0	0	0	
CNS	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**10**	**35**	**9**	**8**	**2**	**0**	**0**	**0**	**0**	**0**	**ND**
Staphylococcus saprophyticus - Kresken	0	0	0	0	0	0	0	0	0	0	0	0	30	0	0	0	0	0	0	
Staphylococcus saprophyticus - Marre	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	
Staphylococcus saprophyticus	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**30**	**0**	**1**	**0**	**0**	**0**	**0**	**ND**
Enterococcus faecalis - Opferkuch	0	0	0	0	0	0	0	0	0	0	0	0	18	148	44	0	0	0	0	
Enterococcus faecalis - Pfister	0	0	0	0	0	0	0	0	0	0	3	20	106	8	1	0	0	0	0	
Enterococcus faecalis - Jacobs	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1	6	0	0	0	
Enterococcus faecalis	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**20**	**124**	**158**	**46**	**6**	**0**	**0**	**0**	**ND**
Enterococcus faecium - Pfister	0	0	0	0	0	0	0	0	0	0	1	8	42	0	0	0	0	0	0	
Enterococcus faecium	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**8**	**42**	**0**	**0**	**0**	**0**	**0**	**0**	**ND**
Enterococcus spp - Marre	0	0	0	0	0	0	0	0	0	0	0	0	6	7	7	0	0	0	0	
***Enterococcus* spp.**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**6**	**7**	**7**	**0**	**0**	**0**	**0**	**ND**
Streptococcus spp - Pfister	0	0	0	0	0	0	0	1	2	2	7	2	0	0	0	0	0	0	0	
***Streptococcus* spp.**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**2**	**2**	**7**	**2**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**ND**
Haemolytic streptococci - Opferkuch	0	0	0	0	0	0	0	0	3	8	6	20	15	0	0	0	0	0	0	
Haemolytic streptococci	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**8**	**6**	**20**	**15**	**0**	**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-offs (ECOFF) and give an indication of the MICs for organisms with acquired or mutational resistance mechanisms. They should not be used to infer resistance rates. Some combined distributions may include distributions truncated at concentrations below 512 mg/L. When there is insufficient evidence no epidemiological cut-off has been determined (ND).

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

	BSAC	CA-SFM	CRG	NAK Germany	NWGA	SRGA	CLSI
General breakpoints	No previous breakpoints						
Species-related breakpoints	No previous breakpoints						
Enterobacteriaceae		≤1 / >32		≤16 / >16[1]			
Pseudomonas spp.							
Stenotrophomonas maltophilia							
Acinetobacter spp.							
Staphylococcus spp.							
Enterococcus spp.							
Streptococcus groups A,B,C,G							
Streptococcus pneumoniae							
Viridans group streptococci							
Haemophilus influenzae							
Moraxella catarrhalis							
Neisseria gonorrhoeae							
Neisseria meningitidis							
Anaerobes, Gram-positive							
Clostridium difficile							
Anaerobes, Gram-negative							
Helicobacter pylori							
Listeria monocytogenes							
Pasteurella multocida							
Campylobacter spp.							
Corynebacterium spp.							

[1] *Escherichia coli* only

5. Pharmacokinetics

Dosage (mg)	200 mg single dose orally[1]	200 mg x 3 orally[1]	250 mg x 3 orally[2]
Cmax (mg/L)	5.59 ± 3.15 after 1.75 ± 1.04 h	8.08 ± 4.42 after 1 h	6,09 – 7,78
Cmin (mg/L)			
Total body clearance (L/h)			
T ½ (h), mean (range)	2.63 ± 2.66		ca. 2
AUC24h (mg.h/L)			
$AUC_{0\text{-}12h,ss}$ (mg.h/L)			
AUC_{∞} (mg.h/L)	32.34 ± 11.34		15.11 – 17.68
Fraction unbound (%)			90
Volume of distribution (L/kg)			
Comments	• Cells are left empty when data are not available. • Two values are given where references differ. • Oral absorption is almost 100%. • Concentrations (mg/L) in urine after application of 2 x 200 mg (bioassay) were as follows[1]: 0-1 h: 46 ± 5; 1-2 h: 216 ± 137; 2-3 h: 187 ± 134; 3-4 h: 220 ± 131; 4-6 h: 105 ± 83; 6-8 h: 84 ± 71; 8-10: 59.5 ± 34		
References	• [1]Bergogne-Berezin E, Berthelot G, Muller-Serieys C, *Pathol Biol (Paris)* 1987; 35: 873-8 (In French) • [2]Nitroxolin forte Fachinformation (SPC), March 2012 (In German)		

6. Pharmacodynamics

f%T>MIC for bacteriostasis				
f%T>MIC for 1 log reduction				
f%T>MIC for 2 log reduction				
f%T>MIC from clinical data				
Comments	• Cells are left empty when data are not available. • Pharmacodynamics parameters for nitroxoline have not been determined. • Nitroxoline usually exerts bacteriostatic activity. Urinary inhibitory titers of nitroxoline for *E. coli, K. pneumoniae* and *S. saprophyticus* were higher at pH 5.5 than at pH 8.0[1]			
References	• [1]Wagenlehner FM, Münch F, Pilatz A, Bärmann B, Weidner W, Wagenlehner CM, Straubinger M, Blenk H, Pfister W, Kresken M, Naber KG, *Antimicrob. Agents Chemother* 2014; 58: 713-21			

7. Monte Carlo simulations and Pk/Pd breakpoints

No data **available**

8. Clinical data

Searching the literature a total of 26 uncontrolled studies including 1206 patients (947 adults and 259 children), two controlled studies including 148 patients (100 adult and 48 children) and one postmarketing observational study comprising 9,800 patients with uncomplicated and complicated UTI were identified. 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 3 and 10 days depending on the indication. Study details are presented in Tables 1-3.

A total of 466 female patients with acute uncomplicated or recurrent cystitis were included in four unpublished prospective open randomized studies. Of these, 234 received 250 mg nitroxoline orally t.i.d. and 232 either 960 mg cotrimoxazole t.i.d. (n=178) or 400 mg norfloxacin b.i.d. (n=54) for 5-10 days. Study details are presented in Table 4. In each the modified microbiological ITT set (at least one outcome result available), in the PP set (test of cure outcome available) and in the modified PP set (missing test of cure rated failure) more than 90% of the patients showed eradication of bacteriuria with nitroxoline, meeting the statistical requirement of a 10%-non-inferiority margin in eradication rates compared to 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. [1]

Data relating MIC to outcome are not available.

[1]Naber KG, Niggemann H, Stein G, Stein G. BMC Infect Dis (submitted for publication)

Table 1. Fifteen uncontrolled clinical studies with nitroxoline in 947 adult patients of both genders

First author	Year	Pat (n)	Indication	Dosage	Duration	Success rate	Adverse events
Kuss	1962	72	T:acute compl. and uncompl. UTI	400 mg/d	20-45 days	78%	1.3% gastrointestinal
Moreau	1962	20	T:acute compl. UTI	400-500 mg/d	8-10 (-45) days	90%	5% gastrointestinal
v. Rütte	1969	200	P:chron. rec. UTI (rUTI)	300-500 mg/d shortly 800 mg/d	2-3 months 1 day	80%	0%
Uhlir	1972	20	T:acute UTI (7), chron. PN (13)	300 mg/d	14 days	100%	0%
Allal	1973	264	T:UTI during pregnancy	300 mg/d	6 days	> 75%	no data
Bittard	1974	50	P:post-op. catheter	7.5-10 mg/kg/d	6 weeks	92%	few gastrointestinal
Schlesinger	1975	65	T:chron. PN (62), chron. prostatitis (3)	300-500 mg/d	10 days	80% clinical	0%
Aubert	1976	28	T:post-op. catheter, after endoscopy	200-300 mg/d	10-15 days	72%	0%
Dufour	1979	15	T:acute prostatitis	900-1600 mg/d	3-5 days	81%	no data
Lenzner	1983	60	T:fungal UTI	750 mg/d	10-20 days	80%	3.3% itching; few cases with nausea and vomiting
Schuelke	1984	50	T:postop., acute UTI after removal of urethral catheter for 3-10 days	750 mg/d	3 days	78%	0%
Sachse	1984	44	P:chron. rec.UTI (rUTI)	750 mg/d	4 months	77% free of rUTI; rUTI rate decreased from 0.33 to 0.11/month	9% gastrointestinal 2.2% exanthema
Demontrond	1986	15	T:candiduria in hospitalised patients	600 mg/d	10-30 days	87%	0%
Frobert	1987	36	T:acute, uncompl. UTI in hospitalised patients	600 mg/d	10 days	93% bacteriological 87% clinical	5.5% gastrointestinal 2.7 % nausea 2.7% dizziness
Cancet	1987	8	T:urogenital fungal infections	600 mg/d	15 days	100%	no data

T-therapy; P-prophylaxis, UTI-urinary tract infection; PN-pyelonephritis

Table 2. Eleven uncontrolled clinical studies on treatment and prophylaxis of UTI with nitroxoline in 259 children

First author	Year	Pat (n)	Indication	Dosage	Duration	Success rate	Adverse events
Lecornu	1974	25 children 0-13 years	T:compl. and uncompl. UTI	50-400 mg/d as suspension	4-12 days	72%	8% nausea
Roussel	1974	24 children 7 days-6 months	T:compl. and uncompl. UTI	10 mg/kg/d as suspension	10 days- 6 months	79%	0%
Raynaud	1974	19 children 0-10 years	T:compl. and uncompl. UTI	10 mg/kg/d as suspension	20 days	69%	10% nausea
Luckel	1975	25 children 0-8.5 years	P:compl. and uncompl. UTI	10-20 mg/kg/d as suspension	17-55 days	83%	0%
Viville	1975	22 children 2 months-17years	P:compl. UTI	10 -30 mg/kg/d as suspension	3-6 months	86%	0%
Chable	1975	28 children 2 month-14.5 years	T:compl. and uncompl. UTI	10-20 mg/kg/d as suspension	10 days	81%	0%
Battin	1975	30 children 2 month-10 years	P:compl. and uncompl. UTI	10 mg/kg/d as suspension	6 weeks	90%	0%
Sorez	1975	30 children 10 days-8 years	T:compl. and uncompl. UTI	10-25 mg/kg/d as suspension	10 – 17 days	73.7% uncompl. UTI 40% compl. UTI	0%
Neimann	1975	21 children 26 days-8 years	T/P:compl. And uncompl. UTI	25-400 mg/d as suspension	4 days-4 months	90%	10% nausea
Machecourt	1976	23 children 21 days-14 years	T:compl. and uncompl. UTI	10-20 mg/kg/d as suspension	10 days	91 %	0%
Lambert-Zechovsky	1987	12 children aver. 4 years	T:uncompl. UTI	20 mg/kg/d as suspension	10 days	66% (91% incl. noncompliance)	-

T-therapy; P-prophylaxis, UTI-urinary tract infection;

Table 3. Two controlled open clinical studies in a total of 99 patients with nitroxoline (NTX) versus norfloxacin (NFX) or cotrimoxazole (CTX); SMX-sulphamethoxazole; TMP-trimethoprim

First author	Year	Pat.(n)	Indication	Antibiotic and Dosage	Duration	Success rate	Adverse events
Schülke	1986	51 NTX 49 NFX	T:postop., uncompl. UTI	750 mg NTX/d vs. 800 mg NFX/d	3 days	60.8% NTX 59.2%NFX	0%
Dodat	1988	48 children 0-8 years	P:postop.UTI (ureteral reflux)	10 mg NTX/kg/d vs. 15mg SMX/ 3 mg TMP /kg/d	30-60 days	95% NTX 95% CTX	6% NTX 5% CTX

T-therapy; P-prophylaxis, UTI-urinary tract infection;

Table 4. Study design of the four meta-analysed prospective, open, randomised clinical studies in female patients with acute uncomplicated and recurrent cystitis treated with nitroxoline (NTX) versus a control antibiotic, cotrimoxazole (CTX) or norfloxacin (NFX)

Study	**Nitroxoline**	**Control**	**Indication**	**Patients (n)**	**Duration**	**Test of cure**
NWNF 10	Nitroxoline (NTX) 3x250 mg	Cotrimoxazole (CTX) 2x960 mg	akute uncompl. cystitis	130 total 67NTX, 63 CTX	5 days	day 12-14
NWNF 11	Nitroxoline (NTX) 3x250 mg	Cotrimoxazole (CTX) 2x960 mg	akute uncompl. cystitis	115 total 56 NTX 59 CTX	5 days	day 12-14
NWNF 13	Nitroxoline (NTX) 3x250 mg	Norfloxacin (NFX) 2x400 mg	akute uncompl. cystitis	105 total 51 NTX 54 NFX	5 days	day 12-14
NWNF 15	Nitroxoline (NTX) 3x250 mg	Cotrimoxazole (CTX) 2x960 mg	acute episode of uncompl. recurrent cystitis	116 total 60 NTX 56 CTX	10 days	day 21-23

9. Clinical breakpoints

PK/PD breakpoints	Not applicable			
Species-related breakpoints	**Organism group**	**MIC breakpoints (mg/L)**		**Notes**
		S ≤	R >	
	E. coli	16	16	The breakpoints is essentially epidemiological cut-off values for *E. coli*
	Enterobacteriaceae	IE	IE	Since there are no data concerning outcome with species other than *E.coli*, no breakpoint are set
	Pseudomonas spp.	-	-	These organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints
	Stenotrophomonas maltophilia	-	-	These organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints
	Acinetobacter spp.	-	-	These organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints
	Staphylococcus saprophyticus	IE	IE	The breakpoints are essentially epidemiological cut-off values since there is little information on the clinical outcome of uncomplicated cystitis caused by staphylococci other than *S. saprophyticus*.
	Enterococcus spp.	IE	IE	There is insufficient evidence that the species in question is a good target for therapy with nitroxoline.
	Streptococcus groups A,B,C,G	-	-	These organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints
	Streptococcus pneumoniae	-	-	These organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints
	Viridans group streptococci	-	-	These organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints
	Haemophilus influenzae	-	-	These organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints

	Moraxella catarrhalis	-	-	These organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints
	Neisseria gonorrhoeae	-	-	These organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints
	Neisseria meningitidis	-	-	These organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints
	Anaerobes, Gram-positive	-	-	These organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints
	Clostridium difficile	-	-	These organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints
	Anaerobes, Gram-negative	-	-	These organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints
	Helicobacter pylori	-	-	These organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints
	Listeria monocytogenes	-	-	These organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints
	Pasteurella multocida	-	-	These organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints
	Campylobacter spp.	-	-	These organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints
	Corynebacterium spp.	-	-	These organisms were considered poor targets for nitroxoline therapy or inappropriate targets for the specified infections and for that reason did not receive breakpoints
Clinical qualifications	Breakpoints apply only to uncomplicated UTI caused by E. coli			
Dosage	Breakpoints apply to nitroxoline standard oral dose 250 mg every 8 h			
Additional comment	No comments			

10. Exceptions noted for individual national committees