

EMWA Professional Development Programme

Writing an Investigator's Brochure

Workshop status: Foundation

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<h3>Pre-workshop assignment</h3>

Objective

To familiarise participants with data to be used during the practical part of the workshop.

Content

Participants should review the tables supplied to become acquainted with the drug they will be discussing during the workshop.

Assessment criteria

Participants will be expected to actively discuss and make recommendations based on the data provided.

Instructions

As preparation for this workshop, please review the following data tables and familiarize yourself with the findings presented. During the workshop exercise, you will be working in teams to decide upon salient findings to present in an Investigator's Brochure.

You do not need to submit anything before the workshop. Just look the tables over to get a general idea about what kinds of data were collected, what the messages of the data are, and how you might present them in an Investigator's Brochure. A good preparation for this would be to attempt to formulate 1 or 2 key messages from each table.

If you are unfamiliar with nonclinical or clinical research, or are unfamiliar with terminology used in the field of anti-infectives, then please use the internet to research any information you are unfamiliar with. This will reduce the amount of catching up you would otherwise have to do during the workshop exercise.

Resources and materials

Tables from an Investigator's Brochure.

Time required

Approximately 2 hours, plus time using the internet to research any information you may be unfamiliar with.

1. NONCLINICAL STUDIES

Table 1-1: Acute toxicity studies

Reference	Species	Route	LD50 (mg/kg)	
			Males	Females
[19]	Mouse	oral	1881	1803
[19]	Rat	oral	1478	1507
[20]	Rat	oral	1754	not available
[21]	Monkey	oral	not available	> 250
[22]	Mouse	intravenous	268	323
[23]	Mouse	intravenous	244	not available
[22]	Rat	intravenous	423	395
[24]	Dog	intravenous	not available	200
[25]	Monkey	intravenous	not available	> 200

LD50 = median lethal dose.

Table 1-2: Mutagenicity studies

Reference	Type of study	Result
[38]	Ames test	negative
[39]	Ames test	negative
[40]	CHO/HGRPT forward mutation assay	negative
[41]	Sister chromatid exchange, in vitro	positive
[42]	Sister chromatid exchange, in vivo	negative
[17]	Unscheduled DNA synthesis, in vivo	negative
[43]	Chromosomal aberration test in vitro	positive
[44]	Chromosomal aberration test in vitro	positive
[45]	Chromosomal aberration test in vitro	positive
[38]	Micronucleus in mice, intraperitoneal	negative
[46]	Micronucleus in mice, intravenous	negative
[47]	Dominant lethal test	negative

CHO/HGRPT = Chinese hamster ovary/hypoxanthine-guanine phosphoribosyl-transferase.

Table 1-3: Special toxicity studies

Reference	Test type	Animal model	Results
[55]	Nephrotoxicity	Rabbits	Negative
[56]	Antigenicity	Guinea pigs	Negative
[57]	Antigenicity	Mice	Negative/low potential
[58]	Antigenicity	Rabbits	Negative
[59]	Arthropathy	Juvenile rats	NEL = 100 mg/kg/day/7 days
[60]	Arthropathy	Juvenile dogs	NEL = 10 mg/kg/day/7 days
[61]	Arthropathy	Juvenile dogs	NEL = 5 mg/kg/day/7 days
[62]	Arthropathy	Young adult dogs	NEL = 10 mg/kg/day/7 days
[63, 64]	Phototoxicity	Mice	ED50 = 526.6 mg/kg
[65]	Phototoxicity	Mice	NEL = 200 mg/kg
[66]	Phototoxicity	Mice	NEL > 100 mg/kg
[67]	CNS toxicity	Mice	Interaction with fenbufen: NEL > 800 mg/kg
[68]	CNS toxicity	Mice	Interaction with biphenylacetic acid: NEL > 100 mg/kg
[69]	Ocular and ototoxicity	Rats	NEL > 100 mg/kg/day/2 weeks
[70]	Haematological	Rats and mice	Minimal decrease in neutrophils in rats at 2 mg/kg/day/14 days
[71]	Urinalytic	Rats	Urinary crystal formation not associated with nephrotoxicity
[72]	Drug interaction	Rats	Renal injuries with interaction with anticancer drugs
[73]	Local irritation intramuscular injection	Rabbits	0.1 % = Grade 1 0.2 % = Grade 2

NEL = No effect level; ED50 = median effective dose.

2. MICROBIOLOGY

Table 2-1: Antibacterial activity of supermycin against gram-positive aerobic bacteria

Organism	MIC90 [$\mu\text{g/ml}$] (number of strains)					
	Ref. [74]	Ref. [1]	Ref. [75]	Ref. [76]	Ref. [77]	Ref. [85]
<i>S aureus</i>	–	–	0.39 (100)	–	0.39 (42)	–
<i>S aureus</i> (MS)	0.50 (25)	0.5 (63)	0.39 (124)	0.78 (43)	–	–
<i>S aureus</i> (MR)	0.50 (25)	0.5 (46)	3.13 (80)d	0.39 (31)	–	–
<i>S epidermidis</i>	–	–	–	0.78 (33)	0.19 (40)	–
<i>S epidermidis</i> (MS)	1.00 (12)	–	–	–	–	–
<i>S epidermidis</i> (MR)	0.25 (14)	–	–	–	–	–
<i>S saprophyticus</i>	–	–	–	–	0.78 (13)	–
Staphylococci (MR)	–	–	–	–	0.78 (42)	–
Coag. neg. staphylococci	–	8.0 (18)	0.39 (98)	–	–	0.5 (23)
<i>S pneumoniae</i>	1.00 (21)	2.0 (19)	1.56 (50)	1.56 (50)	3.13 (54)	–
<i>S pyogenes</i>	0.50 (20)	–	1.56 (100)	0.78 (35)	1.56 (41)	–
<i>S agalactiae</i>	2.00 (20)	–	–	–	–	–
<i>E faecalis</i>	1.00 (31)	2.0 (22)	1.56 (96)	1.56 (30)	3.13 (50)	–
<i>E faecium</i>	–	–	3.13 (26)	3.13 (30)	–	–
<i>E avium</i>	–	–	–	1.56 (14)	–	–
<i>L monocytogenes</i>	1.00 (14)	–	–	–	–	–

MIC90 = minimum inhibitory concentration for 90% inhibition.

MR = methicillin-resistant; MS = methicillin-susceptible.

Table 2-2: Antibacterial activity of supermycin against gram-negative aerobic bacteria

Organism	MIC90 [µg/ml] (number of strains)				
	Ref. [74]	Ref. [1]	Ref. [75]	Ref. [76]	Ref. [77]
E coli	0.06 (30)	0.06 (90)	0.10 (146)	0.10 (42)	0.05 (50)
K pneumonia	0.25 (20)	0.25 (44)	0.10 (100)	0.10 (43)	3.13 (60)
K oxytoca	–	–	0.10 (99)	–	–
E cloacae	0.25 (15)	0.12 (21)	0.39 (100)	0.20 (29)	0.78 (33)
E aerogenes	0.25 (15)	–	–	0.10 (34)	–
Citrobacter spp	–	0.12 (13)	–	–	–
C freundii	1.00 (20)	–	0.78 (93)	0.39 (34)	6.25 (20)
C diversus	0.03 (22)	–	–	–	–
Salmonella spp	–	0.12 (35)	0.10 (100)	–	–
P vulgaris	0.5 (20)	–	0.10 (114)	0.20 (41)	0.19 (49)
P mirabilis	0.25 (20)	0.25 (12)	0.19 (100)	0.20 (29)	
P rettgeri	1.00 (10)	0.5 (15)	3.13 (50)	1.56 (17)	3.13 (18)
P stuartii	1.00 (20)	0.25 (17)	0.39 (75)	–	–
S marcescens	0.25 (28)	0.5 (24)	12.5 (119)	3.13 (43)	12.5 (50)
M morganii	0.12 (20)	–	0.10 (37)	0.39 (28)	6.25 (19)
P aeruginosa	4.00 (30)	8.0 (74)	3.13 (127)	1.56 (43)	50 (50)
P cepacia	4.00 (18)	2.0 (17)	12. (30)	–	–
Acinetobaccter spp	0.50 (18)	16.0 (24)	–	–	–
A calcoaceticus	–	–	0.39 (35)	0.39 (42)	–
M catarrhalis	–	0.06 (29)	0.10 (38)	0.10 (19)	–
N gonorrhoeae	–	0.015 (19)	0.025 (24)	–	0.10 (25)
H influenzae	0.015 (14)	0.015 (34)	0.025 (116)	0.05 (22)	0.025 (22)
A faecalis	–	–	–	–	25 (25)
Legionella spp	–	–	0.05 (15)	–	–
Shigella spp	–	–	0.05 (102)	–	–
X maltophilia	–	2.0 (24)	3.13 (50)	–	25 (24)
Y enterocolitica	–	0.12 (12)	–	–	–

MIC90 = minimum inhibitory concentration for 90% inhibition.

Table 2-3: Antibacterial activity of supermycin against anaerobic bacteria

Organism	MIC90 [µg/ml] (number of strains)				
	Ref. [74]	Ref. [1]	Ref. [75]	Ref. [76]	Ref. [77]
Peptococcus spp	–	–	–	–	3.13 (25)
Peptostreptococcus spp	–	8.0 (11)	–	–	–
C perfringens	0.25 (15)	–	0.78 (16)	–	–
C difficile	–	–	6.25 (21)	–	–
B fragilis	4.00 (18)	2.0 (39)	6.25 (27)	–	6.25 (41)

MIC90 = minimum inhibitory concentration for 90% inhibition.

3. PHARMACOKINETICS

Table 3-1: Mean pharmacokinetic characteristics following single oral daily doses of supermycin for 7 days

	C _{max} (mg/l)		t _{max} (h)		AUC _{0-24h} (mg.h/l)	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
150 mg	2.21	2.31	0.75	0.86	10.07	10.85
300 mg	4.25	4.17	1.04	1.08	21.65	25.10
600 mg	9.10	9.84	1.00	0.91	45.66	52.58

Table 3-2: Mean pharmacokinetic characteristics following twice daily oral doses of supermycin for 7 days

	C _{min} (mg/l)	C _{max} (mg/l)	T _{max} (h)	AUC _{0-48h} (mg.h/l)	Mean plasma concentration at steady state (mg/l)	Elimination half-life (h)
150 mg	0.59	3.42	0.75	18.07	1.51	7.24
300 mg	1.43	6.05	0.88	40.33	3.36	6.98

Table 3-3: Mean pharmacokinetic characteristics of supermycin in healthy volunteers after single and multiple oral doses

Variable	500 mg once daily Single dose ^a	Steady state	500 mg bid Single dose ^b	Steady state
C _{max} (mg/l)	5.19 (1.21)	5.72 (1.4)	5.21 (0.91)	7.8 (1.07)
C _{trough} (mg/l)	-	0.51 (0.17)	-	2.97 (0.87)
AUC (mg.h/l) ^c	47.7 (7.6)	47.5 (6.66)	49.6 (8.8)	59.0 (11.8)
t _{max} (h)	1.3 (0.5)	1.1 (0.4)	1.2 (0.6)	1.3 (0.6)
Cl/F (l/h)	10.5 (1.75)	10.5 (1.47)	10.2 (1.93)	8.6 (1.82)
Vd/F (l)	96.7 (11.9)	102 (21.8)	93.6 (14.2)	102 (16.3)
t _{1/2} (h)	6.5 (0.7)	6.8 (1.3)	6.5 (1.0)	8.4 (1.3)
Ae (%)	64 (8)	67 (14)	63 (11)	-
Cl _r (l/h)	7.5 (1.8)	6.97 (1.85)	7.24 (2.11)	6.24 (1.53)

^a parallel-group study, n = 10 per group; ^b crossover study, n = 20; ^c in the single dose phase: AUC (∞), at steady state: AUC (0-τ) τ = dosing interval; Ae = urinary recovery; Vd/F = volume of distribution; values in parentheses are standard deviations; Cl/F = total clearance after oral administration; Cl_r = renal clearance.

Table 3-4: Comparison of oral pharmacokinetics of supermycin and othermycin

	Supermycin	Othermycin
C _{max} (mg/l)	2.04 (0.47)	2.23 (0.49)
T _{max} (h)	1.48 (0.71)	2.17 (1.07)
AUC (mg·h/l)	19.9 (3.47)	18.7 (4.09)
t _{1/2} (h)	5.97 (0.86)	4.13 (0.81)
Vd (l)	1.25 (0.13)	0.93 (0.14)
MRT (h)	9.27 (1.05)	7.24 (0.64)

MRT = mean residence time.

Table 3-5: Dosage of supermycin in undialysed subjects with renal impairment

Cl_{cr} (ml/min)	Daily dose in normal renal function		
	1 x 250 mg	1 x 500 mg	2 x 500 mg
	Dose adjustment to		
> 50	remains at 1 x 250 mg	remains at 1 x 500 mg	remains at 2 x 500 mg
20 - 49	1 x 125 mg	1 x 250 mg	1 x 500 mg
< 20	1 x 125 mg every 48 h	1 x 125 mg	1 x 250 mg

Cl_{cr} = creatinine clearance.

4. CLINICAL EFFICACY

Table 4-1: 95% confidence intervals for the differences of clinical success rates (supermycin - comparator) in subjects with bacteriologically proven infection

Indication	Dose regimen Supermycin	Dose regimen comparator	Rate supermycin (%)	Rate comparator (%)	Difference (%)	95 % CI
Sinusitis (Clinically proven infection)						
B2	1x500mg po	3x625 mg AMPC/CVA po	88.4	87.3	1.1	[-4.6; 6.8]
AECB						
B4	1x500mg po	3x250mg CCL po	96.1	91.0	5.1	[-1.9; 12.1]
B5	1x500mg po	2x250mg CXM po	94.8	93.2	1.6	[-4.0; 7.1]
Complicated AECB						
B6	1x250 mg po	2x250 mg CXM po	77.6	65.7	11.9	[0.8; 23.0]
	1x500 mg po	2x250 mg CXM po	78.8	65.7	13.1	[1.9; 24.5]
Pneumonia						
B7	1x500 mg po	3x625 mg AMPC/CVA po	95.0	94.3	0.7	[-9.5; 11.0]
	2x500 mg po	3x625 mg AMPC/CVA po	93.3	94.3	-1.0	[-11.6; 9.6]
B8	1x500mg iv/po	2x500 mg CXM po or CTRX iv / CXM po	97.7	88.2	9.5	[3.6; 15.4]
B10	2x500 mg iv/po	1x4g CTRX iv	87.4	86.3	1.1	[-7.0; 9.2]

continued

Table 4-1: 95% confidence intervals for the differences of clinical success rates (supermycin - comparator) in subjects with bacteriologically proven infection (continued)

Indication	Dose regimen supermycin	Dose regimen comparator	Rate supermycin (%)	Rate comparator (%)	Difference (%)	95 % CI
UTI						
B11	1x250 mg po	2x500 mg CPFX po	92.3	91.0	1.3	[-4.3; 7.1]
B12	1x250 mg po	1x400 mg LFLX po	93.5	90.1	3.4	[-1.6; 8.5]
Uncompl. SSTI						
B13	1x 500mg po	2x500mg CPFX po	98.1	92.8	5.3	[0.7; 10.0]
B14	1x500 mg po	2x500 mg CPFX po	96.0	92.8	3.2	[-3.2; 9.6]
B15	1x250 mg po	3x625 mg AMPC/CVA po	95.5	95.5	0.0	[-5.0; 5.0]
	1x500 mg po	3x625 mg AMPC/CVA po	97.1	95.5	1.6	[-2.9; 6.1]
Complicated SSTI						
B16	2x500 mg po	TIPC-CVA po/ AMPC.CVA iv	89.3	83.7	5.6	[-2.3; 13.4]
B17	2x500 mg iv/po	IPM iv/ CPFX po	81.0	86.6	-5.6	[-16.4; 5.1]
Intra-abd. infection						
B18	1x500 mg iv/po	2x200/500 mg CPFX iv/po	95.3	90.0	5.3	[-5.1; 15.8]

Table 4-2: Clinical success and eradication rate by organism - all studies

Organism	No. of pathogens eradicated/total isolated (%)		No. of subjects with clinical success/total (%)	
	Supermycin	Comparator	Supermycin	Comparator
Gram positive	1170/1287 (91)	799/909 (88)	819/894 (92)	536/598 (90)
<i>S. aureus</i>	497/534 (93)	358/408 (88)	322/345 (93)	223/241 (93)
<i>S. pneumoniae</i>	233/262 (89)	116/128 (91)	210/229 (92)	101/118 (86)
<i>S. pyogenes</i>	96/101 (95)	79/88 (90)	51/56 (91)	34/37 (92)
<i>E. faecalis</i>	53/62 (85)	44/60 (73)	22/25 (88)	22/27 (81)
Gram negative	1526/1637 (93)	1060/1205 (88)	1087/1202 (90)	765/876 (87)
<i>H. influenzae</i>	352/371 (95)	120/154 (78)	260/292 (89)	96/121 (79)
<i>H. parainfluenzae</i>	76/80 (95)	57/65 (88)	47/49 (96)	36/42 (86)
<i>M. catarrhalis</i>	134/142 (94)	71/79 (90)	84/99 (85)	48/52 (92)
<i>K.pneumoniae</i>	126/130 (97)	99/111 (89)	76/81 (94)	64/76 (84)
<i>P. aeruginosa</i>	105/140 (75)	71/96 (74)	67/78 (86)	37/47 (79)
<i>E. coli</i>	308/318 (97)	312/321 (97)	250/263 (95)	247/260 (95)
<i>E. cloacae</i>	55/56 (98)	45/53 (85)	22/25 (88)	20/21 (95)
<i>A. calcoaceticus</i>	16/16 (100)	22/29 (76)	2/2 (100)	8/13 (62)
<i>S. marcescens</i>	23/25 (92)	18/20 (90)	12/12 (100)	10/12 (83)
<i>C. freundii</i>	15/17 (88)	14/17 (82)	6/8 (75)	5/5 (100)
<i>M. morganii</i>	15/16 (94)	7/10 (70)	6/7 (86)	4/4 (100)
<i>P. mirabilis</i>	67/70 (96)	52/55 (95)	34/36 (94)	28/32 (88)

Table 4-3: In vitro susceptibility of isolated responsible pathogens - all studies

Pathogen	Number of subjects with pathogen							
	Supermycin				Comparator			
	N	Susceptible	Resistant	Not tested	N	Susceptible	Resistant	Not tested
Gram-negative enterobacteriae	1785	1720	16	49	1785	1556	81	148
<i>Citrobacter</i> spp.	72	68	1	3	72	56	3	13
<i>Edwardsiella</i> spp.	1	1	0	0	1	1	0	0
<i>Escherichia</i> spp.	794	761	6	27	794	727	15	52
<i>Ewingella</i> spp.	1	1	0	0	1	0	0	1
<i>Enterobacter</i> spp.	226	216	2	8	226	172	31	23
<i>Hafnia</i> spp.	3	3	0	0	3	2	0	1
<i>Klebsiella</i> spp.	386	380	3	3	386	344	12	30
<i>Kluyvera</i> spp.	1	1	0	0	1	1	0	0
<i>Morganella</i> spp.	38	38	0	0	38	32	1	5
<i>Proteus</i> spp.	193	185	2	6	193	173	1	19
<i>Providencia</i> spp.	7	6	0	1	7	6	0	1
<i>Salmonella</i> spp.	1	1	0	0	3	2	0	1
<i>Serratia</i> spp.	60	58	2	0	60	40	18	2
Other Gram-negative	1810	1678	53	79	1810	1228	208	374
Other	4	3	0	1	6	3	0	3
<i>Acinetobacter</i> spp.	73	67	6	0	73	58	12	3
<i>Aeromonas</i> spp.	8	7	0	1	8	7	0	1
<i>Agrobacterium</i> spp.	1	1	0	0	1	1	0	0
<i>Alcaligenes</i> spp.	17	14	1	2	17	9	4	4
<i>Bacteroides</i> spp.	55	29	7	19	55	24	11	20

continued

Table 4-3: In vitro susceptibility of isolated responsible pathogens - all studies (continued)

Pathogen	Number of subjects with pathogen							
	Supermycin				Comparator			
	N	Susceptible	Resistant	Not tested	N	Susceptible	Resistant	Not tested
Other Gram-negative (contd.)								
<i>Bordetella</i> spp.	1	1	0	0	1	0	1	0
<i>Cardiobacterium</i> spp.	1	1	0	0	1	1	0	0
<i>Comamonas</i> spp.	1	1	0	0	1	1	0	0
<i>Eikenella</i> spp.	10	10	0	0	10	9	0	1
<i>Flavimonas</i> spp.	1	1	0	0	1	1	0	0
<i>Flavobacterium</i> spp.	1	1	0	0	1	0	1	0
<i>Fusobacterium</i> spp.	10	6	1	3	10	7	0	3
<i>Haemophilus</i> spp.	937	910	0	27	937	667	28	242
<i>Kingella</i> spp.	1	1	0	0	1	0	0	1
<i>Moraxella</i> spp.	297	286	0	11	297	235	0	62
<i>Neisseria</i> spp.	30	26	0	4	30	21	0	9
<i>Oligella</i> spp.	1	1	0	0	1	1	0	0
<i>Pasteurella</i> spp.	9	9	0	0	9	7	2	0
<i>Pseudomonas</i> spp.	328	280	38	10	328	166	136	26
<i>Vibrio</i> spp.	2	2	0	0	2	2	0	0
<i>Weeksella</i> spp.	1	1	0	0	1	1	0	0
<i>Xanthomonas</i> spp.	21	20	0	1	21	7	13	1
Gram-positive	2902	2656	94	152	2902	2298	93	511
Other	2	0	0	2	-	-	-	-
<i>Actinomyces</i> spp.	1	0	1	0	1	1	0	0
<i>Bacillus</i> spp.	7	4	0	3	7	5	0	2
<i>Clostridium</i> spp.	4	2	0	2	4	2	0	2
<i>Micrococcus</i> spp.	1	1	0	0	1	1	0	0

continued

In vitro susceptibility of isolated responsible pathogens - all studies (continued)

Pathogen	Number of subjects with pathogen							
	Supermycin				Comparator			
	N	Susceptible	Resistant	Not tested	N	Susceptible	Resistant	Not tested
Gram-positive (contd.)								
<i>Mycobacterium</i> spp.	1	0	0	1	1	0	0	1
<i>Clostridium</i> spp.	4	2	0	2	4	2	0	2
<i>Corynebacterium</i> spp.	9	9	0	0	9	7	0	2
<i>Enterococcus</i> spp.	194	162	25	7	194	150	27	17
<i>Lactobacillus</i> spp.	2	2	0	0	2	2	0	0
<i>Leuconostoc</i> spp.	1	0	0	1	1	0	0	1
<i>Nocardia</i> spp.	1	1	0	0	1	0	1	0
<i>Peptococcus</i> spp.	1	0	0	1	1	0	0	1
<i>Peptostreptococcus</i> spp.	42	24	5	13	42	25	3	14
<i>Propionibacterium</i> spp.	5	3	0	2	5	3	0	2
<i>Staphylococcus</i> spp.	1379	1290	51	38	1379	1182	44	153
<i>Streptococcus</i> spp.	1248	1156	12	80	1248	918	18	312
Total / (%)	6497 (100)	6054 (93.2)	163 (2.5)	280 (4.3)	6497 (100)	5082 (78.2)	382 (5.9)	1033 (15.9)

5. SAFETY

Table 5-1: Adverse events by body system - all studies

Body System / Adverse Event	Number of subjects (%)							
	All Events				Possibly Related			
	Supermycin		Comparators		Supermycin		Comparators	
(US studies)								
No. of subjects per treatment	3292	(100.0)	2394	(100.0)	3292	(100.0)	2394	(100.0)
No. of subjects with adverse events	1289	(39.2)	933	(39.0)	208	(6.3)	189	(7.9)
(EU studies)								
No. of subjects per treatment	2096	(100.0)	1134	(100.0)	2096	(100.0)	1134	(100.0)
No. of subjects with adverse events	872	(41.6)	531	(46.8)	442	(21.1)	267	(23.5)
Total								
No. of subjects per treatment	5388	(100.0)	3528	(100.0)	5388	(100.0)	3528	(100.0)
No. of subjects with adverse events	2161	(40.1)	1464	(41.5)	650	(12.1)	456	(12.9)
Digestive system	828	(15.4)	654	(18.5)	273	(5.1)	235	(6.7)
Nervous system	581	(10.8)	370	(10.5)	94	(1.7)	44	(1.2)
Body as a whole	469	(8.7)	357	(10.1)	114	(2.1)	70	(2.0)
Respiratory system	348	(6.5)	242	(6.9)	29	(0.5)	20	(0.6)
Cardiovascular system	241	(4.5)	128	(3.6)	15	(0.3)	9	(0.3)
Skin and appendages	239	(4.4)	158	(4.5)	59	(1.1)	34	(1.0)
Metabolic and nutritional disorders	206	(3.8)	132	(3.7)	77	(1.4)	54	(1.5)
Hemic and lymphatic system	158	(2.9)	87	(2.5)	94	(1.7)	46	(1.3)
Urogenital system	118	(2.2)	121	(3.4)	23	(0.4)	32	(0.9)
Musculo-skeletal system	114	(2.1)	52	(1.5)	16	(0.3)	2	(0.1)
Special senses	99	(1.8)	44	(1.2)	18	(0.3)	8	(0.2)
Injection site reactions	68	(1.3)	34	(1.0)	27	(0.5)	17	(0.5)
Endocrine system	4	(0.1)	4	(0.1)	-		-	

Table 5-2: Adverse events in phase I, double-blind, crossover studies

Adverse event	Number of subjects							
	500 mg 1 x (oral)		488 mg 2 x (oral)		500 mg 1 x daily (i.v.)		500 mg 2 x daily (i.v.)	
	Supermycin	Placebo	Supermycin	Placebo	Supermycin	Placebo	Supermycin	Placebo
Total exposed	10	10	20	20	10	10	13	10
Musculoskeletal system								
Myalgia	0	1	-	-	-	-	-	-
CNS								
Dizziness	1	1	0	0	0	1	-	-
Headache	-	-	2	2	1	1	3	3
Lightheadedness	-	-	-	-	-	-	2	0
Twitching	-	-	-	-	-	-	1	0
Gastrointestinal system								
Abdominal pain	1	0	-	-	-	-	-	-
Body as a whole								
Pain	0	1	-	-	-	-	-	-
Back pain	-	-	0	1	-	-	-	-
Tiredness	-	-	1	0	-	-	-	-
Tightness of chest	-	-	-	-	-	-	1	0
Raised temperature	-	-	-	-	-	-	0	1
Bodily discomfort	-	-	-	-	-	-	0	1
Skin/appendages								
Skin disorder	-	-	0	1	-	-	1	0
Pruritus ani	-	-	-	-	-	-	0	1
Erythematous rash	-	-	-	-	-	-	1	0
Blisters	-	-	-	-	-	-	0	1

continued

Table 5-2: Adverse events in phase I, double-blind, crossover studies

Adverse event	Number of subjects							
	500 mg 1 x (oral)		488 mg 2 x (oral)		500 mg 1 x daily (i.v.)		500 mg 2 x daily (i.v.)	
	Supermycin	Placebo	Supermycin	Placebo	Supermycin	Placebo	Supermycin	Placebo
Total exposed	10	10	20	20	10	10	13	10
Gastrointestinal system								
Diarrhoea	-	-	1	0	-	-	-	-
Lower abdominal pain	-	-	0	1	-	-	-	-
Heartburn	-	-	1	0	-	-	1	0
Flatulence	-	-	0	1	-	-	-	-
Vomiting	-	-	-	-	0	1	-	-
Nausea	-	-	-	-	1	0	1	2
Constipation	-	-	-	-	-	-	0	1
Abdominal cramps	-	-	-	-	-	-	3	0
Tooth disorder	-	-	-	-	-	-	0	1
Psychiatric disorders								
Somnolence	-	-	-	-	0	1	-	-
Euphoria	-	-	-	-	-	-	1	0
Nightmares	-	-	-	-	-	-	0	1
Respiratory system								
Rhinitis	-	-	-	-	0	1	-	-
Coughing	-	-	-	-	-	-	0	1
Shortness of breath	-	-	-	-	-	-	1	0
Sore throat	-	-	-	-	-	-	0	1
Application site								
Injection site reaction	-	-	-	-	4	1	9	2
Pain at injection site	-	-	-	-	-	-	5	1
Autonomic nervous system								
Diarrhoea	-	-	-	-	-	-	1	1
Vomiting	-	-	-	-	-	-	0	1
Urinary system								
Micturition disorder	-	-	-	-	-	-	1	0
Frequency	-	-	-	-	-	-	0	1

Table 5-3: Distribution of subjects with adverse reactions in Japanese studies across dosage regimens

Daily dose	Number of subjects		
	Exposed	with ADR	%
100 mg	5	0	-
100 mg b.i.d.	380	12	3.2
100 mg t.i.d.	2750	72	2.6
100 mg q.i.d.	3	0	-
150 mg b.i.d.	1	0	-
200 mg	112	1	<1
200 mg b.i.d.	155	2	1.3
200 mg t.i.d.	215	12	5.6
Varied daily dose	28	2	7.1
TOTAL	3649	101	2.8

Table 5-4: Adverse reactions in subjects treated with supermycin in Japanese studies

Adverse Event	N^a	%^b
Gastrointestinal system	81	2.22
Diarrhoea	18	0.49
Abdominal discomfort	18	0.49
Nausea	10	0.27
Anorexia	7	0.19
Abdominal pain	7	0.19
Vomiting	5	0.14
Enlarged abdomen	4	0.11
Stomatitis	3	0.08
Heartburn	2	0.05
Dry mouth/hoarse	2	0.05
Inflamed tongue	2	0.05
Heavy feeling in stomach	1	0.03
Blood in stool	1	0.03
Constipation	1	0.03
Central nervous system	22	0.60
Insomnia	9	0.25
Headache	8	0.22
Dizziness	4	0.11
Finger tremor	1	0.03
Hypersensitivity reactions	17	0.47
Rash	8	0.22
Pruritus	4	0.11
Erythema	3	0.08
Eczema	2	0.05
Body as a whole	5	0.14
Fatigue	1	0.03
Chills	1	0.03
Fever	1	0.03
Feverish	1	0.03
Decreased body temperature	1	0.03
Other	10	0.27
Back pain	2	0.05
Hot flush	1	0.03
Ill feeling	1	0.03
Respiratory distress	1	0.03
Palpitations	1	0.03
Abnormal taste	1	0.03
Loss of taste	1	0.03
Numb tongue	1	0.03
Feeling faint/sweating	1	0.03
Total number of adverse reactions	135	-
Total number of subjects with adverse reactions out of 3649 subjects exposed	101	2.77

^a Number of mentions.^b % of total of 3,649 subjects.

Table 5-5: Serious adverse events reported in supermycin studies in Europe and the USA (code not broken)

Nature of AE	Causality	Remarks
Hospitalised/deep vein thrombosis	None	
Overdose: alcohol/meprobamate	None	
Vasovagal attack	None	
Life-threatening/pneumonia	None	reassessed nonserious
Arthropathy	Possible	reassessed nonserious
Hospitalisation/seizure	Possible	
Life-threatening/anaphylactoid	Probable	Subject recovered
Pain elbow	Probable	
Death/bronchitis	Unknown	
Hospitalisation/general weakness	Unknown	
Hospitalised/severe vomiting	Unlikely	
Hospitalisation/emphysema	Unlikely	
Life-threatening/hyperkalaemia	Unlikely	
Significant disability/cellulitis	Unlikely	
Hospitalised/depressive syndrome	Unlikely	
Death/cardiopulmonary arrest	Unlikely	
Hospitalised/chest infection worsening	Unlikely	
Death/myocardial infarction	Unlikely	
Cancer/chronic leukaemia	Unlikely	
Hospitalisation/bronchospasm	Unlikely	
Life-threatening/septicaemia	Unlikely	
Death/acute heart failure	Unlikely	
Hospitalisation abdominal pain (lower quadrant)	Unlikely	
Hospitalised/hysterectomy	Unlikely	
Hospitalisation/ecchymosis	Unlikely	
Hospitalised/worsening pneumonia	Unlikely	
Hospitalisation/osteomyelitis	Unlikely	
Death/road traffic accident	Unrelated	