

## 2. Uncomplicated Skin and Skin Structure Infection

### 2.1 Study 154-130

Title: A randomized, double-blind, multicenter trial comparing oral therapy with trovafloxacin (CP-99,219) (100 mg daily) and oral cefpodoxime proxetil (Vantin™)(400 mg bid) for the treatment of uncomplicated infections of the skin and skin structure.

#### Study Dates

1 June 1995 - 18 April 1996

#### 2.1.1 Study Design and Objectives

A randomized, double-blind double-dummy, comparative, multicenter trial. The duration of treatment was 7-10 days. The treatment groups were:

1. Trovafloxacin, 100 mg/day, orally, as a single dose (1 x 100 mg tablet)
2. Cefpodoxime proxetil (Vantin™) 800 mg daily in two equally divided doses (2 x 200 mg capsules)

The safety and efficacy measurements were performed as per the schedule summarized in the following table, which is adapted from a table in the applicant's submission:

Visit number	1	2	3	4
Study day	Day 1	Day 4	End Rx Day + 1	Day 30
Allowable window	(~48 hours)	(Day 3-5)	(Day 8-14)	(Day 28-35)
Treatment period	Day 1 to Day 7 or Day 10			
Follow-up period	Day 8 or 11 to Day 35			
Informed consent	x			
Demographic information	x			
Physical examination	x			
Concomitant medication	x	x	x	x
Vital signs	x	x	x	x
Dosing record		x	x	
Clinical signs & symptoms	x	x	x	x
Microbiology				
exudate (or other specimen)	x	x	x	x <sup>2</sup>
culture & sensitivity				
Safety laboratory tests				
hematology	x	x	x	abn
biochemistry	x	x	x	abn
urinalysis	x		x	abn
Pregnancy test <sup>1</sup>	x			
Adverse events				
routine events		x	x	x
serious adverse events		x	x	x
Investigator's clinical evaluation <sup>3</sup>		x <sup>4</sup>	x	x

abn = abnormal at previous visitor clinically significant adverse event

<sup>1</sup> to be done by local site for women of childbearing potential

<sup>2</sup> to be done if clinically indicated

<sup>3</sup> to be done at time of discontinuation, if applicable

<sup>4</sup> this evaluation is used to determine if total length of therapy will be 7 or 10 days

The objective of this study was to compare the safety and efficacy of trovafloxacin to cefpodoxime in the treatment of uncomplicated infections of the skin and skin structures.

## 2.1.2 Eligibility Criteria

The following inclusion/exclusion criteria are reproduced from the applicant's submission.

Inclusion Criteria

1. Age greater than or equal to 18 years at baseline.
2. Outpatient men or women. Women of childbearing potential (i.e., not surgically sterile or  $\leq 1$  year post-menopausal) were to have had a negative pregnancy test prior to entry into the study, have used adequate contraception both during the study, and for one month after the end of treatment.
3. Clinically documented uncomplicated infection of the skin or skin structure.
4. Culturable material was to be obtained. In the case of cellulitis, a culture of an aspirate from the margin of the infected area was to be attempted, if no other culturable material was present.
5. Written informed consent.

Exclusion Criteria

1. Treatment with other antibiotics under the following conditions:
  - a. Treatment with any other systemic antibiotic for 24 hours or longer, within 72 hours prior to the baseline visit (unless there was documented evidence of clinical failure).
  - b. Treatment with a topical antibiotic within 24 hours prior to the baseline visit or during the study.
  - c. The need for treatment with an antibiotic other than the study drugs or treatment for longer than 14 days.
2. Skin or skin structure infection that requires extensive surgical intervention, or whose severity is sufficient to warrant initial intravenous antibiotic therapy.
3. Evidence of or history of significant gastrointestinal, hematological, neurologic, renal, cardiovascular, or immunological disease.

**Medical Officer Comment**

The following protocol deviations from the inclusion/exclusion criteria were reported :

Patient No.	ID	Treatment arm	Type of deviation	Analyses performed by applicant					
				Clinical			Bacteriological		
				ITT	EOS Eval	EOS Eval	ITT	EOS Eval	EOS Eval
<b>Inclusion criteria</b>				--	--	--	--	--	--
5643-9004*		-----	No informed consent	Y	Y	Y	Y	Y	Y
5149-0633		Trovafloxacin	Age < 18	Y	Y	Y	Y	Y	Y
<b>Exclusion criteria</b>				Y	Y	Y	Y	Y	Y
5034-0668		Trovafloxacin	Known hypersensitivity to quinolones or beta-lactams	Y	Y	Y	N	N	NA
5733-0139		Trovafloxacin	Known hypersensitivity to quinolones or beta-lactams	Y	Y	Y	Y	Y	Y
5149-0268		Cefpodoxime	Known hypersensitivity to quinolones or beta-lactams	Y	Y	Y	Y	Y	Y
5017-0377		Trovafloxacin	Evidence of drug or alcohol abuse	Y	Y	Y	Y	Y	N
5553-0427		Trovafloxacin	Evidence of drug or alcohol abuse	Y	Y	Y	Y	Y	N
5034-0540		Trovafloxacin	Treated with systemic antibiotics for >24 hrs within 72 hours of baseline	Y	N	NA	N	N	NA
5817-0065		Cefpodoxime	Treated with systemic antibiotics for >24 hrs within 72 hours of baseline	Y	N	NA	Y	N	NA
5017-0554		Trovafloxacin	Received topical antibiotics	Y	Y	Y	Y	Y	Y
5839-0238		Trovafloxacin	On chronic immunosuppressive therapy	Y	N	NA	Y	N	NA

\*Patient 5643-9004 withdrew consent on the first day, never receiving any drug.

The case report forms were reviewed for all the patients that had an entry criteria protocol violation. Of the violations that had a potential to alter the clinical or bacteriological outcome, the medical reviewer felt that the violations were not significant enough, in quality or quantity, to have a significant impact on the overall study results.

### *2.1.3 Study Drugs and Randomization Method*

A double-dummy technique was used to maintain blinding. Trovafloxacin tablets and cefpodoxime capsules were provided in blister packs. A computer-generated randomization list was provided to the investigator in the study and the patients were randomized in a 1:1 ratio to one of the following treatment arms:

Trovafloxacin - 100 mg daily as a single dose (1 x 100 mg tablet)

Cefpodoxime proxetil - 800 mg daily in two divided doses (2 x 200 mg capsules)

### *2.1.4 Study Endpoints*

The primary endpoint was to be clinical response at the end of therapy. Clinical and bacteriological response at the end of study were to serve as secondary endpoints.

The definitions for clinical response, bacteriological response, and subject evaluability were the same as for Study 154-131, and will not be reproduced here.

#### **Medical Officer Comment**

As with the other studies performed in the complicated skin and skin structure infections patient population, the timepoint for clinical assessment preferred by the Division was the End of Study visit.

### *2.1.5 Termination and Follow-up*

If the patient discontinued prior to the prescribed end of treatment, a final evaluation was to be performed. If the discontinuation was due to clinical failure, then the final clinical and microbiological evaluations were to be performed. If the discontinuation was due to adverse events, then appropriate therapeutic measures would be taken and the patient would be followed through Visit 4 (Day 30), with performance of all clinical and microbiological evaluations.

### *2.1.6 Sample Size and Statistical Plan*

The study sought to prove equivalence of the study drug to the comparator, defined as having the 95% confidence interval around the point estimates of the difference between the two arms not be more than 10% (when the response rate of the reference drug is 90% or better).

Based on the premise that the reference drug had a 95% efficacy rate, the applicant calculated that the number of evaluable patients that would be needed 75 subjects per treatment arm. This would ensure with 80% probability that the lower limit of the 95% confidence interval for the true difference in efficacy is greater than -10%. Further, the applicant assumed that 10 to 20% of the patients would be non-evaluable, therefore, they anticipated that at least 90 patients/arm would need to be enrolled to protect the power of the study.

The Cochran-Mantel-Haenzel Test was also used to control for center effect.

## 2.1.7 Study Results

## 2.1.7.1 Enrollment and Description of Patients Enrolled in the Study

A total of 446 patients were randomized to therapy - 221 to the trovafloxacin arm, and 225 to the Cefpodoxime (Vantin™) treatment group. Every patient that was randomized received therapy. The demographic features of the treatment arms is summarized in the table below, adapted from the summary table in the applicant's submission (Table 2.1.1).

## Demographic characteristics of treated Subjects

	Trovafloracin 100 mg q d			Vantin™ 400 mg bid		
	Male	Female	Total	Male	Female	Total
<b>Number of Subjects</b>	127	94	221	118	107	225
<b>Age (yr)</b>						
16-44	68 ( 54%)	40 ( 43%)	108 ( 49%)	65 ( 55%)	53 ( 50%)	118 ( 52%)
45-64	36 ( 28%)	30 ( 32%)	66 ( 30%)	34 ( 29%)	35 ( 33%)	69 ( 31%)
>=65	23 ( 18%)	24 ( 26%)	47 ( 21%)	19 ( 16%)	19 ( 18%)	38 ( 17%)
<b>Mean</b>	44.8	49.7	46.9	45.6	45.6	45.6
<b>Minimum</b>						
<b>Maximum</b>						
<b>Race</b>						
White	99 ( 78%)	56 ( 60%)	155 ( 70%)	90 ( 76%)	62 ( 58%)	152 ( 68%)
Hispanic	15 ( 12%)	23 ( 24%)	38 ( 17%)	14 ( 12%)	26 ( 24%)	40 ( 18%)
Black	11 ( 9%)	15 ( 16%)	26 ( 12%)	12 ( 10%)	16 ( 15%)	28 ( 12%)
Asian	2 ( 2%)	0	2 ( <1%)	1 ( <1%)	1 ( <1%)	2 ( <1%)
Mixed Hispanic/Native	0	0	0	1 ( <1%)	0	1 ( <1%)
Native American	0	0	0	0	1 ( <1%)	1 ( <1%)
South American Indian	0	0	0	0	1 ( <1%)	1 ( <1%)

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In addition, the type of skin infections present at baseline are summarized in the table below (Table B from the applicant's Study Report):

<b>Table A. Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure Clinical Intent-to-Treat Subjects</b>				
	<b>Trovafoxacin 100 mg (N=221)</b>		<b>Vantin 400 mg BID (N=225)</b>	
<b>Type of Infection<sup>a</sup></b>	<b>Number and Percentage (%) of Subjects</b>			
Simple Abscess	50	(23%)	56	(25%)
Impetiginous Lesion	15	(7%)	17	(8%)
Furuncle	22	(10%)	21	(9%)
Minor Wound Infection	52	(24%)	37	(16%)
Cellulitis with a Baseline Pathogen	32	(14%)	40	(18%)
Cellulitis without a Baseline Pathogen	25	(11%)	17	(8%)
Other	34	(15%)	52	(23%)
Subjects Requiring Surgical Intervention <sup>b</sup>	59	(26%)	72	(32%)
At Baseline	54	(24%)	68	(30%)
Post-Baseline <sup>c</sup>	4	(1%)	7	(3%)
Before the EOT Assessment	3	(1%)	6	(2%)
After the EOT Assessment	1	(<1%)	1	(<1%)

EOT = End of Treatment

a A subject may have had more than one type of infection.

b Two subjects in the trovafoxacin group (Subjects 5531-0463 and 5606-0359) and two subjects in the Vantin group (Subjects 5531-0340 and 5553-0426) had a surgical procedures done post-baseline; however, the type and timing of the procedure was not listed on the subject's case report forms.

c One subject (5017-0377) in the trovafoxacin group and five subjects (5013-0443, 5125-0283, 5177-0438, 5553-0511, and 5816-0286) in the Vantin group had surgical drainage procedures performed both prior to and post-baseline.

Ref.: Tables 2.3 and 2.4 in the submission.

#### Medical Officer Comment

The demographic characteristics and baseline medical histories were comparable between the treatment groups. It was noted that there was a slight imbalance in the type of baseline diagnoses: more patients in the trovafoxacin treatment group had the diagnosis of "minor wound infection," and fewer had the diagnosis of "other." The first difference was not statistically significant, and the second marginally statistically significant. For additional details regarding the statistical issues, please refer to the Dr. Silliman's (the Division's Biometrics reviewer) review. Neither difference was felt to have had a significant clinical impact on the study.

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## 2.1.7.2 Patient Disposition

The following table summarizes the disposition of the patients in the trial (adapted from Table A of the applicant's Summary Report):

	Trovafloracin 100 mg	Cefpodoxime (Vantin™) 400 mg tid
Number of randomized subjects	221	225
Randomized not treated	0	0
Number of treated subjects	221	225
Withdrawn from treatment	16 (7%)	20 (9%)
Withdrawn from study when treatment stopped	4 (2%)	16 (7%)
Withdrawn from treatment but completed study	12 (5%)	4 (2%)
Completed treatment	205 (93%)	205 (91%)
Withdrawn from study during follow-up	5 (2%)	5 (2%)
Completed treatment and study	200 (90%)	200 (89%)

Of the patients that were discontinued while on treatment, a total of 16 patients (7%) were discontinued from the trovafloxacin arm, and 20 (9%) discontinued from the Vantin™ arm. The reasons for discontinuation are summarized in the following table (adapted from the applicant's submission; Table C of the Summary Report):

	Trovafloracin 100 mg q d	Vantin™ 400 mg bid
Number of Treated Subjects	221	225
Discontinued Subjects	16 (7%)	20 (9%)
Related to Study Drug	10 (5%)	8 (4%)
Adverse event	6 (3%)	6 (3%)
Insufficient response	4 (2%)	2 (<1%)
Not Related to Study Drug	6 (3%)	12 (5%)
Adverse event	0	4 (2%)
Lost to follow-up	0	5 (2%)
Other	3 (1%)	1 (<1%)
Patient died	0	1 (<1%)
Protocol violation	1 (<1%)	0
Withdrawn consent	2 (<1%)	1 (1%)
Completed treatment	205 (93%)	205 (91%)

**Medical Officer Comment**

The patient disposition was comparable between the treatment groups.

## 2.1.7.3 Primary Analyses

Utilizing the criteria described in section 2.2.4 Study Endpoints, the number of patients that were excluded from evaluation from each of the arms was as follows:

1. *Clinical*

In the 221 subjects in the trovafloxacin treatment arm, 10 were not clinically evaluable. In the 225 patients in the Vantin™ arm, 17 were not clinically evaluable. The most common reason was insufficient therapy (6 in the trovafloxacin arm, and 13 in the Vantin™ arm), as well as prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness, no post-baseline clinical assessment, and no post-baseline clinical assessment in the evaluable window

2. *Bacteriological*

Of the 211 clinically evaluable trovafloxacin patients, and 208 clinically evaluable Vantin™ patients, 44 and 46 were not included in the bacteriologically evaluable population, respectively. The predominant reason was lack of a baseline pathogen.

The following table summarizes the number of evaluable patients in each category, for each treatment arm:

	Trovafloracin	Vantin
Number Randomized	221	225
Not treated	0	0
Treated patients	221 (100%)	225 (100%)
Negative baseline cultures	45 ( 20%)	50 ( 22%)
Bacteriological Intent-to-Treat	176 ( 80%)	175 ( 78%)
Clinically Evaluable	211 (95%)	208 (92%)
Negative baseline cultures	43 (19%)	46 (20%)
No post-baseline culture	1 (<1%)	0
Bacteriologically Evaluable	167 (76%)	162 (72%)

### Efficacy Results

The applicant performed several analyses comparing the results of the investigator-defined response rates and the applicant defined response rates. This was done for both timepoints - at the end-of-treatment and at the end-of-study visits. In addition, the patient subgroups analyzed included the clinically intent-to-treat, clinically evaluable, and bacteriologically evaluable patients.

#### 1. Clinically Evaluable

The following table, adapted from Table D in the applicant's submission, summarizes the clinical response rates for the different categories in the clinically evaluable subjects:

Sponsor-Defined Clinical Response Rates at the End of Treatment and at the End of Study Visits (Clinically Evaluable Subjects)			
	Trovafloracin 100 mg (N=211)	Vantin™ 400 mg BID (N=208)	95% CI
Number and Percentage (%) of Subjects			
<b>End of Treatment</b>			
Number of Subjects Assessed	207 (100%)	207 (100%)	
Success (Cure + Improvement)	194 (94%)	192 (93%)	(-3.9, 5.8)
Distribution of Clinical Response:			
Cure	114 (55%)	100 (48%)	
Improvement	80 (39%)	92 (44%)	
Failure	13 (6%)	15 (7%)	
<b>End of Study</b>			
Number of Subjects Assessed	204 (100%)	194 (100%)	
Success (Cure + Improvement)	179 (88%)	168 (87%)	(-5.4, 7.7)
Distribution of Clinical Response:			
Cure	152 (75%)	137 (71%)	
Improvement	27 (13%)	31 (16%)	
Failure	13 (6%)	15 (8%)	
Relapse	12 (6%)	11 (6%)	
CI=confidence interval Ref.: Table 5.1.1 in the submission			

#### 2. Clinical intent-to-treat

The clinically intent-to-treat group analysis yielded similar results: At the end of treatment, the trovafloracin arm had a 93% success rate in 217 subjects assessed out of a possible 221; the Vantin™ arm, 88% success rate in 224 subjects assessed out of a possible 225. The 95% confidence interval around the difference was (-0.3, 10.6).

At the end of study the trovafloxacin arm had a 87% success rate in 221 subjects assessed out of a possible 221; the Vantin™ arm, 83% success rate in 225 subjects assessed out of a possible 225. The 95% confidence interval around the difference was (-2.4, 10.8).

#### Medical Officer Comment

Both analyses support the applicant's claim for therapeutic equivalence compared to Vantin™ in for this indication.

#### 3. Clinical response rate by baseline pathogen

The most commonly isolated pathogens at baseline were *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis*. In the clinically evaluable subjects, the response rate was comparable between the treatment arms. The following table is reproduced from the Study Report (Table F):

#### Most frequently isolated baseline pathogens<sup>a</sup>

Pathogen	Trovafloracin 100 mg (N=211)	Vantin™ 400 mg BID (N=208)	Trovafloracin 100 mg (N=204)	Vantin™ 400 mg BID (N=194)
	Number of Subjects			
	End of Treatment		End of Study	
<i>S. aureus</i>	71/76 (93%)	59/64 (92%)	63/73 (86%)	53/60 (88%)
<i>S. epidermidis</i>	30/34 (88%)	27/29 (93%)	30/35 (86%)	24/27 (89%)
<i>P. aeruginosa</i>	15/15 (100%)	8/8	15/15 (100%)	7/8 (88%)
<i>E. faecalis</i>	13/13	13/13	12/13	10/13
<i>E. coli</i>	5/5	10/11	5/5	10/11
<i>Staphylococcus spp.</i>	10/10	2/2	9/10	2/2
<i>S. haemolyticus</i>	10/10	10/11	10/10	9/10
<i>S. hominis</i>	4/5	4/4	3/5	4/4
<i>S. simulans</i>	1/1	5/5	1/1	4/5
Coagulase Negative staphylococci	0/0	2/2	0/0	1/1
<i>Streptococcus sp.</i>	6/6	6/7	3/4	5/7
<i>S. agalactiae</i>	8/9	10/13	8/10	9/12
<i>S. aginosus</i>	2/2	0/0	2/2	0/0
<i>S. mitis</i>	1/1	0/0	1/1	0/0
<i>S. pyogenes</i>	9/9	6/6	9/9	5/5
<i>S. sanguis I</i>	0/0	1/1	0/0	1/1
<i>S. sanguis II</i>	1/1	2/2	1/1	1/2
Group G Beta streptococci	2/2	1/1	2/2	1/1
Alpha haemolytic streptococci	0/0	1/1	0/0	1/1

a ≥10 isolates of a given pathogen in any treatment group and all staphylococcus and streptococcus species; percents displayed only when denominator is ≥15.  
A subject could have had more than one pathogen isolated at baseline.  
Ref.: Table 5.3.1 in the submission.

#### Medical Officer Comment

Trovafloracin demonstrated good response rates against *Staphylococcus aureus* and *Staphylococcus epidermidis*, comparable to the comparator treatment group:

For *S. aureus* - 93% (trovafloracin) vs. 92% (cefepodoxime) at the end of treatment; 86% (trovafloracin) vs. 88% (cefepodoxime) at the end of study.

For *S. epidermidis* - 88% (trovafloracin) vs. 93% (cefepodoxime) at the end of treatment; 86% (trovafloracin) vs. 89% (cefepodoxime) at the end of study.

#### 2.1.7.4 Secondary Analyses

The applicant also performed the following analyses:

1. Clinical response by type of infection at baseline
2. Clinical response by timing of surgical intervention.
3. Presence of signs and symptoms.

#### **Medical Officer Comment**

**The results were comparable between the treatment arms for the three analyses.**

## 2.2 Study 154-129

Title: A randomized, double-blind, multicenter trial comparing oral therapy with trovafloxacin (CP-99,219) (100 mg daily) and flucloxacillin (500 mg qid) for the treatment of uncomplicated infections of the skin and skin structure.

### Study Dates

10 July 1995 - 10 January 1996

#### 2.2.1 Study Design and Objectives

A randomized, double-blind, double-dummy, comparative, multicenter trial. The duration of treatment was 7 days. The treatment groups were:

1. Trovafloxacin, 100 mg/day, as a single dose (1 x 100 mg tablet)
2. Flucloxacillin, 2000 mg daily, in four equally divided doses of 500 mg

The safety and efficacy measurements were performed as per the schedule summarized in the following table, which is adapted from a table in the applicant's submission:

Visit number	1	2	3
Study day	Day 1	End Rx Day + 1	Day 30
Allowable window	(~48 hours)	(Day 8-14)	(Day 28-35)
Treatment period	Day 1 to Day 7		
Follow-up period	Day 8 to 11 to Day 35		
Informed consent	x		
Demographic information	x		
Physical examination	x		
Concomitant medication	x	x	x
Vital signs	x	x	x
Dosing record		x	x
Clinical signs & symptoms	x	x	x
Microbiology			
exudate (or other specimen)	x	x	x <sup>2</sup>
culture & sensitivity			
Safety laboratory tests			
hematology	x	x	abn
biochemistry	x	x	abn
urinalysis	x		abn
Pregnancy test <sup>1</sup>	x		
Adverse events			x
Investigator's assessment of clinical response		x	x

abn = abnormal at previous visitor clinically significant adverse event

<sup>1</sup> to be done by local site for women of childbearing potential

<sup>2</sup> to be done if clinically indicated

<sup>3</sup> to be done at time of discontinuation, if applicable

#### Medical Officer Comment

Although the table in the submission did not have anything denoted as Footnote # 3, it is believed that it was probably meant to clarify when the investigator's assessment was to be performed.

The objective of this study was to compare the safety and efficacy of trovafloxacin to flucloxacillin in the treatment of uncomplicated infections of the skin and skin structure.

### 2.2.2 Eligibility Criteria

The inclusion and exclusion criteria were similar to study 154-130 except that the age at entry could be as young as 16 years of age.

#### Medical Officer Comment

The following protocol deviations from the inclusion/exclusion criteria were reported :

Patient No.	ID	Treatment arm	Type of deviation	Analyses performed by applicant					
				Clinical			Bacteriological		
				ITT	EOT Eval	EOS Eval	ITT	EOT Eval	EOS Eval
<b>Inclusion criteria</b>									
5883-0197		Trovafloxacin	Target infection was a post-surgical infection	Y	Y	Y	Y	Y	Y
<b>Exclusion criteria</b>									
5867-0281*		Trovafloxacin	Treated with systemic antibiotics within 72 hours of baseline	Y	N	NA	N	N	NA
5272-0099		Trovafloxacin	Treated with a topical antibiotic within 24 hours of baseline	Y	Y	Y	N	N	A

\*The study report indicates this patient identification number, however it does not appear in the data listings, nor is there a case report form for this patient. After review of the case report forms, it is believed that this represents a typographical error in the study report, i.e. a transposition of two digits in the identification number. It is believed that the patient identification number should be #5876-0281 - a patient that had been treated with systemic antibiotics and subsequently deemed unevaluable.

After review of the case report forms, it was that the protocol violations were not significant enough to potentially affect the patient's result, nor have a significant impact on the overall study results.

### 2.2.3 Study Drugs and Randomization Method

A double-dummy technique was used to maintain blinding. Trovafloxacin tablets and flucloxacillin capsules were provided in blister packs. The patients were randomized in a 1:1 ratio to one of the following treatment arms:

- Trovafloxacin - 100 mg daily as a single dose (1 x 100 mg tablet)
- Flucloxacillin - 2000 mg daily in four divided doses (1 x 500 mg capsules)

### 2.2.4 Study Endpoints

As with all the other studies for this indication, the primary efficacy endpoint was the clinical response at the end of therapy. The bacteriological response at the end of therapy, and the clinical and bacteriological responses at the end of study were secondary endpoints.

The definitions for the clinical response, bacteriological response, and subject evaluability were similar to Study 153-131, except for the following:

1. The bacteriological response classifications included "Eradication with Infection."
2. The evaluability criteria stipulated that a subject must receive at least 3 days of dosing.

#### Medical Officer Comment

As with all the other studies, the timepoint preferred by the Division for the primary efficacy endpoint was the end-of-study visit.

2.2.5 Termination and Follow-up

Visit # 2 was the end-of-treatment visit, at which time safety and efficacy assessments were performed. Patients were followed until Day 30 (Visit #3), which was considered the end-of-study visit, at which time end of study safety and efficacy assessments were repeated. If a subject was discontinued from therapy prior to the end of the study, they were still to be followed until Visit #3 for safety.

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2.2.6 Sample Size and Statistical Plan

Study sample size was calculated as before, with the intent to show equivalence to the comparator arm as previously defined. The applicant assumed an efficacy response rate of 95% for the reference drug, and determined that at least 90 subjects per treatment arm would need to be enrolled. This would allow for the potential loss of 10 to 20% of subjects, and still ensure with 80% probability that the lower limit of the confidence interval for the true difference in efficacy would not exceed 10%.

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2.2.7 Study Results

2.2.7.1 Enrollment and Description of Patients Enrolled in the Study

A total of 280 patients were randomized to therapy - 141 to the trovafloxacin arm, and 139 to the flucloxacillin treatment group. One patient in each treatment arm did not receive therapy. The demographic features of the treatment arms is summarized in the table below, adapted from the summary table in the applicant's submission (Table 2.1.1).

Demographic characteristics of treated Subjects

	Trovafoxacin 100 mg q d			Flucloxacllin 500 mg qid		
	Male	Female	Total	Male	Female	Total
Number of Subjects	69	71	140	70	68	138
Age (yr)						
16-44	41 ( 59%)	37 ( 52%)	78 ( 56%)	37 ( 53%)	30 ( 44%)	67 ( 49%)
45-64	20 ( 29%)	20 ( 28%)	40 ( 29%)	18 ( 26%)	19 ( 28%)	37 ( 27%)
>=65	8 ( 12%)	14 ( 20%)	22 ( 16%)	15 ( 21%)	19 ( 28%)	34 ( 25%)
Mean	42.1	46.0	44.1	46.5	48.3	47.3
Minimum						
Maximum						
Race						
White	69 ( 100%)	70 ( 99%)	139 ( >99%)	68 ( 97%)	68 ( 100%)	136 ( 99%)
Asian	0	1 (<1%)	1 (<1%)	2 ( 3%)	0	2 ( 3%)

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In addition, the type of skin infections present at baseline are summarized in the table below (Table A from the applicant's Study Report):

Summary of Type of Skin Infection at Baseline and Number of Subjects with a Surgical Drainage Procedure Clinical Intent-to-Treat Subjects		
	Trovafoxacin 100 mg (N=141)	Flucloxacillin 500 mg QID (N=139)
Type of Infection <sup>a</sup>	Number and Percentage (%) of Subjects	
Simple Abscess	28 (20%)	24 (17%)
Impetiginous Lesion	23 (16%)	24 (17%)
Minor Wound	17 (12%)	21 (15%)
Cellulitis with a Baseline Pathogen	12 (9%)	19 (14%)
Cellulitis without a Baseline Pathogen	19 (13%)	19 (14%)
Otitis Externa	19 (13%)	19 (14%)
Paronychia	16 (11%)	11 (8%)
Leg Ulcers	8 (6%)	3 (2%)
Other	11 (8%)	12 (9%)
Subjects Requiring Surgical Intervention	18 (12%)	13 <sup>b</sup> (9%)
At Baseline	14 (9%)	9 (6%)
Post-Baseline	5 (3%)	3 (2%)
Before the EOT Assessment	4 (2%)	2 (1%)
After the EOT Assessment	1 (<1%)	1 (<1%)
EOT = End of Treatment		
a A subject may have had more than one type of infection.		
b Subject 6080-0239 had a surgical procedure done post-baseline. The type and timing of the procedure was not listed on the subject's case report form.		
Ref.: Tables 2.3 and 2.4 in the submission.		

#### Medical Officer Comment

The baseline demographics, baseline diagnoses, and baseline medical histories were comparable between the treatment arms.

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#### 2.2.7.2 Patient Disposition

The following table summarizes the disposition of the patients in the trial:

	Trovafoxacin 100 mg	Flucloxacillin 500 mg qid
Number of randomized subjects	141	139
Randomized not treated	1 (<1%)	1 (<1%)
Number of treated subjects	140	138
Withdrawn from treatment	12 (9%)	5 (4%)
Withdrawn from study when treatment stopped	5 (4%)	2 (2%)
Withdrawn from treatment but completed study	7 (5%)	3 (2%)
Completed treatment	128 (91%)	133 (96%)
Withdrawn from study during follow-up	1 (<1%)	2 (2%)
Completed treatment and study	127 (90%)	131 (94%)

Of the patients that were discontinued while on treatment, a total of 12 patients (9%) were discontinued from the trovafoxacin arm, and 5 patients (4%) discontinued from the flucloxacillin

arm. The reasons for discontinuation are summarized in the following table (adapted from the applicant's submission; Table B of the Summary Report):

	Trovafloracin 100 mg q d	Flucloxacillin 500 mg qid
<b>Number of Treated Subjects</b>	140	138
<b>Discontinued Subjects</b>	12 (9%)	5 (4%)
<b>Related to Study Drug</b>	9 (6%)	4 (3%)
Adverse event	8 (6%)	3 (2%)
Insufficient clinical response	1 (<1%)	1 (<1%)
<b>Not Related to Study Drug</b>	3 (2%)	1 (<1%)
Adverse event	2 (1%)	0
Lost to follow-up	1 (<1%)	1 (<1%)
<b>Completed treatment</b>	128 (91%)	133 (96%)

**Medical Officer Comment**

More patients were withdrawn from the trovafloracin arm than the flucloxacillin arm, and more of these withdrawals were attributed to the study drug. This will be further addressed in the safety section of this review.

**2.2.7.3 Primary Analyses**

Utilizing the criteria described in section 2.2.4 Study Endpoints, the number of patients that were excluded from evaluation from each of the arms was as follows:

**1. Clinical**

In the 141 subjects randomized to the trovafloracin treatment arm, 11 were not clinically evaluable; and in the flucloxacillin arm, 6 were not evaluable. The most common reason was insufficient therapy (8 in the trovafloracin arm and 4 in the flucloxacillin arm). Other reasons included randomized but not treated, prior antibiotic therapy, concomitant antibiotic therapy for intercurrent illness, no post-baseline clinical assessment, and no post-baseline clinical assessment in the evaluable window.

**2. Bacteriological**

Of the 130 bacteriologically evaluable patients in the trovafloracin arm, only 76 patients were bacteriologically evaluable because of lack of baseline pathogen in 54 patients. In the flucloxacillin arm, 50 patients lacked baseline pathogens, therefore only 83 were bacteriologically evaluable.

The following table summarizes the number of patients in each of the categories:

	Trovafloracin	Flucloxacillin
<b>Number Randomized</b>	141	139
Not treated	1 (<1%)	1 (<1%)
<b>Treated patients</b>	140 (99%)	138 (99%)
Negative baseline cultures	60 (43%)	53 (38%)
<b>Bacteriological Intent-to-Treat</b>	80 (57%)	85 (61%)
<b>Clinically Evaluable</b>	130 (92%)	133 (96%)
Negative baseline cultures	54 (38%)	50 (36%)
<b>Bacteriologically Evaluable</b>	76 (54%)	83 (60%)

**Efficacy Results**

The applicant performed several analyses comparing the results of the investigator-defined response rates and the applicant defined response rates. This was done for both timepoints - at the end-of-treatment and at the end-of-study visits. In addition, the patient subgroups analyzed included the clinically intent-to-treat, clinically evaluable, and bacteriologically evaluable patients.

**1. Clinically Evaluable**

The following table, adapted from Table C in the applicant's submission, summarizes the clinical response rates for the different categories in the clinically evaluable subjects:

Sponsor-Defined Clinical Response Rates at the End of Treatment and at the End of Study Visits (Clinically Evaluable Subjects)			
	Trovafloracin 100 mg (N=130)	Flucloxacillin 500 mg QID (N=133)	95% CI
Number and Percentage (%) of Subjects			
<b>End of Treatment</b>			
Number of Subjects Assessed <sup>a</sup>	129 (100%)	133 (100%)	
Success (Cure + Improvement)	117 (91%)	115 (86%)	(-3.4, 11.9)
Distribution of Clinical Response:			
Cure	72 (56%)	60 (45%)	
Improvement	45 (35%)	55 (41%)	
Failure	12 (9%)	18 (14%)	
<b>End of Study</b>			
Number of Subjects Assessed	125 (100%)	123 (100%)	
Success (Cure + Improvement)	106 (85%)	97 (79%)	(-3.6, 15.5)
Distribution of Clinical Response:			
Cure	97 (78%)	92 (75%)	
Improvement	9 (7%)	5 (4%)	
Failure	12 (10%)	18 (15%)	
Relapse	7 (6%)	8 (7%)	
CI=confidence interval			
a Subject 5895-0252 in the trovafloracin group was not assessed at the end of treatment visit.			
Ref.: Table 5.1.1 in the submission.			

**2. Clinical intent-to-treat**

The clinically intent-to-treat group analysis yielded similar results: At the end of treatment, the trovafloracin arm had a 88% success rate in 138 subjects assessed out of a possible 141; the flucloxacillin arm, 86% success rate in 139 subjects assessed out of a possible 139. The 95% confidence interval around the difference was (-5.9, 10.1).

At the end of study the trovafloracin arm had a 83% success rate in 141 subjects out of a possible 141; the flucloxacillin arm, 79% success rate in 139 subjects out of a possible 139. The 95% confidence interval around the difference was (-5.3, 130.).

**Medical Officer Comment**

Both analyses support the applicant's claim for therapeutic equivalence compared to flucloxacillin in for this indication.

**3. Clinical response rate by baseline pathogen**

The most commonly isolated pathogens at baseline was *Staphylococcus aureus*. In the clinically evaluable subjects, the response rate was comparable between the treatment arms. The following table is reproduced from the Study Report (Table E):

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Most frequently isolated pathogens<sup>a</sup>

Pathogen	Trovafoxacin 100 mg (N=130)		Flucloxacillin 500 mg QID (N=133)		Trovafoxacin 100 mg (N=125)		Flucloxacillin 500 mg QID (N=123)	
	Number of Subjects							
	End of Treatment				End of Study			
<i>S. aureus</i>	39/42	(93%)	42/47	(89%)	34/40	(85%)	33/42	(79%)

a ≥10 isolates of a given pathogen in any treatment group; percents displayed only when denominator is ≥15.  
 A subject could have had more than one pathogen isolated at baseline.  
 Ref.: Table 5.3.1 in the submission.

Medical Officer Comments

It is uncertain why this was the only baseline pathogen identified in this study. However, the findings are supportive of Study 154-130.

2.2.7.4 Secondary Analyses

Additional analyses performed by the applicant included:

1. Clinical response by type of infection at baseline.
2. Clinical response by timing of surgical intervention.
3. Presence of signs and symptoms.

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Medical Officer Comment

The findings were overall comparable between the treatment arms for the resolution of signs and symptoms. There were not enough patients in the surgical intervention subsets to be able to make any definitive conclusions. However, with regards to the baseline diagnoses, there appeared to be a trend for higher clinical success rate with trovafoxacin compared to flucloxacillin with respect to simple abscess. It was noted that in this study, trovafoxacin was less effective against leg ulcers, but the number of patients with this diagnosis was small.

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ON 05/03/04

2.3 Efficacy Summary

For this indication, the pivotal study was 154-130, a multi-center, randomized, double-blind, controlled study, using cefpodoxime (Vantin™) as the comparator. The second study, 154-129, was entirely supportive in nature. It was a multi-center, randomized, unblinded, controlled study, and used flucloxacillin as the comparator, which is presently not approved for use in this country.

The findings of Study 154-130 support the applicant's claim of efficacy for trovafoxacin, at a dose of 100 mg per day, for 7-10 days, for the treatment of uncomplicated skin/skin structure infections due to *Staphylococcus aureus*.

In addition, the study provided evidence that trovafoxacin had demonstrated efficacy against *Streptococcus agalactiae*, but there were not enough patients studied. In view of the fact that this organism was evaluated in the complicated infections studies, and that the response rates were comparable to what was found in those studies, it is believed that Study 154-130 would have shown effectiveness against *Streptococcus agalactiae* if the frequency of isolation would have been greater. Therefore the recommendation is to include this organism in the list of organisms for this indication.

Furthermore, it is noted that trovafoxacin had shown efficacy against *Streptococcus pyogenes*, but again, there were a limited number of patients identified with this organism as a baseline pathogen. However, it is believed that this organism should be included in the list of organisms, citing the caveats identified in the Division's Points to Consider

document, which are referenced on page 4 of this review (Section A5: Regulatory Background).

With respect to the other organisms requested by the applicant, the number of patients identified with pure cultures for those organisms was not sufficient to adequately evaluate trovafloxacin's efficacy.

This was also true for *Staphylococcus epidermidis* (*S. epidermidis*), for which only 14 patients were deemed to be bacteriologically evaluable, out of an initial 17 patients identified as having pure cultures at baseline. However, *S. epidermidis* posed additional concerns because, although a potential pathogen, it is also a component of normal skin flora and a common culture contaminant. Therefore, whenever *S. epidermidis* is isolated from a culture, it becomes imperative to ascertain whether its role is as a pathogen or a contaminant in order to determine whether treatment is warranted.

It is believed that if *S. epidermidis* is included in the list of organism for this indication, there is a risk that it would be interpreted that trovafloxacin is indicated for the treatment of the isolation of *S. epidermidis* from skin cultures. Realizing that with human nature it is often natural to seek the path of least resistance, there is the potential that clinicians might find it easier to use trovafloxacin to "treat" the *S. epidermidis* that was isolated, rather than make a determination as to whether treatment is warranted. This could result in the inappropriate use of trovafloxacin, with all of the concerns that would accompany that situation - including the possibility of the development of microbial resistance.

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**2.4 Safety Assessment**

**2.4.1 Integrated Safety Assessment**

Since the baseline demographic data of the two studies were comparable enough to allow both studies were evaluated for safety simultaneously. As described in the study design section, the doses of trovafloxacin used in the uncomplicated studies was less than in the complicated studies.

**2.4.2 Extent of Drug Exposure**

The applicant reported the following amounts of subject-day exposures.

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	Study 154-129		Study 154-130	
	Trovafloxacin (100 mg q d)	Vantin™ (400 mg bid)	Trovafloxacin (100 mg q d)	Flucloxacillin (500 mg qid)
Subject-days of exposure	1954	1997	984	995

**Medical Officer Comment**

Within each study, the number of subject-day exposures were comparable between the treatment groups.

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**2.4.3 Adverse Events**

The following table summarizes information regarding the number of patients that experienced adverse events, and is adapted from Table 6.1 from the applicant's submission:

	Study 154-130		Study 154-129	
	Trovafloxacin	Vantin	Trovafloxacin	Flucloxacillin
Number of subjects . . . who were treated	221	225	140	138
with at least 1 AE*	71 (32%)	86 (38%)	31 (22%)	27 (20%)
with serious AE's	3 (1%)	5 (2%)	3 (2%)	0
with severe AE's	4 (2%)	8 (4%)	7 (5%)	1 (<1%)
who discontinued due to AE's	8 (4%)	11 (5%)	12 (9%)	3 (2%)
with dose reductions/ temp. discontinuation due to AE's	3 (1%)	0	1 (<1%)	4 (3%)
who discontinued due to objective test findings	0	0	0	0

\*AE - Adverse event

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**Medical Officer Comment**

Overall, trovafloxacin compared favorably against the comparator arm. However, there were more dose reductions or temporary discontinuations due to adverse events in the

trovafloxacin arm compared to Vantin™, and more discontinuations due to adverse events in the trovafloxacin arm compared to flucloxacillin.

2.4.3.1 All causalities

The type of adverse event, by WHO term classification are summarized in the following table, adapted from the respective "All-Causalities Adverse Events" tables from the Study Reports:

Most Commonly Reported Adverse Events by Body System - All Causalities

	Study 154-130 a,b		Study 154-129 b,c	
	Trovafloxacin (N=221)	Vantin (N=225)	Trovafloxacin (N=140)	Flucloxacillin (N=138)
No. of Subjects With at Least One Adverse Event	71 (32%)	86 (38%)	31 (22%)	27 (20%)
<b>Body System (WHO Terminology)</b>				
<b>CENTRAL AND PERIPHERAL NERVOUS SYSTEM</b>				
Dizziness	9 (4%)	6 (3%)	4 (3%)	1 (<1%)
Headache	14 (6%)	15 (7%)	5 (4%)	2 (1%)
<b>GASTROINTESTINAL SYSTEM</b>				
Abdominal Pain	5 (2%)	3 (1%)	--	--
Diarrhea	10 (5%)	20 (9%)	--	--
Dyspepsia	0 (0%)	4 (2%)	1 (<1%)	7 (5%)
Flatulence	0 (0%)	5 (2%)	--	--
Nausea	7 (3%)	9 (4%)	4 (3%)	4 (3%)
Vomiting	3 (1%)	4 (2%)	4 (3%)	2 (1%)
<b>URINARY SYSTEM</b>				
Urinary Tract Infection	--	--	2 (1%)	5 (4%)
<b>GENERAL</b>				
Fatigue	5 (2%)	4 (2%)	--	--
<b>OTHER</b>				
Accidental Injury	4 (2%)	1 (<1%)	--	--
<b>SKIN/APPENDAGES</b>				
Rash	4 (2%)	2 (<1%)	--	--

a ≥2 % of subjects in any treatment group.  
 b Includes data up to 7 days after last dose of active study medication  
 c ≥3 % of subjects in any treatment group.  
 Ref.: Tables 6.2 and 6.4 in the submission

Medical Officer Comment

Dizziness was one of the more commonly reported adverse event, and consistently greater in the trovafloxacin treatment group. The other systemic category commonly affected was the gastrointestinal system.

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## 2.4.3.2 Treatment related

The following table is adapted from the treatment-related adverse event summary tables in the applicant's submission:

**Most Commonly Reported Adverse Events by Body System - Treatment related**

	Study 154-130 a,b		Vantin		Study 154-129 a,b		Trovafloracin		Flucloxacillin	
	(N=221)	(17%)	(N=225)	(21%)	(N=140)	(9%)	(N=138)	(13%)		
No. of Subjects With at Least One Adverse Event	38	(17%)	48	(21%)	13	(9%)	18	(13%)		
Body System (WHO Terminology)										
CENTRAL AND PERIPHERAL NERVOUS SYSTEM	15	(7%)	10	(4%)	7	(5%)	0			
Dizziness	7	(3%)	5	(2%)	3	(2%)	0			
Headache	9	(4%)	3	(1%)	4	(3%)	0			
GASTROINTESTINAL SYSTEM	14	(6%)	34	(15%)	7	(5%)	15	(11%)		
Diarrhea	7	(3%)	18	(8%)	--	---	--	---		
Dyspepsia	--	---	--	---	1	(<1%)	7	(5%)		
Flatulence	0	(0%)	4	(2%)	--	---	--	---		
Nausea	5	(2%)	7	(3%)	2	(1%)	3	(2%)		
Vomiting	--	---	--	---	3	(2%)	2	(1%)		
URINARY SYSTEM	--	---	--	---	2	(1%)	5	(4%)		
Urinary Tract Infection	--	---	--	---	0	(0%)	4	(3%)		

a ≥2 % of subjects in any treatment group.

b Includes data up to 7 days after last dose of active study medication

Ref.: Tables 6.2 and 6.4 in the submission

**Medical Officer Comment**

This table highlights that dizziness remained a significant type of adverse event that was reported by the patients on the trovafloxacin treatment group. It was difficult to ascertain from the case report form as to the degree of severity of the dizziness, but the applicant indicates that no untoward events were reported in which dizziness was considered a precipitating factor.

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## 2.4.3.3 Serious adverse events

The following table summarizes the number of serious events reported for the treatment arms in the two studies:

	Study 154-130		Study 154-129	
	Trovafloracin (N=221)	Cefpodoxime (N=225)	Trovafloracin (N=140)	Flucloxacillin (N=138)
No. of subjects with serious adverse events	5	8	3 (2%)	1 (<1%)
No. of subjects with serious adverse events - treatment related	0	1	0	0

**Medical Officer Comment**

The number of serious adverse events were comparable between the treatment groups.

## 2.4.3.4 Discontinuation from studies

## 2.4.3.4.1 Discontinuation due to adverse events

The following table summarizes the number of patients that were discontinued from the studies, and were adapted from the applicant's submission:

	Study 154-130		Study 154-129	
	Trovafloxacin (N=221)	Cefpodoxime (N=225)	Trovafloxacin (N=140)	Flucloxacillin (N=138)
No. of subjects discontinued due to adverse events	8 (4%)	11 (5%)	12 (9%)	3 (2%)
No. of subjects discontinued due to adverse events - treatment related	6 (3%)	6 (3%)	10 (7%)	3 (2%)
Temporary discontinuations	3	0	0	2 (1%)

**Medical Officer Comment**

The number of patients that discontinued due to adverse events (all-causality and treatment related) were comparable in the study against cefpodoxime (Vantin™). However, more patients discontinued for these reasons when compared to flucloxacillin. Although it is helpful to do cross-studies comparisons to evaluate for trends in type and/or incidences of adverse events, it is difficult to deduce a reason as to the possible reason for this observation. It is particularly difficult since the adverse event causality attribution is not always an objective finding and subject to the individual center's investigator's assessment.

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## 2.4.3.4.2 Discontinuation due to laboratory abnormalities

The following table is adapted from the applicant's submission. The number of patients assessed in each treatment group has changed to account for the patients that baseline laboratory abnormalities:

	Study 154-130		Study 154-129	
	Trovafloxacin (N=210)	Cefpodoxime (N=208)	Trovafloxacin (N=128)	Flucloxacillin (N=132)
No. of subjects with clinically significant lab. abnormalities	28 (13%)	26 (13%)	21 (16%)	16 (12%)
Liver enzyme abnormalities	5 (2%)	2 (1%)	3 (2%)	1 (<1%)
Creatinine abnormalities	1 (<1%)	0	0	0
Decrease in hemoglobin	0	0	0	3 (2%)
No. of subjects discontinued due to lab. abnormalities	0	0*	0	0

\*One subject was discontinued on Day 3 of the study due to a high baseline alkaline phosphatase value.

**Medical Officer Comment**

There were more patients in the trovafloxacin treatment group that experienced elevated liver enzymes, but were otherwise comparable to the comparators. Of the liver transaminases, two patients had elevations in alanine aminotransferase and two had elevations in aspartate aminotransferase. The overall incidence was felt to not be significant.

#### 2.4.3.5 Mortality experience

There was one death reported for both studies. It was in Study 154-130, in the cefpodoxime (Vantin™) treatment group, on Day 7 of the study. Review of the case report form confirmed that it was not study-drug related.

### C. Medical Reviewer Conclusions

The five studies provided in the NDA support the applicant's claim that alatrofloxacin and trovafloxacin are effective in treating complicated and uncomplicated infections of skin and skin structure, utilizing the applicant's dosage guidelines:

Skin and Skin Structure Infections, Complicated, including diabetic foot infections  
200 mg oral or 200 mg I.V. followed by 200 mg oral for 10-14 days duration

Skin and Skin Structure Infections, Uncomplicated  
100 mg oral for 7-10 days duration

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However, due to the minimal data provided regarding certain pathogens in the uncomplicated studies, it is believed that it will not be possible to maintain the indication as presently written, combining the two types of infections for all the pathogens listed. Separation of the two types of infection would also maintain consistency with the Points to Consider document, which recommends separation. In addition, there should a statement in the label indicating that trovafloxacin has not been studied in the treatment of osteomyelitis. This caveat will be important in patients with complicated skin and skin structure infections, which included patients with diabetes mellitus.

It was also noted that although the alatrofloxacin/trovafloxacin treatment group had a higher incidence of adverse events and discontinuations in these studies, the cost/benefit ratio is in favor of the applicant's product in this patient population with this disease process. It is acknowledged that the incidence of adverse events noted in the uncomplicated skin/skin structure infection studies, except for the complaint of dizziness, was comparable between the treatment groups.

Therefore, the recommendation is for approval, with the condition that the label should be re-written as follows for this indication:

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Streptococcus agalactiae*.

Complicated skin and skin structure infections, including diabetic foot infections, caused by *Staphylococcus aureus*, *Streptococcus agalactiae*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Escherichia coli*, or *Proteus mirabilis*. **Note:** Trovan™ has not been studied in the treatment of osteomyelitis. The safety and efficacy of Trovan™ given for > 4 weeks have not been studied.

*TSI*  
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Rigoberto A. Roca, M.D.  
Reviewing Medical Officer  
HFD-590

Concurrences:

/S/

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Brad Leissa, M.D.  
Medical Team Leader  
Division of Special Pathogen and  
Immunologic Drug Products

/S/

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Mark Goldberger, M.D., M.P.H.  
Division Director  
Division of Special Pathogen and  
Immunologic Drug Products

APPROVED FOR  
SUBMISSION

cc:  
Original NDA 20-759/20-760  
HFD-590/Div. Dir/Goldberger  
HFD-590/Dep. Div. Dir/Albrecht  
HFD-590/MTL/Leissa  
HFD-590/MO/Roca  
HFD-590/Chem/  
HFD-590/Micro/  
HFD-590/Pharmtox/  
HFD-590/CSO/  
HFD-880/Biopharm/

#### 2.4.3.5 Mortality experience

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### C. Medical Reviewer Conclusions

The five studies provided in the NDA support the applicant's claim that alatrofloxacin and trovafloxacin are effective in treating complicated and uncomplicated infections of skin and skin structure, utilizing the applicant's dosage guidelines:

Skin and Skin Structure Infections, Complicated, including diabetic foot infections  
200 mg oral or 200 mg I.V. followed by 200 mg oral for 10-14 days duration

Skin and Skin Structure Infections, Uncomplicated  
100 mg oral for 7-10 days duration

APPEARS THIS WAY  
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However, due to the minimal data provided regarding certain pathogens in the uncomplicated studies, it is believed that it will not be possible to maintain the indication as presently written, combining the two types of infections for all the pathogens listed. Separation of the two types of infection would also maintain consistency with the Points to Consider document, which recommends separation. In addition, there should a statement in the label indicating that trovafloxacin has not been studied in the treatment of osteomyelitis. This caveat will be important in patients with complicated skin and skin structure infections, which included patients with diabetes mellitus.

It was also noted that although the alatrofloxacin/trovafloxacin treatment group had a higher incidence of adverse events and discontinuations in these studies, the cost/benefit ratio is in favor of the applicant's product in this patient population with this disease process. It is acknowledged that the incidence of adverse events noted in the uncomplicated skin/skin structure infection studies, except for the complaint of dizziness, was comparable between the treatment groups.

Therefore, the recommendation is for approval, with the condition that the label should be re-written as follows for this indication:

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Streptococcus agalactiae*.

Complicated skin and skin structure infections, including diabetic foot infections, caused by *Staphylococcus aureus*, *Streptococcus agalactiae*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Escherichia coli*, or *Proteus mirabilis*. **Note:** Trovan™ has not been studied in the treatment of osteomyelitis. The safety and efficacy of Trovan™ given for > 4 weeks have not been studied.

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Concurrences:

/S/

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Immunologic Drug Products

/S/

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Mark Goldberger, M.D., M.P.H.  
Division Director  
Division of Special Pathogen and  
Immunologic Drug Products

APPROVED THIS WAY  
OR ORIGINAL

cc:  
Original NDA 20-759/20-760  
HFD-590/Div. Dir/Goldberger  
HFD-590/Dep. Div. Dir/Albrecht  
HFD-590/MTL/Leissa  
HFD-590/MO/Roca  
HFD-590/Chem/  
HFD-590/Micro/  
HFD-590/Pharmtox/  
HFD-590/CSO/  
HFD-880/Biopharm/

JUL 15 1998

NDA 20-759

Medical Review of Original NDA Indication: Uncomplicated Gonorrhea

**Name of Drug:** Trovan (trovafloxacin mesylate)

**Name of Applicant:** Pfizer Inc, East Point Road, Groton, CT 06340  
(203) 441-4100

**Date of NDA Submission:** December 30, 1996

**Date of Medical Review:** October 17, 1997

**INTRODUCTION:**

The original NDA's for Trovan Tablets, NDA 20-759 and for Trovan IV (atrofloxacin mesylate injection), NDA 20-760, were submitted December 30, 1996 and the applicant requested approval for seventeen different indications:

nosocomial pneumonia, community acquired pneumonia, acute exacerbations of chronic bronchitis, acute sinusitis, complicated intra-abdominal infections (including post-surgical infections), gynecologic and pelvic infections (including post-surgical infections) surgical prophylaxis in colorectal surgery, vaginal and abdominal hysterectomy; uncomplicated and complicated skin and skin structure infections, uncomplicated bacterial prostatitis, uncomplicated gonorrhea, pelvic inflammatory disease, and

The review of these indications has been divided among several reviewers. This document summarizes the results of the medical review of the indication for UNCOMPLICATED GONORRHEA.

**COMMENT:**

*In addition to completing the review of the indication, a second goal of this process was to learn and use the electronic version of the NDA submission to perform this review. However, based on several demonstrations, instruction sessions and attempts by other reviewers to use the electronic version of the SAS PH Clinical software, it was concluded that this particular electronic submission of data had severe limitations. Thus, the review was conducted using the paper submission of the study report, tables and related line summaries in Appendixes. In addition, the electronic version of some case report forms were examined; CRFs picked at random were examined and other CRFs were examined if specific questions about a given patient. In all, approximately 10% of the electronically-submitted CRF's were examined in part in or whole. Unfortunately, poor resolution of many CRF pages and especially of the ad hoc pages*

*of laboratory forms added to the case report forms made the review process unusually tedious. Even magnification of the images did not always allow resolution of data elements.*

*An interesting phenomenon was that sometimes a very poor image on the screen could be more easily discerned when the page was printed out. Other times the entry was still not legible (see examples in appendix to this report). However, as can be imagined, printing out CRF pages just to be able to read and check/verify a date of culture or a site of the specimen source is both a waste of time and paper.*

*The organization of the paper and electronic submission was good, however, the various subgroupings of patient data across multiple appendixes made review labor-intensive. Specifically, some lists or tables presented All Randomized patients, others All Trovafloxacin or All Ofloxacin patients, still others Trovafloxacin Female, Trovafloxacin Male, Ofloxacin Female and Ofloxacin Male. Then within these groupings, separate listings were presented for Evaluable patients, or Nonevaluable patients, etc. Thus trying to obtain an overall picture of the patient disposition, etc. involved flipping back and forth among multiple listings both in paper CRTs and electronic CRTs.*

#### **PROPOSED INDICATION:**

The applicant is requesting approval of the following wording for the gonorrhea indication:

Acute, uncomplicated urethral, cervical, pharyngeal and rectal gonorrhea due to *Neisseria gonorrhoeae*, including both penicillinase- and non-penicillinase producing strains (See WARNINGS.)

Within the WARNINGS section, there is the class labeling statement,

Trovafloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high doses for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis.

Under DOSAGE AND ADMINISTRATION, the proposed regimen for the treatment of uncomplicated gonorrhea is 100 mg of trovafloxacin, given as a single oral dose.

#### **STUDIES SUBMITTED:**

In support of the proposed labeling statements, the applicant has submitted results of two clinical trials.

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**Study Report 154-120:**

A randomized, multicenter, double-blind, double-dummy trial comparing single dose oral therapy of trovafloxacin (CP-99,219) (100 mg) with that of ofloxacin (400 mg) for the treatment of uncomplicated gonorrhea. In this trial, a total of 625 male and female patients were enrolled by 10 investigators. The applicant reports a bacterial efficacy of greater than 95% in the eradication of *Neisseria gonorrhoeae* from urethral and cervical sites. Information on some rectal and pharyngeal data were also presented.

**Study Report 154-107:**

An open randomized, non-comparative, single center dose-ranging study of trovafloxacin (CP-99,219) in the treatment of uncomplicated gonorrhea. In this single-center dose-ranging trial, 39 patients were randomized to a single dose of trovafloxacin 50 mg, 100 mg or 200 mg. The applicant reports 100% bacterial eradication of *Neisseria gonorrhoeae* from all evaluable patients. This trial served as the basis for dose selection for the multicenter randomized trial, 154-120.

**REGULATORY CONSIDERATIONS:**

In 1992, the Division of Anti-Infective Drug Products (DAIDP) made available the POINTS TO CONSIDER document and in 1997, the Guidance to Industry document on Evaluating Clinical trials of Antimicrobials in the DAIDP was made available. Both of these documents address the topic of uncomplicated gonorrhea.

For approval of the indication of uncomplicated gonorrhea, it is expected that at least 100 male and at least 100 female patients be evaluable for bacterial eradication and that at least 95% of these patients have *Neisseria gonorrhoeae* eradicated from the urethral and cervical site, respectively. For the approval of rectal and pharyngeal infections, it is recommended that data from at least 20 patients per gender per site (per drug) be evaluated and that at least 90% of the isolates for each of these subgroups be eradicated.

In the Guidance to Industry document, it is recommended that results of clinical trials of uncomplicated gonorrhea focus on bacterial eradication of *Neisseria gonorrhoeae* as the primary endpoint, and that eradication be assessed from a repeat culture taken 3-7 days after the (usually) single-dose treatment.

**COMMENT:**

*A brief examination of the studies submitted in preparation for the 45-day filing meeting indicates that these issues were taken into consideration by the company. However, it is noted that there is a probability that not all sites in all genders will be approvable. This is addressed in greater detail in this review.*

**REVIEW OF STUDIES:**

The two studies are reviewed below:

**STUDY 154-120:****TITLE:**

A randomized, multicenter, double-blind, double-dummy trial comparing single dose oral therapy of trovafloxacin (CP-99,219) (100 mg) with that of ofloxacin (400 mg) for the treatment of uncomplicated gonorrhea.

**PURPOSE:**

To demonstrate the safety and effectiveness of trovafloxacin 100 mg orally, compared to ofloxacin 400 mg orally, in the treatment of uncomplicated gonorrhea in male and female patients.

**STUDY DESIGN:**

The study was a double-blind, double-dummy trial conducted at 10 centers in the USA, comparing single dose trovafloxacin to ofloxacin for the treatment of gonorrhea. The plan was to enroll up to 500 patients ages 16 and over.

**STUDY CONDUCT:** December 20, 1994 to October 11, 1995

**INCLUSION CRITERIA:**

- outpatient men or women  $\geq 16$  years of age were enrolled and treated with either trovafloxacin tablets or ofloxacin capsules, packaged in blister packs
- written informed consent was obtained from the patient or parent/legal guardian in patients under 18 years of age
- women of childbearing potential had to have a negative pregnancy test prior to study
- females with presumptive gonococcal urethritis and/or cervicitis, defined as urethral or cervical discharge which on Gram stain showed PMLs with intracellular Gram-negative diplococci or a history of sexual exposure within 2 weeks to a man with urethral gonorrhea.
- men with presumptive gonococcal urethritis, defined as the presence of a urethral discharge which on Gram stain shows polymorphonuclear leucocytes with intracellular Gram-negative diplococci

**EXCLUSION CRITERIA:**

- pregnant or nursing women
- known hypersensitivity to quinolone class
- inpatient
- clinical evidence of gonococcal pharyngitis\*, proctitis\* (see comment below), disseminated gonococcal infection, or the presence of any other infection at enrollment that may require additional antimicrobial treatment
- treatment with any systemic antibiotic within 72 hours prior to entry into study

- treatment with another investigational drug within 30 days prior to entry
- evidence of significant gastrointestinal disorder that may inhibit absorption
- evidence of clinically significant hematologic, renal, cardiovascular disease or immunologic compromise or AIDS
- history of epilepsy or seizures
- prior enrollment in the protocol
- subject suspected to be noncompliant with the protocol

**COMMENT:**

*The protocol and resulting study report state that "subject with clinical evidence of gonococcal pharyngitis, proctitis, disseminated gonococcal infection..." were to be excluded. Clearly, this is in part contrary to the goal of the study and the proposed label, which specifically requests approval of the treatment of pharyngeal and rectal gonorrhea. Dr. Johnson at Pfizer explained that the key word was "clinical" evidence of disease, thus patients who had symptoms of pharyngitis or proctitis were excluded. However, if these patients had cultures at these sites and the cultures were positive, this information was included in the microbiological evaluation. And, as noted in the results below, some patients did have cultures positive at these sites and met all other protocol criteria and were thus included in the evaluation.*

**DRUGS AND DOSAGE REGIMEN:**

**Trovafloxacin** 100 mg orally, single-dose administered as one tablet (or matching placebo)

**Ofloxacin** 400 mg orally, single-dose administered as two capsules (or matching placebo).

Ofloxacin at this dose is approved for the treatment of uncomplicated cervical and/or urethral gonorrhea.

All drug doses were administered in the clinic under direct observation. Dosing was to be done two hours before or two hours after a meal or after use of antacid.

A randomization schedule was provided, with different blocks of numbers for male patients and female patients (to ensure adequate enrollment of each gender).

An amendment to the protocol was made November 14, 1994 changing the ofloxacin from tablet to capsule and administering 2x200 mg capsules; 2 ofloxacin placebo capsules were given to maintain the blind.

**CONCOMITANT MEDICATIONS:**

No concomitant systemic antibiotic was allowed, unless the patient was a treatment failure.

After completion of the final evaluation visit, patients were treated with either doxycycline or other agent for culture-positive *Chlamydia trachomatis*.

**COMMENT:**

*Approximately of the bacteriologically evaluable men and of the bacteriologically evaluable females had a culture positive for Chlamydia trachomatis. Approximately one-half of all enrolled patients received treatment for Chlamydia that was started at the time of the test-of-cure visit and thus did not confound the assessment of bacteriological outcome and interpretation of gonorrhea treatment.*

**EFFICACY EVALUATION:**

Patients were evaluated at baseline when a history was taken and physical examination and laboratory testing was performed. The patients were then seen at 7 days post therapy (range of 5-9 days), and follow-up evaluation, including all bacteriology was to be repeated.

**COMMENT:**

*As noted above, the Guidance document recommends a follow-up culture at 3 - 7 days after treatment of uncomplicated gonorrhea. However, because trovafloxacin has a half-life of 10 hours (appx), it is justified to use a longer follow-up period for evaluation. Therefore, the timing selected in the protocol is acceptable.*

Bacteriology: swab specimens were obtained from the following sites:

- Men: urethra and pharynx. Anorectal cultures were necessary only if history indicated rectal sexual exposure.
- Women: endocervix, pharynx, and rectum. (Women who had hysterectomy would have a urethral culture performed.)

Susceptibility testing was to be performed by agar dilution for all *N. gonorrhoeae* isolates, the tentative interpretive criteria were as follows: Susceptible  $\leq 2$ , Intermediate 4, Resistant  $\geq 8$ .

Patients were also evaluated for syphilis (FTA or RPR) and *Chlamydia trachomatis*.

Treatment for *C. trachomatis* was to be initiated at the time of the second visit, as noted above.

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Bacteriological response to therapy was to be assessed based on a comparison of the bacterial culture pre-therapy and at the 7 day evaluation time point (5 - 9 days post treatment).

*COMMENT: Bacterial response, by site of infection, is considered the primary efficacy endpoint. Thus, all patient case report tabulations (CRTs) were examined for consistency with the protocol. In addition, a random sample of case report forms (CRFs) was evaluated to determine consistency in data transfer from the CRF to the CRTs, and to evaluate interpretation of patient data. The majority of this examination consisted of verifying the bacteriological data, although some demographic, dosing,*

*concomitant medication and conditions, clinical course and adverse events were also checked. As stated below, there was general agreement with the information presented.*

**Bacteriological outcome** was classified as follows:

**Eradication:** *N. gonorrhoeae* not present in the post-treatment culture at 5-9 days.

**Persistence:** Isolation of *N. gonorrhoeae* from the post-treatment culture at 5-9 days.

Clinical response to therapy was to be assessed by the sponsor on day 7 (between day 5 and 9) and based on the investigator's global assessment of the patient's clinical condition before and after treatment.

**COMMENT:**

*It was noted that among the bacteriologically-evaluable population, men in the study were symptomatic, and approximately 10-20% of women were clinically asymptomatic. A brief examination of several case report forms and tabulations did not reveal any major disagreement in assessment of this secondary efficacy endpoint. Thus, for the purpose of this review, the applicant's evaluation of clinical response is considered acceptable.*

**Clinical outcome** was classified by the applicant as the following:

**Cure:** complete resolution of signs and symptoms

**Improvement:** incomplete resolution of signs and symptoms

**Failure:** no apparent response or progression of signs and symptoms

The applicant performed a variety of clinical and bacteriological analyses on the evaluable population as well as intent-to-treat (ITT) populations, including various subsets. These can be located in the submission but are not presented here. In general, these showed comparability between the two regimens although in some analyses the reported rates were lower than in the evaluable sets because protocol noncompliance was classified as failure in the ITT analyses.

**SAFETY EVALUATION:**

Adverse events and laboratory tests were monitored at the post-therapy visit.

**COMMENT:**

*Because this drug is also being evaluated for multiple other indications at multiple dose regimens ranging from 50 - 200 mg for up to two weeks, a full assessment of trovafloxacin's safety profile is deferred to the primary reviewer. A summary is provided in this review.*