CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050762

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA:	**50-762**
Submission Date:	December 19, 1997
Drug Product:	Trovafloxacin 100 mg Tablet Azithromycin 1 gm Packet (powder for oral suspension)
Trade Name:	TROVAN/ZITHROMAX Compliance Pak
Sponsor:	Pfizer Inc New York, NY
Category:	4S
OCPB Reviewer:	Philip M. Colangelo, Pharm.D., Ph.D.
OCPB Log In Date:	January 5, 1998

I. BACKGROUND

This submission seeks market approval for a two-drug treatment pack consisting of a single dose of trovafloxacin 100 mg tablet (TROVAN®) and a single 1 gm dose of azithromycin formulated as a powder for suspension (ZITHROMAX®). It is intended for the TROVAN® tablet and ZITHROMAX® packet (or sachet) for suspension to be co-administered. The proposed indication for this single therapy "Compliance Pak" is for the treatment of sexually transmitted disease (STD) due to *Neisseria gonorrhoeae* and *Chlamydia trachomatis.* The rationale for this product stems from a CDC recommendation to treat patients diagnosed with urethritis/cervicitis infections for both *Chlamydia* and *N. gonorrhoeae*, since a significant percentage of male and female patients who have these infections caused by *N. gonorrhoeae* are also infected with *Chlamydia*. The sponsor contends that the Compliance Pak will afford a convenient form of treatment since both drugs will be administered together as a single therapy for STD (i.e., in the clinic), and thus, will eliminate problems with patient compliance.

Trovafloxacin, a synthetic fluoronaphthyridone antibiotic, is similar in structure and mechanism of action to the fluoroquinolone class of antibiotics. It was recently approved by the Agency in December 1997 for a variety of infections and is marketed as 100 mg and 200 mg tablets (NDA 20-759) and as an alatrofloxacin (NDA 20-760). The approved oral dosage of trovafloxacin for treatment of uncomplicated gonorrhea caused by *N. gonorrhoeae* is 100 mg as a single dose.

Azithromycin is an azalide antibiotic, a subclass of the macrolides, which is currently approved and marketed in a variety of dosage forms including tablets, capsules, i.v. injection, pediatric suspension, and the single dose packet (or sachet) of powder for oral suspension. The single 1 gm packet was approved by the agency in September 1994

for the treatment of non-gonococcal urethritis/cervicitis due *C. trachomatis* (NDA 50-693).

II. SUMMARY

Indications and Dosage

Proposed Indications: Uncomplicated urethral gonorrhea in males and endocervical and rectal gonorrhea in females caused by susceptible strains of *Neisseria gonorrhoeae*; non-gonococcal urethritis/cervicitis due to susceptible strains of *Chlamydia trachomatis.* Sex partners of symptomatic or asymptomatic patients with gonorrhea are to be treated also.

Proposed Dosage: Azithromycin 1 gm single dose packet reconstituted in water as a suspension and one trovafloxacin 100 mg tablet. Both are to be co-administered.

The proposed labeling for this product is provided as ***Appendix 2.***

Clinical Pharmacology / Biopharmaceutics

Item 6 of the Compliance Pak NDA consists of one human pharmacokinetics study to evaluate the effect of co-administration of the 1 gm azithromycin packet, as a suspension, on the bioavailability of the trovafloxacin 100 mg tablet in healthy subjects. The NDA's for trovafloxacin and azithromycin have been previously reviewed and approved, and therefore, the remaining sections of the current Compliance Pak NDA cross-reference each of the corresponding trovafloxacin and azithromycin NDA's.

. However, since there is currently no clinical data which evaluates the safety/toleration or the potential for a pharmacokinetic (PK) interaction with co-administration of trovafloxacin and azithromycin, it was recommended by the Agency that such a safety, toleration and PK study be conducted in healthy adult subjects.

The major concern from a PK perspective is the potential for azithromycin to affect the oral absorption of trovafloxacin from the gastrointestinal tract presumably via a local alteration in gastric pH. The solubility profile of trovafloxacin is pH-dependent, with maximal solubility occurring at low pH (i.e., ~2) and minimal solubility occurring at neutral to high pH . Since the pH of the constituted 1 gm azithromycin suspension is >9.5, it is possible that the solubility, and hence, oral bioavailability, of co-administered trovafloxacin may be decreased.

A summary of **Protocol 156-056: The Effect of Azithromycin Sachet on the Absorption of a 100 mg Trovafloxacin Tablet** follows; *a more detailed review can be found in* ***Appendix 1.*** This was a randomized, open-label, two-way crossover study in 20 young healthy male (N = 4) and female (N = 16) subjects. All 20 subjects received a single 100 mg trovafloxacin tablet dose alone and with a single 1 gm dose of the azithromycin powder, reconstituted with water as a suspension, on separate occasions and under fasting conditions. The bioavailability of trovafloxacin was evaluated when co-administered with azithromycin and compared to when given alone. Subjects were monitored for adverse events and vital signs during the study. The mean PK and statistical results are shown in the following table:

Trovafloxacin Mean PK and Statistical Parameters

Parameter	Treatment	Mean* ± SD [Range] %CV	Mean Ratio** ± SD [Range]	Confidence Intervals (CI)
AUC(0-last) (mcg.hr/mL)	Trova + Azithro N = 20	14.2 ± 4.7 33.3%	0.99 ± 0.44	95% CI (0.80, 1.23)
	Trova N = 20	14.3 ± 6.3 44.1%		90% CI*** (0.83, 1.19)
Cmax (mcg/mL)	Trova + Azithro N = 20	1.3 ± 0.5 40.4%	0.92 ± 0.51	95% CI (0.71, 1.20)
	Trova N = 20	1.4 ± 0.6 44.0%		90% CI*** (0.75, 1.15)
Tmax (hr)	Trova + Azithro N = 20	1.7 ± 0.8 47.5%	Mean Difference** ± SEM 0.10 ± 0.24	95% CI (-0.4, 0.6)
	Trova N = 20	1.6 ± 0.8 51.8%		

*Adjusted geometric means for AUC(0-last) and Cmax; Adjusted arithmetic mean for Tmax
**Ratio for adjusted geometric means for AUC(0-last) and Cmax (i.e., [Trova + Azithro] / Trova); Difference between adjusted arithmetic means for Tmax (i.e., [Trova + Azithro] – Trova)
***Reviewer-determined 90% CI using two one-sided test procedure

The results indicated there was no significant effect of co-administration of azithromycin on the mean estimate of systemic exposure to trovafloxacin (AUC(0-last)). Although the mean peak serum concentration of trovafloxacin (Cmax) was slightly reduced when co-administered with azithromycin, this reduction will most likely be of minor clinical importance. The mean Tmax for trovafloxacin was not significantly affected by co-administration with azithromycin. In general, co-administration of the 1 gm single dose packet of azithromycin with a single 100 mg tablet dose of trovafloxacin had no significant effect on the systemic availability of trovafloxacin.

When co-administered with trovafloxacin, the serum azithromycin levels determined at 1.5 hrs postdose (i.e., approximately Cmax) ranged (mean (± SD) 0.867 ± 0.306 mcg/mL). This range of concentrations was similar to those reported in previous NDA reports for the 1 gm sachet at 1 to 2 hours after dosing (i.e., NDA 50-693, Studies 066-034 and 066-057).

Although there was no significant PK interaction when trovafloxacin and azithromycin were co-administered, the number of gastrointestinal (GI) side effects associated with the combination was substantial. Twenty-seven (27) of the 30 total adverse events associated with co-administration of trovafloxacin and azithromycin were GI related, and included nausea, abdominal pain, vomiting, diarrhea/loose stools. The GI adverse effects appeared to be primarily due to the administration of the 1 gm azithromycin dose. It is also important to note that two subjects experienced emesis at ~1.25 to 1.5 hrs after the co-administration of trovafloxacin with azithromycin. However, it appeared that the occurrence of emesis, with respect to the time of dosing, did not appreciably alter the systemic availability of either trovafloxacin or azithromycin. In addition, 2 other subjects, who had a substantial reduction in the systemic availability of trovafloxacin

when co-administered with azithromycin, also had diarrhea/loose stools within ~2 hrs after being dosed with the combination (*see* ***V. GENERAL COMMENTS*** *below for more details*).

III. RECOMMENDATION

Protocol 156-056; Section 6 of NDA 50-762 has been reviewed by OCPB. The sponsor's conclusion of no pharmacokinetic interaction when a single tablet dose of trovafloxacin 100 mg and a single dose of azithromycin 1 gm sachet are co-administered was found to be acceptable.

IV. COMMENTS FOR THE SPONSOR

There are no specific comments for the sponsor. The only comments to be conveyed to the sponsor pertain to the labeling and are provided in Appendix 2.

V. GENERAL COMMENTS NOT TO BE SENT TO THE SPONSOR

1. The following table summarizes the PK and adverse event data for subjects exhibiting trovafloxacin bioavailability at the extremes:

Subject #	Trt*	Trovan PK Parameters Cmax** (µg/mL)	Cmax** Ratio (A/B)	AUC** (µg.hr/mL)	AUC** Ratio (A/B)	Azithro Conc.*** (µg/mL)	Adverse Event (AE) Related to Trt A	Time of AE Post Dose (hr)
0004	A	1.8	1.00	20.8	1.10	1.059	Vomiting	1.6
	B	1.8		18.9				
0011	A	1.2	0.80	12.2	0.85	0.694	Vomiting	1.2
	B	1.5		14.4				
0006	A	0.6	0.43	7.3	0.60	0.281	Loose Stool	2.0
	B	1.4		12.2				
0007	A	0.9	0.53	10.1	0.48	1.204	Diarrhea	0.3
	B	1.7		21.0				
0014	A	0.4	0.20	9.5	0.43	0.858	Muscskel	2.4
	B	2.0		22.2			CNS	0.5
0016	A	1.2	1.71	15.9	1.79	0.924	None	—
	B	0.7		8.9				
0018	A	1.1	3.67	11.1	3.58	0.918	None	—
	B	0.3		3.1				

*A = Trova + Azithro; B = Trova alone

**Mean Trovafloxacin PK values for all 20 subjects:

A: Cmax 1.3 µg/mL; AUC 14.2 µg.hr/mL

B: Cmax 1.4 µg/mL; AUC 14.3 µg.hr/mL

Ratios (A/B): Cmax 0.92; AUC 0.99

***Determined at 1.5 hrs postdose; Mean (± SD) azithromycin conc. for all 20 subjects 0.867 ± 0.306 µg/mL

It appeared that the occurrence of vomiting, with respect to the time of co-administration of trovafloxacin and azithromycin, did not appreciably alter the systemic availability of either trovafloxacin or azithromycin for subjects 0004 and 0011. In another 3 subjects (0006, 0007, 0014), trovafloxacin bioavailability was substantially reduced by approximately 50% or greater, and 2 of these subjects (0006 and 0007) had diarrhea or

loose stools within 2 hrs of co-administration of trovafloxacin with azithromycin. The incidence of a substantial reduction in trovafloxacin oral availability in this study was 15% (i.e., 3/20 subjects). As can be seen in the table below, the incidence of a similar reduction in trovafloxacin availability was observed to be 3.6% (1/28 subjects) in one single dose PK study of the 100 mg TROVAN® tablet in NDA 20-759; the combined incidence for all three 100 mg NDA tablet studies was 2.4% (1/42 subjects).

NDA 20-759: Single Dose PK Studies of Trovan® 100 mg Tablet in Healthy Subjects

Study #	Mean ± SD Cmax (mcg/mL) [Range]	Mean ± SD AUC (mcg.hr/mL) [Range]
154-043 N=28 **Values ≤ 50% of Mean**	1.0 ± 0.3 (CV 30%) **0.4 mcg/mL (1/28; 3.6%)**	12.5 ± 3.8 (CV 30%) **6.2 mcg.hr/mL (1/28; 3.6%)**
154-002 N=8 **Values ≤ 50% of Mean**	1.0 ± 0.3 (CV 30%) **None**	11.2 ± 2.2 (CV 20%) **None**
154-006 N=6 **Values ≤ 50% of Mean**	1.1 ± 0.2 (CV 18%) **None**	9.0 ± 1.7 (CV 19%) **None**

Although the incidence of low trovafloxacin bioavailability in the present study (15%) does not appear to be consistent with that of previous NDA studies, it is important to note that the range of all subjects' values for Cmax and AUC are consistent between the present and previous NDA studies.

The apparent increase in trovafloxacin bioavailability observed for subjects 0016 and 0018 of the present study appeared to be due to the below average values for AUC(0-last) and Cmax when trovafloxacin was given alone, rather than an above average increase in these parameters when the two drugs were given in combination.

Although there appears to be no consistent link between low trovafloxacin bioavailability and GI adverse events observed from the present study, the GI side effects may still be a *potential* concern with respect to both safety and efficacy when the 100 mg trovafloxacin tablet and the 1 gm azithromycin sachet are co-administered in the clinical setting to patients with sexually transmitted disease.

2. concern was expressed by the Agency (i.e., OCPB, DPE 3/HFD-880) over the potential for a tissue displacement interaction between trovafloxacin and azithromycin. Since both drugs appear to distribute extensively into various tissues and/or intracellular components (e.g., azithromycin into cell lysosomes), displacement of one drug by the other from the target site(s) of action may result in a reduction in therapeutic effect. Displacement may also result in an unexpected increase in serum trovafloxacin or azithromycin concentrations, which may be misinterpreted as being the result of, for example, altered metabolism, excretion, oral bioavailability, etc. In view of this, it was recommended that the sponsor consider

performing an *in vitro* displacement interaction study between trovafloxacin and azithromycin using peripheral polymorphonuclear cells (i.e., PMN's). It was also recommended that if the sponsor believed this type of study was not needed, then a response in writing providing the rationale against it should be submitted to the Agency.

The response from the sponsor was that such a displacement interaction between trovafloxacin and azithromycin, when co-administered, would be unlikely primarily because the intracellular location and mechanism of cellular uptake of the two drugs appear to be different. This reasoning was supported by literature citations provided by the sponsor. Azithromycin is primarily found in cell lysosomes , with the remainder found in the cytosolic fraction. Trovafloxacin and other quinolones appear to be primarily localized in the cytosolic portion of the cell. For azithromycin, the mechanism of uptake into PMN's and other cell lines appears to involve both active, as well as passive, transport processes. Intracellular accumulation of azithromycin appears to be rapid, extremely extensive, saturable, and energy and pH dependent. Trovafloxacin uptake by PMN's appears to be primarily via passive diffusion, since it has been shown to be reversible, nonsaturable and not energy dependent. Thus, the reviewer agrees with the sponsor's conclusion that a displacement interaction would not be expected to occur.

/S/ 8/12/98

Philip M. Colangelo, Pharm.D., Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

APPEARS THIS WAY
ON ORIGINAL

/S/ 8/12/98

RD/FT signed by Funmi Ajayi, Ph.D (TL)
Clin Pharm/Biopharm Briefing Attendees (8/6/98): F. Ajayi, J. Lazor, A. Selen, B. Leissa, R. Alivisatos, L. Kimzey
cc:
Div. File: NDA 50-762
HFD-590 (R. Alivisatos, MO; B. Leissa, TL/MO)
HFD-590 (R. Anderson, PM/CSO)
//
//
HFD-340 (Viswanathan)
HFD-205 (FOI)
HFD-880 (Division File)
HFD-880 (F. Ajayi; P. Colangelo)
CDR (Barbara Murphy)

APPEARS THIS WAY
ON ORIGINAL

7 PAGES REDACTED

CONTAINED TRADE SECRETS and/or CONFIDENTIAL/ COMMERCIAL INFORMATION

5 Page(s) Redacted

DRAFT LABELING

APPENDIX 2:

PROPOSED LABELING
(Version 8-20-1998)

With
SUGGESTED CHANGES / COMMENTS

32 Page(s) Redacted

DRAFT LABELING

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050762

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

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ORIGINAL

NEW CORRESP
NC

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Malvina Laudicina
Director
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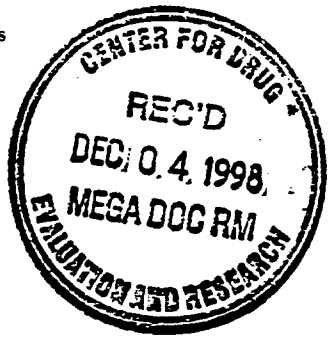


December 3, 1998

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research (HFD-590)
Office of Drug Evaluation IV
ATT: Document Control Room # 12B-30
5600 Fishers Lane
Rockville, MD 20857

RE : NDA 50-762-TROVAN/ZITHROMAX Compliance Pak for STDs
(trovafloxacin tablets)/(azithromycin for oral suspension)

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Goldberger:

Per our conversation with Ms. Robin Anderson, enclosed please find the debarment statement for NDA 50-762.

"In accordance with the requirements of the Generic Drug Enforcement Act of 1992, and in connection with this Application, to the best of its knowledge, Pfizer Inc. did not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetics Act."

Questions or comments on the attached should be forwarded to the undersigned.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Malvina Laudicina

14. PATENT CERTIFICATION

With respect to the antibacterial drug, TROVAN® (trovafloxacin mesylate) Tablets, which is the subject of this application (NDA-50-762) and the U.S. patent which is listed in Section 13 of NDA 50-762, Pfizer certifies that TROVAN® and formulations and uses thereof are claimed by U.S. Patent No. 5,164,402.

APPEARS THIS WAY
ON ORIGINAL

Attachment I

TROVAN® Tablets (Trovafloxacin Mesylate)

13. PATENT AND EXCLUSIVITY INFORMATION FOR TROVAFLOXACIN

1.	Active ingredients:	a)	**Trovafloxacin mesylate** (1a, 5a, 6a)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monomethanesulfonate
2.	Strength	a)	**Trovafloxacin mesylate** 100 mg
3.	Trade Name:	a)	**Trovafloxacin mesylate** TROVAN® Tablets
4.	Dosage Form/Route of Administration:	a)	**Trovafloxacin mesylate** Tablets/Oral
5.	Applicant Firm Name:	**Pfizer Inc.**	
6.	NDA Number:	a)	NDA 50-762 (See **Trovafloxacin mesylate** NDA-20-759)
7.	Exclusivity Period:	a)	**Trovafloxacin mesylate** Sixty months (5 years) from the date of approval of NDA-20-759
8.	Applicable Patent Number and Expiration Date:	**Patent Number:** 5,164,402 **Expiration Date:** November 17, 2009	

EXCLUSIVITY SUMMARY FOR NDA # 50-762 SUPPL #_____

Trade Name:Trovan/Zithromax Combination Pak
Generic Name: trovafloxacin/azithromycin
Applicant Name: Pfizer, Inc. HFD # 590
Approval Date If Known: 12/ /98

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES /X/ NO /___/

b) Is it an effectiveness supplement? YES /___/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") YES /__/ NO /X/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

At the 6/27/98 pre-NDA meeting for this dual treatment package Pfizer was advised by FDA to perform a pharmacokinetic study to assess the effect of azithromycin in the absorption of trovafloxacin. This application contained a single clinical study report for the interaction study that was done to satisfy that requirement.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety? No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

Form OGD-011347 Revised 10/13/98
cc: Original NDA Division File HFD-93 Mary Ann Holovac

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such) YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is

marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.) YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

TROVAN	NDA# 20-759 and 20-760	12/18/97
ZITHROMAX	NDA# 50-693	9/28/94

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation. YES /___/ NO /X/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement? YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application? YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO. YES /___/ NO /___/
If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product? YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and

the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #_____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

Signature: /S/ Date: 12/7/98
Title: Project Manager

Signature of Office/Division Director: /S/ Date: 12/18/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	50762	**Trade Name:**	TROVAN/ZITHROMAX(TROVAFLOXACIN/AZITHROMY
Supplement Number:		**Generic Name:**	TROVAFLOXACIN/AZITHROMYCIN ORAL SUSP
Supplement Type:		**Dosage Form:**	
Regulatory Action:		**Proposed Indication:**	Sexually Transmitted Diseases

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Status -
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Not intended for pediatric use.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, ROBIN ANDERSON

/S/
Signature

12/2/98
Date

APPEARS THIS WAY
ON ORIGINAL

Pfizer Pharmaceuticals Group
Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York. NY 10017-5755
Tel 212 573 1106 Fax 212 857 3558
Email laudim@pfizer.com

ORIGINAL

NEW CORRESP

NC

Pfizer Pharmaceuticals

December 8, 1998

Malvina Laudicina
Director
Regulatory Affairs

Robin Anderson, CSO
Food and Drug Administration
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research HFD –590
Room S-438
Office of Drug Evaluation IV
9201 Corporate Boulevard
Rockville, MD 20857

APPEARS THIS WAY
ON ORIGINAL

RE: Patient Information Leaflet

Dear Ms. Anderson:

Reference is made to our pending NDA 50-762 for Zithromax/Trovan Compliance Pak filed on December 17, 1997.

Attached please find the revised version of the patient information leaflet for NDA 50-762 "Zithromax/Trovan Compliance Pak".

We have incorporated all the changes received by the division.

If you have any questions, please call the undersigned at (212) 573-1106.

Sincerely,

Malvina Laudicina
ML/rr

APPEARS THIS WAY
ON ORIGINAL

Cc: Felicia Feldman (FIO File)

Pfizer Pharmaceuticals Group
Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 1106 Fax 212 857 3558
Email laudim@pfizer.com

ORIGINAL

Pfizer Pharmaceuticals

NEW CORRESP
NC

Malvina Laudicina
Director
Regulatory Affairs

December 3, 1998

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research (HFD-590)
Office of Drug Evaluation IV
ATT: Document Control Room # 12B-30
5600 Fishers Lane
Rockville, MD 20857

RE : NDA 50-762-TROVAN/ZITHROMAX Compliance Pak for STDs
(trovafloxacin tablets)/(azithromycin for oral suspension)

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Goldberger:

Per our conversation with Ms. Robin Anderson, enclosed please find the debarment statement for NDA 50-762.

"In accordance with the requirements of the Generic Drug Enforcement Act of 1992, and in connection with this Application, to the best of its knowledge, Pfizer Inc. did not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetics Act."

Questions or comments on the attached should be forwarded to the undersigned.

APPEARS THIS WAY
ON ORIGINAL

Sincerely,

M Laudicina
Malvina Laudicina

ORIGINAL

Pfizer Pharmaceuticals Group
Regulatory Affairs Division
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 1106 Fax 212 857 3558
Email laudim@pfizer.com

NDA ORIG AMENDMENT
BB

Pfizer Pharmaceuticals

Malvina Laudicina
Director
Regulatory Affairs

November 30, 1998

Robin Anderson , RN, MBA
Project Manager
Division of Special Pathogens and Immunologic
Drug Products (HFD 590)
Office of Drug Evaluation IV
Document Control Room # 12B-30
9201 Corporate Boulevard
Rockville, Maryland 20850

APPEARS THIS WAY
ON ORIGINAL

RE: Revised version of the PI for the "Compliance Pak" for NDA 50-762.

Dear Robin:

This is the second submission of this document and disk as the first one was never received.

Attached is the revised version of the PI for the "Compliance Pak" for NDA 50-762.
Per your request, the document is in Word format. The new revisions are in Italics and Courier New font for the convenience of the reviewer.
Dr. Leissa requested that a table with the pharmacokinetic data for the simple dose was introduced on page 7. The data used to create the table was obtained from study 066-057 entitled: "Protocol 057. A Phase I Open, Randomized Study of the Clinical Pharmacology of Azithomycin after 1g of the sachet with and without food Compared with the intravenous formulation in Normal Healthy Subjects", which was submitted as part of the original application on February 15, 1994 to NDA 50-711.

If you have any questions do not hesitate to call me.

Sincerely,

Malvina Laudicina/J. Delcossche.

Malvina Laudicina

APPEARS THIS WAY
ON ORIGINAL

Pfizer Pharmaceuticals Group
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

BB
ORIG AMENDMENT

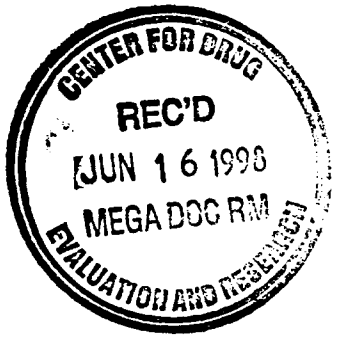
ORIGINAL

Pfizer Pharmaceuticals

Robert B. Clark
Associate Director/Group Leader—Drug Regulatory Affairs

June 15, 1998

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research HFD-590
Office of Drug Evaluation IV
ATT: Document Control Room #12B-30
5600 Fishers Lane
Rockville, Maryland 20857



RE: NDA 50-762
TROVAN (trovafloxacin mesylate) Tablets/ZITHROMAX (azithromycin for oral suspension) Compliance Pak for STDs

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Goldberger:

Reference is made to our New Drug Application for TROVAN (trovafloxacin mesylate) Tablets/ZITHROMAX (azithromycin for oral suspension) Compliance Pak for STDs, NDA 50-762 submitted on December 18, 1997. Further reference is made to a May 19, 1998 request from Dr. Philip Colangelo of HFD-590 for a compilation of the adverse event data that was reported for the various food effect pharmacokinetic studies conducted with doses of 1000 mg or greater of azithromycin.

The requested information is attached. Also included, per Dr. Colangelo's request, is disk with the current proposed package insert for this application included as an MS WORD file.

Please include this information in the subject file.

APPEARS THIS WAY
ON ORIGINAL

Sincerely,

Robert B Clark

Robert B. Clark
Desk Copy: Dr. Philip Colangelo (HFD-590), Ms. Robin Anderson (HFD-590)

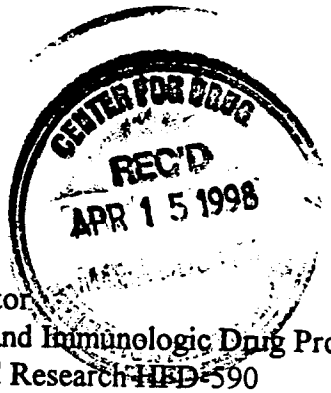
Pfizer Pharmaceuticals Group
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

NC
ORIGINAL

Pfizer Pharmaceuticals

Robert B. Clark
Associate Director/Group Leader—Drug Regulatory Affairs

April 14, 1998



Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research HFD-590
Office of Drug Evaluation IV
ATT: Document Control Room #12B-30
5600 Fishers Lane
Rockville, Maryland 20857

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Goldberger:

RE: NDA 50-762 TROVAN/ZITHROMAX Compliance Pak for STDs
(trovafloxacin mesylate tablets)/(azithromycin for oral suspension)

Dear Dr. Goldberger:

Reference is made to our pending New Drug Application for a Trovan/Zithromax Compliance Pak, NDA 50-762 filed on December 18, 1997. This NDA requested approval of a dual treatment pack consisting of a single 100 mg TROVAN (trovafloxacin mesylate) tablet and a 1 gram Single Dose Packet of Zithromax (azithromycin for oral suspension). The product will be used as a single dose regimen (allowing directly observed therapy) in subjects with acute gonococcal urethritis/cervicitis due to *Neisseria gonorrheae* and non-gonococcal urethritis/ cervicitis due to *Chlamydia trachomatis*.

During a recent conversation between Dr. Philip Colangelo of the division and the undersigned, Pfizer was requested to confirm that the pharmacokinetic data contained in the clinical study report was identical to the data provided earlier in an electronic format to Dr. Colangelo.

Please be assured that the pharmacokinetic data contained in the final clinical study report are identical to the electronic version of the data provided to Dr. Colangelo in support of his review of this application.

Questions or comments on this issue should be addressed to Mr. Robert Clark at (212) 573-3412.

Sincerely,

Robert B. Clark

APPEARS THIS WAY
ON ORIGINAL

Robert B. Clark

Desk Copy: Ms. Ellen Frank, Supervisory Project Manager (HFD-590)
Dr. Philip Colangelo, Biopharmaceutics Reviewer (HFD-590)

APPEARS THIS WAY
ON ORIGINAL

Pfizer Pharmaceuticals Group
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

Pfizer

ORIG AMENDMENT

ORIGINAL

Pfizer Pharmaceuticals

Robert B. Clark
Associate Director/Group Leader—Drug Regulatory Affairs

March 17, 1998

ark Goldberger, M.D., Director
ivision of Special Pathogens and Immunologic
rug Products (HFD 590)
ffice of Drug Evaluation IV
TT: DOCUMENT CONTROL ROOM #12B-30
600 Fishers Lane
ockville, MD 20857

APPEARS THIS WAY
ON ORIGINAL

ear Doctor Goldberger:

E: NDA-50-762 - TROVAN®/ZITHROMAX® Compliance Pak for STDs (trovafloxacin tablets)/(azithromycin for oral suspension)
RESPONSE TO FDA REQUEST FOR INFORMATION

eference is made to our pending New Drug Application, submitted on December 18, 1997. eference is also made to a February 11, 1998 telecon with Ms. Pauline Fogarty, Project anager and Dr. Regina Alivisatos, Medical Reviewer.

nclosed is the final study report for this study. Please note that preliminary data provided to e Division in the NDA is no different than that contained in the final study report.

desk copy of this submission is being provided to Drs. Alivisatos and Philip Colangelo, and a opy of the cover letter will be provided to Ms. Fogarty.

you have any questions regarding this submission, please contact the undersigned at (212) 73-3412. Please include this information in our files for NDA-50-762.

Sincerely yours,

for Robert B. Clark

APPEARS THIS WAY
ON ORIGINAL

54-056- entitled, "The Effect of Azithromycin Sachet on the Absorption of a 100 mg Trovafloxacin Tablet."

esk Copy: Dr. Alivisatos, Dr. Colangelo (Complete)
Ms. Fogarty (Cover Letter Only)

Pfizer Pharmaceuticals Group
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

BC
Amendment
NC
NEW CORRESP
ORIGINAL

Pfizer Pharmaceuticals

Robert B. Clark
Associate Director/Group Leader—Drug Regulatory Affairs

February 27, 1998

reviewed
/S/ 4/15/98

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research HFD-590
Office of Drug Evaluation IV
ATT: Document Control Room #12B-30
5600 Fishers Lane
Rockville, Maryland 20857

APPEARS THIS WAY
ON ORIGINAL

RE: NDA 50-762 TROVAN/ZITHROMAX Compliance Pak for STDs
(trovafloxacin mesylate tablets)/(azithromycin for oral suspension)

Dear Dr. Goldberger:

Reference is made to our pending New Drug Application for a Trovan/Zithromax Compliance Pak, NDA 50-762 filed on December 18, 1997. This NDA requested approval of a dual treatment pack consisting of a single 100 mg TROVAN (trovafloxacin mesylate) tablet and a 1 gram Single Dose Packet of Zithromax (azithromycin for oral suspension). The product will be used as a single dose regimen (allowing directly observed therapy) in subjects with acute gonococcal urethritis/cervicitis due to *Neisseria gonorrheae* and non-gonococcal urethritis/ cervicitis due to *Chlamydia trachomatis*.

Following conversations with Ms. Pauline Fogarty of the division, Pfizer was requested to provide Environmental Assessment information related to this NDA. Attached please find a Claim for Categorical Exclusion per 21 CFR 25.15(a)(d). Please include this information in the subject file. Questions or comments on this issue should be addressed to the undersigned at (212) 573-3412.

Sincerely,

Robert B. Clark

APPEARS THIS WAY
ON ORIGINAL

Desk Copy: Ms. Pauline Fogarty (HFD-590)

Pfizer Pharmaceuticals Group
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

Pfizer Pharmaceuticals

Robert B. Clark
Associate Director/Group Leader—Drug Regulatory Affairs

BL

ORIGINAL

February 2, 1998

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research HFD-590
Office of Drug Evaluation IV
ATT: Document Control Room #12B-30
5600 Fishers Lane
Rockville, Maryland 20857

APPEARS THIS WAY
ON ORIGINAL

RE: NDA 50-762
TROVAN (trovafloxacin mesylate) Tablets/ZITHROMAX (azithromycin for oral suspension) Compliance Pak for STDs

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Goldberger:

Reference is made to our New Drug Application for TROVAN (trovafloxacin mesylate) Tablets/ZITHROMAX (azithromycin for oral suspension) Compliance Pak for STDs, NDA 50-762 submitted on December 18, 1997.

At this time we are submitting an updated package insert reflecting the inclusion of information regarding the final approved labeling for NDAs 20-759 and 20-760 (TROVAN tablets and I.V.)

Please include this information in the subject file.

APPEARS THIS WAY
ON ORIGINAL

Sincerely,

Robert B. Clark Jr

Robert B. Clark

Desk Copies: Ms. Pauline Fogarty, Project Manager (HFD-590)
8 full sets

Pfizer Pharmaceuticals Group
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 3412 Fax 212 573 1563

ORIGINAL

BM

ORIG ARCHIVE

Pfizer Pharmaceuticals

obert B. Clark
ssociate Director, Group Leader—Drug Regulatory Affairs

New Dr 1/22/98

January 21, 1998

oldberger, M.D., Director
of Special Pathogens and Immunologic
oducts (HFD 590)
of Drug Evaluation IV
OCUMENT CONTROL ROOM #12B-30
ishers Lane
lle, MD 20857

Doctor Goldberger:

NDA-50-762 - TROVAN®/ZITHROMAX® Compliance Pak for STDs (trovafloxacin tablets)/(azithromycin for oral suspension)
RESPONSE TO FDA REQUEST FOR INFORMATION
GENERAL CORRESPONDENCE

ence is made to our pending New Drug Application, submitted in hard-copy on December 997. Reference is also made to a teleconference on January 9, 1998 with Dr. Regina atos, Medical Reviewer and her request that all of the Case Report Forms (CRFs) for **#154-056*** be provided electronically.

anuary 21, 1998 Pfizer delivered electronic copies of the CRFs per Dr. Alivisatos' request nstalled them on the Pfizer Esub server.

se note that on this date the electronic archive copy of the CRFs and CRTs were also nitted to the Document Control Room. However the details regarding this submission are g provided in a separate cover letter.

isk copy of this cover letter is being provided to Ms. Pauline Fogarty, Project Manager, Dr. satos, and Dr. Brad Leissa, Medical Team Leader.

ou have any questions regarding this submission, please contact the undersigned at (212) -3412. Please include this information in our files for NDA-50-762.

Sincerely yours,

Linda Bulkowitch

for: Robert B. Clark

ik Copies: Ms. Fogarty
Dr. Alivisatos
Dr. Leissa

ial No. 0 0 2

154-056, entitled, "The Effect of Azithromycin Sachet on the Absorption of 100 mg Trovafloxacin Tablet."

MEMORANDUM OF TELEPHONE CONFERENCE WITH INDUSTRY

DATE: July 9, 1998

NDA: 20-759 and 20-760

DRUG: Trovan®

APPLICANT: Pfizer, Inc.
235 E. 42nd Street
New York, NY 10017
Telephone 212-573-3412
Fax 212-573-1563

MEETING CHAIR: Brad Leissa, M.D.
SPONSOR CHAIR: Robert Clark
MEETING RECORDER: Mary Dempsey

FDA ATTENDEES:
Dianne Murphy, M.D., ODE IV Office Director
Mark Goldberger, M.D., M.P.H., Division Director
Brad Leissa, M.D., Medical Team Leader
Regina Alivisatos, M.D., Medical Officer
Sally Singer, R.Ph., Pharmacist
Toni Piazza-Hepp, R.Ph., Pharmacist
Carolyn McCloskey, M.D., Medical Officer
David Graham, M.D., Medical Officer
Evelyn Rodriquez, M.D., Medical Officer
Jo Ann Spearmon, M.P.A., Pharm.D.
Mary Dempsey, Project Manager

APPLICANT ATTENDEES:
Robert Clark, Associate Director Regulatory Affairs
Gretchen Dieck, M.D.
Ann Kolokathis, M.D.
Scott Hopkins, M.D.
Debra Williams
Judy Lieberman
Maggie Longshore

This teleconference is a follow up to our FAX of June 30, 1998 and your subsequent FAX of July 7, 1998. The purpose of this telecon is to negotiate final TROVAN labeling changes.

Pfizer and the FDA representatives agreed to the following TROVAN labeling changes:

FDA representatives explained the Agency's concern that the current TROVAN drug reporting (as it pertains to patients who fit the case definition) appears to be incomplete and untimely. We reminded the company of the original May 14, 1998 teleconference where a case definition was established and the timeframe for how serious and non-serious events should be reported.

While we appreciate the efforts of Pfizer to achieve this reporting objective, we emphasized that the amount of information and timelessness of reporting is the means by which we can accurately characterize the drug's toxicity. With this in mind, we all agreed that we might need to revisit the label and/or address the means to inform prescribers in the future. (E.g., the association of TROVAN-induced pancreatitis and underlying diabetes mellitus becomes more certain.)

The telecon closed amicably.

Signature, minutes preparer /S/ Date 7/10/98

Concurrence Chair (or designated signatory) /S/ Date 7/10/98