

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 050762**

**MEDICAL REVIEW(S)**

Medical Officer's Review of NDA 50 - 762

Date Received: December 17, 1997  
Date Assigned: December 30, 1997  
Date Review Started: January 7, 1998  
Date 1<sup>st</sup> Draft Completed: January 30, 1998  
Date 2<sup>nd</sup> Draft Completed: May 15, 1998

Applicant: Pfizer Inc.  
235 East 42<sup>nd</sup> St.  
New York, NY  
10017

Drug Name: Trovafloxacin Mesylate/Azithromycin

Proprietary Name: Trovan®/Zithromax®

Pharmacologic Category: Trovafloxacin: a fluoronaphthyridone related to the fluoroquinolone antimicrobials.

Azithromycin: an azalide, a subclass of the macrolide antimicrobials.

Chemical Name: Trovafloxacin: (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

Azithromycin: (2R,3S,4R, 5R, 8R, 10R, 11R, 12S, 13S, 14R)-[(2,6-dideoxy-3-C-methyl-O-a-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[[3,4,6-trideoxy-3-(dimethylamino)-b-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

Dosage Form: Tablet/Oral suspension

Route of Administration: Oral

Strengths: 100mg/ 1g suspension

Proposed Indication and Usage: Compliance Pak for the treatment of sexually transmitted diseases. This product will be used as a single dose therapy in patients with acute gonococcal urethritis/cervicitis due to *Neisseria gonorrhoeae* and non-gonococcal urethritis/cervicitis due to *Chlamydia trachomatis*.

Proposed Dosage and Administration: 1 gm oral suspension (single dose packet reconstituted in 60 mL water) azithromycin and a single 100 mg tablet of trovafloxacin "Drink the entire contents immediately after reconstitution: add an additional 2 ounces of water, mix, and rinse. Use the rinse to swallow the tablet and drink the entire contents to ensure complete consumption of the dosage."

Related INDs and NDAs: NDA 20-759  
NDA 50-693

List of Currently Approved Indications: None for this dual formulation.

Materials Reviewed: Electronic Submission/January 15, 1998

10 Volume submission dated December 17, 1997

NDA 50-693/Section 6/Clinical Study Report for a Phase I Bioequivalency Study comparing Azithromycin Sachet to 250 mg capsules dated April 4, 1992.

NDA 50-670/Vol. 237/Clinical Study Report of a pilot study to compare the gastrointestinal effects of oral azithromycin when given as a single dose and over a defined period of time in parallel groups of healthy volunteers.

Clinical study Report of protocol 066-072/”A Placebo-Controlled Study to Compare the Gastrointestinal Effects of Different Formulations of Azithromycin when given as a Single Dose to Parallel Groups of Healthy Volunteers.”

**Regulatory Background:**

- Trovafloxacin 100 mg orally (single dose), was approved (NDA 20 – 759/December 18, 1997) for the treatment of uncomplicated gonorrhea in males and endocervical and rectal gonorrhea in females (caused by *Neisseria gonorrhoeae*). Additionally it was approved for the treatment of cervicitis due to *Chlamydia trachomatis* at a dose of 200 mg orally for 5 days. NOTE: In males with nongonococcal urethritis, trovafloxacin was somewhat less effective than doxycycline.
- Azithromycin 1 gm orally (single dose) was approved (NDA 50 –693/September 28, 1994) for the treatment of non-gonococcal urethritis and cervicitis due to *Chlamydia trachomatis*. It has also been approved as a single 2 gm oral dose for the treatment of gonorrhea however this dose is not well tolerated (gastrointestinal AEs).
- CDC recommendation is to treat for *Chlamydia trachomatis* sexually-related infections when treating patients for gonorrhea as approximately \_\_\_\_\_ of males and \_\_\_\_\_ of females diagnosed with urethritis/cervicitis caused by *Neisseria gonorrhoeae* are also infected with *Chlamydia trachomatis*. As per the applicant, “it would be very convenient to treat both infections at the same time with a single treatment.”

**Chemistry/Manufacturing Controls:** Please see the Chemistry Review

**Microbiology:** The applicant submitted the results of susceptibility assays of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* to azithromycin and trovafloxacin in combination.

For *Chlamydia trachomatis* the MIC at which there was a 90% reduction in ifu was determined by comparing the ifu in the antibiotic-free well with the number of ifu at each concentration of azithromycin and trovafloxacin. The MIC-100 was the concentration at which there were no inclusions.

Similarly, for *Neisseria gonorrhoeae*, the concentration at which there was no visible growth was plotted. Fractional inhibitory concentrations were plotted for all MICs and were in all cases less than 2mcg/mL, indicating that there was no antagonism between the antimicrobial agents.

The applicant concluded that the addition of trovafloxacin did not raise the MIC of azithromycin for *Chlamydia trachomatis*. For all isolates tested (N = 20), the measurement of the MIC-100 showed a synergistic interaction between azithromycin and trovafloxacin. In the case of the MIC-90s, a synergistic interaction was shown for 15 of the isolates tested and no interaction was shown in the remaining 5.

The addition of azithromycin did not increase the MIC of trovafloxacin for *Neisseria gonorrhoeae*. 20 isolates were tested and in 12 of these, a synergistic interaction was shown between the 2 agents. In the remaining 8, no interaction was shown.

The applicant concluded “for these 2 organisms, trovafloxacin and azithromycin appear to work in some degree in synergy or they are autonomous (i.e. they do not interact significantly).”

The MIC (mcg/mL) for trovafloxacin versus *Neisseria gonorrhoeae* is  $\leq 0.125$  and the MIC for azithromycin versus this organism is  $\leq 2$ .

**Human Pharmacokinetics:** This application contained a single clinical interaction study (#154-056) intended to examine the effect of co-administration of the commercially approved 1 gram packet of azithromycin on the bioavailability of the 100 mg tablet of trovafloxacin.

The results are summarized below:

1. Co-administration with the 1 gram packet (sachet) of azithromycin does not effect the bioavailability of a 100 mg tablet of trovafloxacin.
2. Co-administration with a 100 mg tablet of trovafloxacin produced serum concentrations 1.5 hr post-dose similar to or greater than those observed in a previous study with the 1 gram packet of azithromycin.

**Relationship of Pharmacokinetics and Efficacy:**

The pharmacokinetics of trovafloxacin were unaltered by co-administration with azithromycin and azithromycin had some activity versus *Neisseria gonorrhoeae*. Therefore, as per the applicant, dual therapy with trovafloxacin and azithromycin should be at least as effective as monotherapy with trovafloxacin in treatment of infections due to *Neisseria gonorrhoeae*.

Additionally, since the concentrations of azithromycin were at least as high as those observed following another study with the 1 gram packet and trovafloxacin has some activity against *Chlamydia trachomatis*, dual therapy with azithromycin and trovafloxacin should be at least as effective as azithromycin alone in treatment of sexually transmitted disease due to infection with *Chlamydia trachomatis*.

For further information, refer to the pharmacokinetic review.

**Human Clinical Experience:** The proposed dual packet has not been tested previously in humans in the US or foreign markets.

**Clinical Studies:** Pertinent to this review was a single PK study performed to satisfy FDA PK requirements. This study, #154-056 entitled "The Effect of Azithromycin Sachet on the Absorption of a 100 mg Trovafloxacin Tablet" also provided safety information in 20 subjects who received the 1 gm azithromycin single dose packet and a single dose trovafloxacin 100 mg tablet concurrently. No studies pertaining to efficacy were included in the current submission.

**Clinical Study Review:**

**Study Title:** The Effect of Azithromycin Sachet on the Absorption of a 100 mg Trovafloxacin Tablet.

**Study Dates:** July 24, 1997 – August 24, 1997

**Study Sites:** (Copied from page 4 of the study report)

		PRINCIPAL INVESTIGATOR
		SUBINVESTIGATORS
COUNTRY	CENTER	LOCATION OF STUDY SITE
United States	9599	Thomas Hunt, M.D. Jacque Haas Aziz Laurent, M.D. Olga Obrda Carla Sargent Joyce Winkle, D.P.M.
		PPD Pharmaco, Inc., Clinics 706A Ben White Boulevard West Austin, TX 78704

**Study Objective:**

To study the effect of co-administration of a 1 gram dose of azithromycin formulated as a sachet on the bioavailability of trovafloxacin from the commercial 100 mg tablet and to examine the safety/tolerability of the combined medication.

**Study Design:**

This was an open, randomized, two-way, crossover study, in which healthy, fasting volunteers received the 100 mg commercial tablet of trovafloxacin on one occasion and on another occasion the 100 mg commercial tablet of trovafloxacin co-administered with 1 gm of azithromycin formulated as a sachet.

Subjects were assigned to one of two possible randomization sequences with equal frequency according to a computer generated pseudo-random list. There was a washout period of at least 14 days between the treatments. The study had institutional review board approval and all subjects provided written informed consent.

Prior to inclusion in the study, subjects underwent a complete medical history. A blood sample was collected for clinical chemistry and hematology, and a urine sample was obtained for urinalysis and drug screen. Further clinical laboratory tests were not done unless required. Blood pressure and pulse rate were measured at screening and prior to dosing on days 1 and 15. Upon satisfaction of the entrance criteria, subjects were enrolled in the study and assigned a subject identification number. In females of child-bearing potential a serum pregnancy test was done at screening, and a urine pregnancy test was done prior to dosing on days 1 and 15.

For each treatment, subjects were confined to the clinical research facility under continuous medical or paramedical observation for at least 8 hours prior to and at least 24 hours following dosing. Subjects fasted at least 8 hours before and 4 hours after study drug administration. Trovafloxacin or trovafloxacin plus azithromycin was administered on study days 1 and 15 in open fashion under clinical supervision at approximately 7:00 AM. The 100 mg tablet of trovafloxacin was administered with 240 mL of water when it was administered alone.

The dosing regimen for the combined treatment was as follows: Following the approved procedure for administration of the 1 gram sachet of azithromycin, the contents of a single 1 gm packet were transferred into a glass container. 60 mL of water was added to the powder and stirred to dissolve/suspend the powder. This suspension was then ingested. 60 mL of additional water was then added to the glass container and stirred to suspend any remaining powder. The 100 mg tablet of trovafloxacin was then swallowed with this additional 60 mL of water. Two additional 60 mL rinses of the glass container were then consumed for a total volume of 240 mL of water.

Blood sufficient to provide a minimum of 2.5 mL of serum for the determination of trovafloxacin concentrations was collected at 0 (just prior to dosing), 0.5, 1, 2, 3, 4, 8, 12, 16, 24, and 36 hr after drug administration. At the discretion of the investigator, subjects might have been discharged after the 24 hr sample but returned to the clinic for the collection of the remaining blood sample. Blood sufficient to provide a minimum of 2.0 mL serum for determination of azithromycin concentrations was collected from subjects receiving azithromycin at 1.5 hr after drug administration. Serum samples were analyzed for trovafloxacin utilizing \_\_\_\_\_ Serum samples of azithromycin were to be analyzed with \_\_\_\_\_ which had \_\_\_\_\_

The pharmacokinetic parameters of  $C_{max}$ ,  $T_{max}$ , and  $AUC_{last}$  for trovafloxacin were calculated.

Subjects were monitored for adverse experiences throughout the study period. All observed or volunteered adverse experiences were recorded and documented according to onset, duration, severity (mild, moderate, severe), and the investigator's assessment of the possible relationship to study drugs. All serious adverse events regardless of treatment group or suspected relationship to study drug were reported immediately to \_\_\_\_\_

the applicant by telephone. If a subject dropped out or was terminated from the study by the investigator, a final physical exam was performed.

**Protocol Overview:**

This was an open, randomized, 2-period, 2-treatment, crossover study, using single doses of 100 mg of trovafloxacin with and without 1 gm of azithromycin. Subjects were screened within a 28 day period prior to starting the study and randomized if they met the inclusion and exclusion requirements. Subjects were confined to the clinic for at least 8 hours prior to each trovafloxacin dose and for at least 24 hours following each dose. They were obligated to return to the clinic 36 hours after the dose for blood sampling.

As stated above, 20 subjects were enrolled in this small trial. The inclusion and exclusion criteria are listed below:

**Inclusion criteria:**

- Subjects of either gender
- Women of childbearing potential had to have been either surgically sterilized or at least 2 years post-menopausal or practicing successful contraception for at least 3 consecutive months prior to enrollment.
- Subjects must have been determined to be healthy based on a detailed medical history, vital signs, and clinical laboratory tests.
- Subjects had to be within 10% of their weight range for age, gender, height, and frame.
- The following laboratory parameters had to be within the reference range: WBC, absolute neutrophil count, BUN, creatinine, albumin, hemoglobin, hematocrit, SGOT, SGPT, Alkaline phosphatase, and total bilirubin.
- Additionally, a urine drug screen and a serum pregnancy test had to be negative.
- Subjects had to have been off all prescription drugs, OTC drugs, or drugs of abuse for at least 2 weeks prior to participation and could not have received an investigational drug for at least 4 weeks prior.
- Subjects had to provide written informed consent.

**Exclusion Criteria:**

Excluded were subjects who did not meet the above and who had any condition affecting drug absorption, significant underlying disease, history of allergic reaction to either class of antimicrobial, or who had a history of drug abuse.

***Medical Officer's Comment:*** *The inclusion and exclusion criteria were standard and essentially ensured a healthy population of appropriate age for the indication requested.*

**Drug Administration:**

Trovafloxacin with or without azithromycin was administered on study days 1 and 15. No drug was administered on days 2–14 or after day 15. One of the following regimens was administered openly and under supervision at 7AM on study days:

- Trovafloxacin- one 100 mg tablet with azithromycin.

- Trovafloxacin-one 100 mg tablet with water.

The procedure for the administration of azithromycin was reviewed above.

**Pharmacokinetic Analyses:**

Serum for analysis of trovafloxacin:

Blood sufficient to provide 2.5 mL of serum was collected at the following times: 0 or just prior to dosing, 0.5, 1, 2, 3, 4, 8, 12, 16, 24, and 36 hours after dosing. Specimens were allowed to clot and then separated and frozen. Analyses were performed at a separate facility.

Serum for analysis of azithromycin:

Blood sufficient to provide 2 mL of serum was collected at the following time: 1.5 hours after dosing. Specimens were allowed to clot and then separated and frozen. Analyses were performed at a separate facility.

**Safety Reporting:**

The safety reporting was standard. All AEs were recorded on the CRF and a determination of causality was made by the investigators. All abnormal laboratory test results that occurred during the study were repeated until they returned to baseline.

**Discontinuations:**

Any discontinuations had to be accompanied by a reason on the CRF and reported immediately if associated with a serious AE.

**Statistical Methodology:**

Please refer to the statistical review for comment.

***Medical Officer's Comment:*** *The MO found the protocol to be well designed in order to attain the stated objective. The protocol was followed in terms of design. No efficacy analyses were performed and the only clinical objective was an assessment of safety. The Reviewer agreed with the design and conduct of the clinical study as presented by the applicant.*

**Study Results:**

(The MO presents only safety results in this section. Please refer to the PK review for comment on the analyses performed):

**Demographics:**

20 subjects were enrolled: 4 males and 16 females. All subjects completed the study and were included in the PK and safety analyses. There were no discontinuations. The subjects ranged in age with a mean age of 26.9 years for all subjects. Fifteen subjects were white, 4 were Hispanic, and one was black. The mean weight for the female subjects was 63.8 kgm and for the males it was 79.4

**Safety Analysis:**

As per the applicant:

5/20 (25%) subjects experienced a total of 7 AEs after receiving trovafloxacin alone. None of the events were classified as serious or severe and none caused a discontinuation or temporary reduction in therapy.

The events were classified as being related to body as a whole (2), digestive (1), hemic and lymphatic (1), and the nervous system (2). Three adverse events (experienced by 2 subjects) were judged to be treatment-related. These events were related to the nervous system and included 2 episodes of dizziness and one of somnolence, all of which were mild.

In addition to the above, and classified as unrelated to treatment were 2 episodes of headache, 1 of stomatitis and 1 episode of lymphadenopathy. All of the above were classified as mild.

14/20 subjects (71%) experienced a total of 28 AEs after receiving the azithromycin/trovafloxacin combination. None of the events were classified as serious or severe and none caused a discontinuation or temporary reduction in therapy. The events were classified as being related to the body as a whole (7), digestive (12), musculoskeletal (1), and the nervous system (4). Of these, those related to the body as a whole occurred in 7 subjects and 6 were mild, 1 of moderate severity. 5 subjects had abdominal pain of mild severity, 1 had chills of mild severity, and 2 had headache 1 mild and 1 moderate. 12 subjects had digestive complaints, 10 of mild, and 2 of moderate severity. 10 subjects had nausea (9 mild and 1 moderate), 2 had diarrhea (mild), and 2 had vomiting of moderate severity. Myalgia of mild severity occurred in 1 subject and 4 subjects experienced mild dizziness. All of the above events were considered treatment-related with the exception of 1 event of dizziness.

*Medical Officer's Comment: At the time of this review, the applicant had not provided further information with regard to the relatively high incidence of nausea associated with the product under review. The MO was unable to clearly delineate if the incidence seen in this small study was higher than that seen previously for azithromycin patients alone. On January 9, 1998, the Reviewer requested that the applicant supply this information for purposes of comparison.*

On January 15, 1998, the MO received a copy of the clinical study report for a phase I bioequivalency study (#066-034) comparing azithromycin 1 gm sachet to the equivalent dose in 250 mg capsules (NDA 50-693/Section 6). A review of this document revealed the following:

- The bioequivalency study was designed in a similar fashion to the study currently submitted.
- The demographics of the population studied were very similar to those in the current study.
- 37 patients were studied and monitored for safety.
- The sachet was equivalent to the same dose in capsule form. The C<sub>max</sub> of the sachet formulation was attained faster and was higher than that of the corresponding capsule formulation by approximately 13%. This difference was not determined to be significant.
- 4/37 patients (9.5%) developed AEs, 3 of which were determined to be related to the sachet formulation.
- The 3 events related to the study drug included 1 episode each of nausea, vomiting, and dyspepsia. All 3 events were of mild severity and occurred within 30 min. of ingestion of the sachet. In all cases, the AE resolved within a 2 hour period without therapeutic intervention.
- Similar events were not seen with the capsules.

From the above, the MO concluded that in study 154-056, the incidence of GI-related AEs was much higher (70% vs. 10%) than that seen in study 066-034. No obvious explanation existed for this large difference with the exception that trovafloxacin was given concurrently with the sachet in the present study.

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**Trovafloxacin/Azithromycin Combination Pack:**

- 14 of the 20 patients who received the trovafloxacin/azithromycin combination experienced an AE (14 patients, 29 events).
- Patient #95990010 referred to above, again experienced dizziness/lightheadedness as well as nausea. Both events occurred 18 min. after receiving the combination regimen and the nausea resolved spontaneously after 4.4 hours whereas the dizziness resolved after 7.8 hours.
- Patient #95990011 did not experience dizziness with the combination regimen. She did however experience vomiting of moderate severity 1 hour and 20 min. after receiving the medication. This event resolved spontaneously and a duration was not assigned. In addition, she also experienced flatulence occurring 2.5 hours after receiving the dose and lasting approximately 2 hours. This event was classified as mild and resolved without therapy.
- 10/12 patients complained of nausea which was related to the study drug. This event usually occurred within 30 – 45 min. of taking the combination package and in all except one patient was classified as mild. In patient # 95990004, this event was classified as moderate. No action was taken in any case. The duration of these episodes ranged
- 2 of the patients experienced concurrent vomiting (#95990011 and #95990004) occurring 1.6 and 1.2 hours post-dose. Both events were classified as being of moderate severity and of no duration. No action was taken.
- 5 patients experienced abdominal pain (#95990006, #95990007, #95990008, #95990012, and #95990019). All of these episodes were classified as being of mild severity and all resolved spontaneously. This AE usually occurred within 2 hours of dosing (within the exception of #95990006 where it occurred after 8.5 hours), and lasted between 1 – 2 hours (with the exception of #95990006 where it lasted 39 hours).
- All of the episodes of abdominal pain were associated with other complaints including headache, diarrhea, nausea, and dizziness.
- 3 patients experienced dizziness/lightheadedness that was attributed to the study drug. All of these episodes occurred in young women, usually within 15 min to 90 min post-dose. All episodes resolved spontaneously within 4 – 8 hours post-dose.
- 1 patient complained of other adverse events classified as related to the study drug, myalgia and chills (#95990014).
- 1 patient complained of headache unrelated to the study drug (#95990008).
- 1 patients had an episode of dizziness (vaso-vagal), unrelated to the study drug.

**Table 1**  
**Treatment-Related Adverse Events/ As per the MO**  
**(N = number of patients enrolled/AE = number of times event occurred)**

Adverse Event	Trovafloxacin 100 mg capsule N = 20		154-056		Azithromycin 1 gm sachet Trovafoxacin 100 mg capsule N = 20		066-034	
	n	%	n	%	n	%	n	%
STUDY								
Nausea	0	-	10	50	1	2.7	0	-
Vomiting	0	-	2	10	1	2.7	0	-
Dyspepsia	0	-	0	-	1	2.7	0	-
Abdominal Pain	0	-	5	25	0	-	0	-
Diarrhea	0	-	2	10	0	-	1	6.2
Dizziness/Lightheadedness	2	10	3	15	0	-	0	-
Nausea and Vomiting	0	-	2	10	0	-	0	-
Nausea and Diarrhea	0	-	0	-	0	-	0	-
Abdominal Pain & Nausea	0	-	3	15	0	-	0	-
Abdominal Pain & Diarrhea	0	-	1	5	0	-	0	-
Abdominal Pain & Headache	0	-	1	5	0	-	0	-
Abdominal Pain & Flatulence	0	-	0	-	0	-	0	-
Abdominal Pain & Tenesmus	0	-	0	-	0	-	0	-
Flatulence	0	-	1	5	0	-	0	-
Headache	0	-	0	-	0	-	0	-
Tinnitus								
<b>Cumulative Treatment- Related AE Rate</b>	<b>2/20</b>	<b>10</b>	<b>12/20</b>	<b>60</b>	<b>3/37</b>	<b>8.1</b>	<b>1/16</b>	<b>6.2</b>

Adverse Event	Placebo Arm N = 16	
	n	%
Nausea	0	-
Vomiting	0	-
Dyspepsia	0	-
Abdominal Pain	0	-
Diarrhea	1	6.2
Dizziness/Lightheadedness	0	-
Nausea and Vomiting	0	-
Nausea and Diarrhea	0	-
Abdominal Pain & Nausea	0	-
Abdominal Pain & Diarrhea	0	-
Abdominal Pain & Headache	0	-
Abdominal Pain & Flatulence	0	-
Abdominal Pain & Tenesmus	0	-
Flatulence	0	-
Headache	0	-
Tinnitus	0	-
<b>Cumulative Treatment- Related AE Rate</b>	<b>1/16</b>	<b>6.2</b>

**Medical Officer's Comment:** *From the above it became apparent that there were 2 distinct AE profiles occurring with the administration of the combination pack. The AE (related to study drug) most commonly associated with trovafloxacin was dizziness. This event usually occurred in women approximately 30 – 90 min. post-dose and lasted up to 4 – 6 hours.*

*From the combination package the AEs more commonly seen were nausea, vomiting, abdominal pain, and diarrhea. These events occurred in a variety of combinations and appeared to be more clearly attributable to the azithromycin portion of the combination. The nausea and vomiting were usually noted about 30 min post-dose and resolved within 4 – 5 hours. The abdominal pain and diarrhea occurred later (> 6 hours post-dose) and resolved within 24 – 48 hours.*

*Once again, the high incidence of AEs related to the digestive tract is remarked upon. As per the MO, these events occurred in 12/20 or 60% of the patients receiving this regimen.*

#### **Laboratory Safety Tests:**

Laboratory tests were done only at screening, except for urine pregnancy test which was done at screening and prior to dosing. No clinically significant abnormalities were noted.

#### **Other Safety Parameters:**

Vital signs were performed prior to treatment and if clinically indicated. No clinically significant trends were noted.

#### **Conclusions:**

##### **As per the applicant:**

Co-administration of 1 gm of azithromycin administered as a sachet had no significant effect on the pharmacokinetics of a 100 mg dose of trovafloxacin administered as the commercial tablet. Absorption of azithromycin, estimated from serum concentrations at 1.5 hr after dosing, did not appear to be affected adversely by concomitant administration of 100 mg of trovafloxacin.

Seventy percent of the subjects receiving trovafloxacin co-administered with 1 gm of azithromycin experienced an adverse event compared to 25% of the subjects receiving trovafloxacin alone. Treatment-related adverse events were observed in 65% and 10% of the trovafloxacin/ azithromycin and trovafloxacin groups, respectively. Of the 27 treatment-related adverse events in the trovafloxacin/azithromycin group, 23 were related to the digestive system (mostly nausea) and the body as a whole (mostly abdominal pain). All adverse events were mild to moderate in severity. No serious adverse events were observed.

In summary, co-administration of 1 gm of azithromycin administered as a sachet did not effect the pharmacokinetics of trovafloxacin nor the absorption of azithromycin. Adverse events were observed in 65-70% of the subjects. Seventy-one percent of all adverse events were related to the digestive system and abdominal pain, and 85% of these were mild.

**Benefit/Risk Analysis:** Because co-infection with *Chlamydia trachomatis* is common in patients with gonorrhea, the CDC has recommended that persons treated for gonorrhea should also be treated presumptively with a regimen that is effective against *Chlamydia trachomatis*. Most experts agree that other regimens recommended for the treatment of *Chlamydia trachomatis* infection are likely to be satisfactory for the treatment of gonorrhea. However, studies have not been conducted to investigate possible interactions between other treatment for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, including interactions influencing the effectiveness and adverse events of co-treatment.

Azithromycin is one of the most widely used treatments for genital chlamydia infections and has the advantage of single dose administration. Single dose therapy for gonorrhea with quinolones, such as

ciprofloxacin, in combination with azithromycin for chlamydia, is a common approach to meeting the recommendations for therapy effective against both organisms. However, as indicated above, studies have not been conducted to determine the interaction between the 2 agents. Trovafloxacin is effective as a single dose therapy for gonorrhea, and has the potential advantage of greater *in vitro* activity against *Neisseria gonorrhoeae* than ciprofloxacin or ofloxacin. In addition, both azithromycin and trovafloxacin have activity against *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.

The proposed "Compliance Pak" consisting of a single 1 g dose of Zithromax® and a single 100 mg dose of Trovan®, administered simultaneously, would obviously provide single dose treatment for both chlamydia and gonorrhea. A human PK and bioavailability study has demonstrated that co-administration of these agents does not result in the reduction of bioavailability of one agent or the other. In addition, the study conducted by Dr. Robert Jones at Indiana University, has demonstrated that neither agent reduces the efficacy of the other regarding *in vitro* activity against *Neisseria gonorrhoeae* or *Chlamydia trachomatis*.

It is proposed that this single dose package will be used in patients with infections of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*: in patients with gonorrhea, as presumptive treatment for *Chlamydia trachomatis*; and in the sex partners of symptomatic or asymptomatic patients with gonorrhea. Obviously, the administration of a single dose dual therapy eliminates the concern regarding compliance, while simultaneously reducing the concern about the spread of infection and the long-term sequelae associated with these infections.

**RISKS:** While 14/20 (70%) of the subjects in the interaction study demonstrated mild to moderately severe AEs associated primarily with the GI tract, it is unlikely that any of these AEs would reduce the efficacy of the "Compliance Pak." However, since both azithromycin and trovafloxacin can be administered with meals without a reduction in bioavailability, the minimum tolerability risk associated with their simultaneous administration, may be further reduced by their administration with meals. In addition, as the interaction study suggests, the duration of any AE is likely to be short lived with resolution within minutes to several hours.

In conclusion, it is felt that the benefits provided by the single dose "Compliance Pak" for concomitant genital and chlamydial infections in terms of ease of administration, compliance, prevention of spread of disease, and reduction of complications of disease far outweigh the minimal risks associated with co-administration of these agents, which may be further reduced by their administration with meals. Additionally, its single packaging negates the necessity for dual prescriptions, thereby reducing the concern for confusion or incomplete dosing.

**As per the MO:**

The MO recommends approval for the combination package of azithromycin 1 gm sachet with trovafloxacin 100 mg tablet for the requested indications.

The MO determined that the benefit associated with the administration of the combination package for the treatment of sexually transmitted diseases (decreased rate of transmission, decreased infertility) outweighed the risks with regards to the AEs. It is however strongly recommended that a cautionary statement be appended to the labeling with regards to the high incidence of AEs seen and their duration. It should be noted that this recommendation is a medical decision and not a financial one. After receipt of the FDA recommendations, the applicant, Pfizer, is reassessing the feasibility of marketing the azithromycin/trovafloxacin combination product. It is the applicant's opinion that the potential financial benefits may be outweighed by the adverse event profile in the label especially with regard to the azithromycin portion of the product

The current submission did not provide any material with regards to the efficacy of this combination and therefore no conclusions could be drawn.

The applicant submitted a bioequivalency study performed in 20 patients. Conclusions were drawn with regards to the safety of the combination regimen.

The co-administration of 100 mg of trovafloxacin and 1 gm of azithromycin in the form of a combination package for the treatment of sexually transmitted diseases did not appear to have an effect on the bioavailability of either antimicrobial agent. The MO defers to the PK reviewer for further comment.

Additionally, there was no microbiologically antagonistic effect between the agents versus the targeted pathogens, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis*.

As per the MO, 2/20 (10%) of the patients receiving trovafloxacin alone experienced the known to be associated with this agent, AE of dizziness and/or lightheadedness. This event usually occurred in women approximately 30 – 90 min. post-dose and had a duration of 4 – 6 hours. The current trovafloxacin insert indicates that dizziness/lightheadedness occur in 3% and 2% of patients receiving trovafloxacin 100 mg tablets respectively. As per the package insert “Dizziness/lightheadedness on TROVAN® is generally mild, lasts a few hours following a dose, and in most cases, resolves with continued dosing.” The MO agrees with this statement although the incidence of dizziness was higher in this small study (10% on trovafloxacin alone, 20% on the combination regimen). Although no patients complained of nausea and/or vomiting on the trovafloxacin arm of this study, nausea has been a complaint in 4% of patients in multiple-dose trials at the 100 mg dose. Additionally, 1.9% of patients in the population studied for the initial approval of this agent (all doses), discontinued therapy because of this complaint. Vomiting occurred in < 1% of the patients at the proposed 100 mg dose and therapy was discontinued in 1% of the patients overall.

The MO agreed with the applicant’s determination that 25% of patients receiving trovafloxacin alone experienced an AE, all causality.

As per the MO, 12/20 patients (60%) receiving the combination regimen of azithromycin 1 gm sachet and trovafloxacin 100 mg tablet, had complaints from the gastrointestinal tract that were determined to be related to the study drug. The MO also agreed with the applicant’s determination that 14/20 (71%) of patients had an AE, all causality.

The MO determined that the incidence of nausea and vomiting was far greater in this small study than in a similar bioequivalency study performed on the 1 gm azithromycin sachet in 1992 (066-034). In that study only 3/37 patients had nausea or abdominal complaints related to the study drug (10%). In the current ZITHROMAX® package insert (1 gm sachet) “the most common side effects associated with multiple-dose regimen of ZITHROMAX® were related to the gastrointestinal system with diarrhea/loose stools (5%), nausea (3%), and abdominal pain (3%) being the most frequently reported.”

The MO was unable to determine a cause for the high incidence of gastrointestinal AEs noted in this study (066-056) with the azithromycin 1 gm/trovafloxacin 100 mg combination as compared to study 066-034 of the 1 gm sachet azithromycin formulation alone where the incidence was much lower.

Possibly the concurrent administration of trovafloxacin altered the sensitivity of the GI tract of the subjects or alternatively the study was not designed to make an accurate assessment of the true incidence of these events. However, all events were mild and usually resolved with 4 – 24 hours. In general it is postulated that the high incidence of gastrointestinal adverse events seen in patients receiving azithromycin is due to the antimicrobial’s activity as a motilin receptor agonist, the stimulation of motilin release, or a combination of both. This has not been described with trovafloxacin at the present time.

**RECOMMENDED REGULATORY ACTION:**

1) The following statement can be added to the **Indications and Usage** section of the labeling:

2) The above statement should be modified to reflect the reduced activity of trovafloxacin in non-gonococcal urethritis in males.

3) Under **PRECAUTIONS: Information for Patients**, a statement should be added to reflect the increased GI toxicity seen with this product. An example of this statement is as follows:

4) The **Adverse Reactions** section should be modified to reflect the adverse event profile seen with this product only.

5) A clinical studies section is proposed in which the AE profile seen in the current study can be outlined (see below modified MO Table 1).

Adverse Event	Trovafoxacin 100 mg capsule N = 20		Azithromycin 1 gm sachet Trovafoxacin 100 mg capsule N = 20	
	n	%	n	%
STUDY	154-056			
Nausea	0	-	10	50
Vomiting	0	-	2	10
Dyspepsia	0	-	0	-
Abdominal Pain	0	-	5	25
Diarrhea	0	-	2	10
Dizziness/Lightheadedness	2	10	3	15
Nausea and Vomiting	0	-	2	10
Nausea and Diarrhea	0	-	0	-
Abdominal Pain & Nausea	0	-	3	15
Abdominal Pain & Diarrhea	0	-	1	5
Abdominal Pain & Headache	0	-	1	5
Abdominal Pain & Flatulence	0	-	0	-
Abdominal Pain & Tenesmus	0	-	0	-
Flatulence	0	-	1	5
Headache	0	-	0	-
Cumulative Treatment- Related AE Rate	2/20	10	12/20	60

APPEARS THIS WAY  
ON ORIGINAL

/S/

Regina Alivisatos, MD  
DSPIDP, HFD-590

APPEARS THIS WAY  
ON ORIGINAL

- Cc:  
 Orig. NDA 50-762  
 HFD-590  
 HFD-520  
 HFD-590/DivDir/MGoldberger /S/16  
 HFD-590/DepDivDir/RAIhnrecht  
 HFD-590/MTL/BLeissa /S/9/24/98  
 HFD-590/Biopharm/PCelo  
 HFD-590/Micro/Dionne  
 HFD-590/Chem/Holbert  
 HFD-590/Pharm/Hundley  
 HFD-520/DivDir/GChikami  
 HFD-520/MO/NMoledina  
 HFD-590/CSO/PFogarty  
 HFD-725/Biostat/Chakravarty  
 HFD-520/Biopharm/Sun  
 HFD-520/CSO/Cintron

APPEARS THIS WAY  
ON ORIGINAL