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*APPLICATION NUMBER:*

**20-677/S-001, S-002**

**APPROVAL LETTER**

NDA 20-677/S-001, S-002

OCT 19 1999

Mylan Pharmaceuticals  
Attention: Frank R. Sisto  
Vice President, Regulatory Affairs  
781 Chesnut Ridge Road  
P. O. Box 4310  
Morgantown, West Virginia 26504

Dear Mr. Sisto:

Please refer to your supplemental new drug applications dated September 18, 1998, received September 21, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ZAGAM<sup>®</sup> (sparfloxacin tablets) Tablets, 200 mg.

We acknowledge receipt of your submissions dated November 25, 1998, April 16, 1999, May 4, 1999, received November 27, 1998, April 19, 1999, May 5, 1999.

These supplemental new drug applications provide for the following changes to the label:

1. A box with "Rx only" was added directly above the **DESCRIPTION**.

## 2. WARNINGS

• The seventh paragraph in this section was revised to read:

"In a covariate analysis, age did not have a statistically significant contribution to the change in QT<sub>c</sub> recorded in patients taking sparfloxacin. However, in controlled clinical trials, QT<sub>c</sub> interval prolongation was more frequently reported as an adverse event in patients ≥65 years of age than in younger patients. In these clinical trials, QT<sub>c</sub> interval prolongation was reported more frequently as an adverse event (defined as QT<sub>c</sub> ≥0.440 sec or ≥15% change from baseline) in elderly patients treated with sparfloxacin than in elderly patients treated with a comparator drug. During post marketing surveillance, cardiovascular events including torsades de pointes and other arrhythmias were more frequent in the elderly than in younger patients treated with sparfloxacin although a history of underlying cardiac disease in this population was more common. Sparfloxacin is contraindicated in patients with known QT<sub>c</sub> prolongation (see **CONTRAINDICATIONS**)."

- The eighth paragraph was revised to read:

**“THE SAFETY AND EFFECTIVENESS OF SPARFLOXACIN IN PEDIATRIC PATIENTS, ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pediatric Use, Pregnancy, and Nursing Mothers subsections.)”**

### 3. PRECAUTIONS

- In the **Information for Patients** subsection, the eighth bullet was revised to read:

“that sucralfate or magnesium- and aluminum-containing antacids or Videx® (Didanosine), chewable/buffered tablets or the pediatric powder for oral solution may be taken 4 hours after sparfloxacin administration. (See **PRECAUTIONS: Drug Interactions.**)”

- In the **Information for Patients** subsection, an eleventh bullet was added to read:

“that convulsions have been reported in patients taking quinolones, including sparfloxacin, and to notify their physician before taking this drug if there is a history of this condition.”

- In the **Drug Interactions** subsection, a sentence was added to the *Antacids and Sucralfate* paragraph and is now the third sentence as follows:

“Similarly, the oral bioavailability of sparfloxacin may be reduced when Videx®, (Didanosine), chewable/buffered tablets or the pediatric powder for oral solution is administered between 2 hours before and 2 hours after sparfloxacin administration.”

- The **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection was revised to read:

**“Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:**  
Sparfloxacin was not carcinogenic in mice or rats when administered for 104 weeks at daily oral doses 3.5 - 6.2 times greater than the maximum human dose (400 mg), respectively, based upon  $\text{mg}/\text{m}^2$ . These doses corresponded to plasma concentrations approximately equal to (mice) and 2.2 times greater than (rats) maximum human plasma concentrations.

In a study of repeated exposure (5 days per week for 40 weeks) of hairless albino mice (SKH-1) to a low dose (0.272 Caucasian human minimal erythema dose [MED]) of solar simulated UV radiation, skin tumors were induced with a median onset time of 43 weeks. As expected for this model, the gross appearance of the tumors in this study was consistent with squamous cell carcinoma or its precursors. When sparfloxacin (6.0 or 12.5 mg/kg/day) was administered by the oral route, the median tumor onset time was reduced to 38 and 32 weeks, respectively. This reduction in median onset time was similar to that observed when mice were exposed to a higher dose (0.476 Caucasian human MED) of solar simulated UV radiation alone. At a dose level of 12.5 mg/kg/day,

mice had skin sparfloxacin concentrations ( $\pm$  SD) of approximately 1.8  $\mu\text{g/g}$  ( $\pm$  0.26, N=6). Following a 400 mg dose of sparfloxacin, skin levels measured in human subjects averaged 5.5  $\mu\text{g/g}$  ( $\pm$  6.5, N=11). A similar effect on the time to the development of skin tumors has been observed in this mouse strain with some other fluoroquinolone antibiotics. The clinical significance of these findings to humans is unknown.

*Mutagenesis:* Sparfloxacin was not mutagenic in *Salmonella typhimurium* TA98, TA100, TA1535, or TA1537, in *Escherichia coli* strain WP2 uvrA, nor in Chinese hamster lung cells. Sparfloxacin and other quinolones have been shown to be mutagenic in *Salmonella typhimurium* strain TA102 and to induce DNA repair in *Escherichia coli*, perhaps due to their inhibitory effect on bacterial DNA gyrase. Sparfloxacin induced chromosomal aberrations in Chinese hamster lung cells *in vitro* at cytotoxic concentrations; however, no increase in chromosomal aberrations or micronuclei in bone marrow cells was observed after sparfloxacin was administered orally to mice.

When Chinese hamster ovary cells were incubated with sparfloxacin in the presence of solar simulated UV radiation, chromosome aberrations were induced at concentrations of sparfloxacin that were not associated with aberrations in the absence of UV. The low level of UV used in the experiment, approximately 375  $\text{mJ/cm}^2$ , was not, by itself, associated with chromosome aberrations, while the high level of UV used in the experiment, approximately 750  $\text{mJ/cm}^2$ , induced fewer aberrations than sparfloxacin plus low or high dose UV.

*Impairment of Fertility:* Sparfloxacin had no effect on the fertility or reproductive performance of male or female rats at oral doses up to 15.4 times the maximum human dose (400 mg) based upon  $\text{mg/m}^2$  (equivalent to approximately 12 times the maximum human plasma concentration)."

- In the **Pediatric Use** subsection, the following sentence was added and is now the first sentence in this subsection:

"Safety and effectiveness in pediatric patients and adolescents under the age of 18 years have not been established."

- A **Geriatric Use** subsection was added as follows:

**Geriatric Use:** In controlled clinical trials conducted in the United States and Europe, sparfloxacin tablets have been administered to approximately 458 elderly ( $\geq$ 65 years of age) patients. It is known that the  $\text{QT}_c$  interval increases with increasing age. In a covariate analysis, age did not have a statistically significant contribution to the change in  $\text{QT}_c$  recorded in patients taking sparfloxacin. However, in controlled clinical trials,  $\text{QT}_c$  interval prolongation was more frequently reported as an adverse event in patients  $\geq$ 65 years of age than in younger patients. In addition,  $\text{QT}_c$  interval prolongation was reported more frequently as an adverse event (defined as  $\text{QT}_c \geq 0.440$  sec or  $\geq 15\%$  change from

baseline) in sparfloxacin treated elderly patients (7/314) than elderly patients treated with a comparator drug (0/301). Finally, the majority of patients with postmarketing cardiovascular events were elderly; however, it is not possible to exclude the roles of other contributing factors such as underlying cardiovascular diseases and concomitant medications. There were no other apparent overall differences in safety and efficacy observed between the elderly and younger individuals in controlled clinical trials. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Sparfloxacin is known to be excreted renally and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See **CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION** and **WARNINGS**.)

The pharmacokinetic parameters of sparfloxacin in the elderly were consistent with those observed in normal healthy subjects. (See **CLINICAL PHARMACOLOGY:Special Populations**.)”

#### 4. DOSAGE AND ADMINISTRATION

- A new sentence was added and is now the second sentence in this section as follows:

“Antacids containing magnesium and aluminum or sucralfate or Videx®, (Didanosine), chewable/buffered tablets or the pediatric powder for oral solution may be taken 4 hours after administration of Zagam (sparfloxacin).”

#### 5. CLINICAL STUDIES

- The table describing the pathogen eradication rates in the acute bacterial exacerbations of chronic bronchitis study was revised to read:

Organism	Sparfloxacin		Ofloxacin	
<i>H. parainfluenzae</i>	102/107	(95.3%)	89/93	(95.7%)
<i>H. influenzae</i>	49/55	(89.1%)	60/63	(95.2%)
<i>C. pneumoniae</i>	35/43	(81.4%)	35/39	(89.7%)
<i>M. catarrhalis</i>	33/35	(94.3%)	30/31	(96.8%)
<i>S. pneumoniae</i>	30/34	(88.2%)	20/22	(90.9%)
<i>S. aureus</i>	16/19	(84.2%)	13/14	(92.9%)
<i>K. pneumoniae</i>	17/17	(100%)	15/17	(88.2%)
<i>E. cloacae</i>	12/13	(92.3%)	12/15	(80%)

6. HOW SUPPLIED

- This section was revised to read:

Strength	Size	NDC 62794-	Description / Markings
200 mg	Blister Pack of 11 (RespiPac™)	011-11	A white film-coated, round bi-convex, tablet debossed with B over 11 on one side of the tablet and blank on the other side.
	Bottle of 55	011-55	

Store at Controlled Room Temperature 20 to 25°C (68 to 77°F) [see USP].

7. The company logo, distribution and manufacturing information were revised to read:

(INSERT BERTEK LOGO)

Distributed by  
**BERTEK PHARMACEUTICALS INC.**  
Sugar Land, TX 77478 USA

Manufactured by  
**RHÔNE-POULENC RORER PHARMACEUTICALS INC.**  
COLLEGEVILLE, PA 19426 USA

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted May 4, 1999).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 20-677/S-001, S-002." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Robin Anderson, Regulatory Review Officer, at (301) 827-2127.

Sincerely,



Mark J. Goldberger, M.D., M.P.H.  
Director  
Division of Special Pathogen and Immunologic Drug  
Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

**APPEARS THIS WAY  
ON ORIGINAL**