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APPLICATION NUMBER:

20-677/S-001, S-002

MEDICAL REVIEW

NDA 20-677/S-001 Sparfloxacin geriatric labeling
NDA 20-677/S-002

APR 14 1999

Medical officer review of labeling supplement

Submission date: September 18, 1998
Receipt date: September 21, 1998
Amendment: November 25, 1998
Received: November 27, 1998
Review complete: April 14, 1999

Applicant: Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O.Box 4310
Morgantown
West Virginia 26504-4310

Drug: Trade: Zagam
Generic: Sparfloxacin

Therapeutic category: Fluoroquinolone antimicrobial

Dosage form: Tablet

Route of administration: oral

Contents of submission: One volume describing labeling change in compliance with geriatric rule, and responses to Agency letters of May 29 and July 27 addressing interaction with DDI and CNS toxicity respectively
One volume of supplementary geriatric data as requested by FDA (submitted Nov 27 1998)
Telefaxes 3/26/99, 4/5/99, 4/9/99 addressing wording of the label

Purpose of submission:

To provide for geriatric use information in the Zagam Tablet package insert in accordance with the August 27, 1997 Federal Register final rule titled "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of "Geriatric Use" Subsection in the Labeling".

Scope of this review:

This review covers the proposed geriatric labeling changes. CNS class labeling and DDI interaction will be addressed in a separate document. The proposed inclusion by the sponsor of information on the activity of sparfloxacin against resistant *Streptococcus pneumoniae* isolates in the label will also be separately addressed.

Background: Sparfloxacin has been indicated for the treatment of community acquired pneumonia and acute exacerbations of chronic bronchitis due to specified organisms. Among its adverse effects, photosensitive skin reactions are common (reported in 7.9% of patients given the drug), and they may be severe. Torsade de pointes has been described in patients who were taking amioderone or disopyramide together with sparfloxacin. Given alone, Sparfloxacin has resulted in prolongation of the QTc interval in healthy volunteers. The existing text in the label indicates that "The pharmacokinetics of Sparfloxacin are not altered in the elderly with normal renal function". Thus despite its toxicity, use of the drug has occurred in the geriatric population.

Sparfloxacin was originally manufactured by Rhone Poulenc Rorer, who developed the original database. The current manufacturers have been able to supply the information provided to them by Rhone Poulenc Rorer. A breakdown of patients over 74 years of age was not available from this database.

Proposed addition to existing label:

Geriatric use: Sparfloxacin tablets were administered to approximately 458 elderly individuals (≥ 65)



Comments:

Geriatric data was derived from 458 patients ≥ 65 years of age from 8 phase three studies. These studies conducted in the US and Canada (314 patients) and Europe (144 patients) examined the use of Sparfloxacin in the treatment of community acquired pneumonia, acute purulent sinusitis, COPD superinfections, complicated UTI, bronchitis and skin and skin structure infections.

Safety:

Safety data was derived from phase 3 clinical trials and post-marketing data.

a) Postmarketing data

Of a total of 1181 patient reports of adverse events, 202 patients were ≥ 65 years of age. The frequency of most adverse events was equivalent for elderly and younger patients. However cardiovascular events constituted 17 of 270 adverse events in elderly patients (6%) compared with 0 of 1207 adverse events in younger patients. These included Torsades de pointes (4 patients), ventricular tachycardia (4 patients), syncope (3 patients), QT interval prolonged (3 patients) and arrhythmia (3 patients). The sponsor stated that most of the elderly patients experiencing adverse cardiac events had a history of past cardiovascular disorders. Other adverse events reported more frequently in elderly than in younger patients included hallucination (7 adverse events in the elderly and 2 in younger patients), thrombocytopenia (7 and 5 respectively) and drug interaction (4 and 1).

b) Data from controlled phase 3 studies in the USA and Canada showed that cardiovascular AE reports as a whole were more common in elderly patients treated with Sparfloxacin than in those treated with comparator drugs (table 1). QT prolongation was approximately three times more common in elderly than in young patients (table 2). However ventricular extrasystoles were rare in both elderly and young patients treated with sparfloxacin and were no more often reported in patients who received Sparfloxacin than in those who received the comparator drug (table 3).

Table 1: Incidence of all cardiac adverse events

	Sparfloxacin	Comparator
<65 years	74/2264 (3.3%)	52/1631 (3.2%)
≥ 65 years	23/314 (7.3%)	18/301 (5.9%)

Table 2: Incidence of QT interval prolongation

	Sparfloxacin	Comparator
<65 years	14/2264 (0.6%)	8/1631 (0.5%)
≥ 65 years	7/314 (2.2%)	0/301 (0%)

Table 3: Incidence of ventricular extrasystoles:

	Sparfloxacin	Comparator
<65 years	1/2264 (<0.1%)	5/1631 (0.3%)
≥ 65 years	1/314 (0.3%)	2/301 (0.6%)

Deaths by age, treatment group and protocol were not provided

Dizziness was also more common in elderly patients treated with sparfloxacin than in control-drug treated patients or younger patients treated with sparfloxacin.

Table 4: Incidence of dizziness

	Sparfloxacin	Comparator
< 65 years	73/2264 (3.2%)	43/1631 (2.6%)
>= 65 years	19/314 (6.0%)	11/301 (3.6%)

Efficacy:

Clinical response rates for patients < 65 and >=65 years of age treated with sparfloxacin or a comparator drug are shown below.

Table 5: Clinical response rates by indication, age and treatment group

Indication	Age	Sparfloxacin	Comparator
Community acquired pneumonia	<65	216/248 (87.1%)	188/225 (83.6%)
	>=65	53/63 (84.1%)	50/64 (78.1%)
Acute exacerbation of chronic bronchitis	<65	205/230 (89.1%)	203/235 (86.4%)
	>=65	85/105 (81%)	93/102 (91.2%)
Lower respiratory tract infection	<65	421/478 (88.1%)	391/460 (85%)
	>=65	138/168 (82.1%)	143/166 (86.1%)
Acute sinusitis	<65	349/414 (84.3%)	159/189 (84.1%)
	>=65	25/28 (89.3%)	17/22 (77.3%)
Skin & skin structure infections	<65	170/184 (92.4%)	165/188 (87.8%)
	>=65	40/49 (81.6%)	46/54 (85.2%)
Total	<65	1361/1554 (88%)	1106/1297 (85%)
	>=65	341/413 (83%)	349/408 (86%)

Calculated response rates were slightly lower in elderly than young patients treated with sparfloxacin for all indications except acute sinusitis although these differences did not appear to be clinically significant. The responses of elderly patients to sparfloxacin and to comparator appeared similar.

Pharmacokinetics No additional pharmacokinetic data was supplied. The existing label states that the pharmacokinetics of sparfloxacin are not altered in the elderly with normal renal function.

Medical officer's comments: There is concern about the increase in QT prolongation in elderly patients treated with sparfloxacin and there is a suggestion from post-marketing data that other cardiovascular events were also more common in the elderly treated with sparfloxacin. It is not known whether the incidence of QT prolongation increases in patients 75 years of age and older. The proposed labeling statement on geriatric use reflects the concern regarding QT prolongation and cardiotoxicity. However it suggests that QT prolongation was also more common in elderly patients treated with the comparator drug. The data supplied regarding AE's during clinical trials did not indicate this (table 2). This should be corrected. A statement addressing this issue should also be included in the warnings section as recommended below. The following should be added at the end of this paragraph

Labeling recommendations:

The Geriatric Use subsection should be revised as follows:

Geriatric use:

[]

The following should be added to the **WARNINGS** section below the paragraph which addresses increases in the QT interval, beginning:

[]

For comments on the clinical pharmacology section of the label, please refer to the clinical pharmacology review of this supplement.

Subsequent correspondence regarding the wording of the label:

Fax from Mylan Pharmaceuticals to FDA on 3/26/99. Proposed labeling by the sponsor was presented, incorporating in the Geriatric use and **WARNINGS** subsections, a statement that:

[]

The FDA was concerned that this did not reflect that QT prolongation was more commonly observed in elderly patients treated with sparfloxacin than in elderly patients treated with comparator drugs, or younger patients treated with sparfloxacin.

Fax from Mylan Pharmaceuticals to FDA on 4/5/99. A revised label was proposed by the sponsor incorporating the above.

The FDA remained concerned that the original statement on QT prolongation was unclear. In a telecon on 4/9/99 between FDA and Mylan pharmaceuticals, it was suggested that the statement that:

[] should be removed.

Fax from Mylan Pharmaceuticals to FDA on 4/9/99. New wording was submitted by the sponsor addressing these issues. The wording as presented in this Fax was satisfactory to the FDA.

NDA 20-677/S-001 Sparfloxacin geriatric labeling
NDA 20-677/S-002

/S/

Leonard Sacks, M.D.
Medical officer, DSPIDP

Concurrence

HFD-590/MTL/Hopkins

/S/ 2/14/99

CC:

NDA 20-087

HFD-590/PM/AndersonR

HFD-590/MTL/HopkinsR

HFD-590/MO/SacksL

HFD-590/Biopharm/AjayiF

HFD-590/DivDir/GoldbergerM

**APPEARS THIS WAY
ON ORIGINAL**

OCT 19 1999

Medical Review of NDA Labeling Supplement**NDA 20-677/S-001/S-002**

Submission Date: September 18, 1998
Product: Zagam (sparfloxacin) Tablets, 200 mg
Sponsor: Mylan Pharmaceuticals Inc
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, West Virginia 26504-4310
Date Received: September 21, 1998
Date Assigned: September 21, 1998
Date Completed: April 15, 1999

Material Reviewed:

1 Volume submission (dated September 18, 1998) containing revised labeling was reviewed in conjunction with a previous submission dated October 30, 1997. This review addresses all proposed labeling changes not related to the Agency rule on "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs: Addition of Geriatric Use Subsection in the Labeling" issued August 27, 1997. The Sponsor's response to the final rule was previously reviewed by Dr. Leonard Sacks (See MO review of Geriatric Supplement dated April 14, 1999.).

Regulatory Background:

In this submission, Mylan responded to the Division of Special Pathogen and Immunologic Drug Products' letters dated May 29, 1998 and July 27, 1998 that address 1) CNS toxicity with quinolones in the **Information for Patients** subsection of the **PRECAUTIONS** section, 2) pediatric wording in the **WARNINGS** section and **Pediatric Use** subsection of the **PRECAUTIONS** section, and 3) drug-drug interactions with quinolones and certain formulations of DDI as described in the **Information for Patients** and **Drug Interactions** subsections of the **PRECAUTIONS** section, and **DOSAGE AND ADMINISTRATION** section.

In a previous correspondence dated October 30, 1997, Rhone-Poulenc Rorer (RPR) responded to the Division's request to re-analyze their studies 355 (urinary tract infection), 356 (bronchitis), and 359 (sinusitis) excluding Dr. Fiddes' data. RPR performed these re-analyses but did not propose to include this information into the **CLINICAL TRIAL** section that summarizes bacteriologic success rates by pathogen. Mylan has proposed an updated version of the **CLINICAL TRIAL** section that details

Conclusions

This submission was provided, in part, to respond to FDA's letters dated May 28, 1998 and July 27, 1998 that requested specific changes to the **Information for Patients**

Labeling Review for NDA 20-677/S-001/S-002

subsection of the **PRECAUTIONS** section, **Drug Interactions** subsection of the **PRECAUTIONS** section, **WARNINGS** section, and **Pediatric Use** subsection of the **PRECAUTIONS** section of the labeling. The changes to the **Drug Interactions** subsection of the **PRECAUTIONS** section incorporate new information referred to in the July 27, 1998 letter regarding the potential interaction of quinolones and Videx® (Didanosine), chewable/buffered tablets and the pediatric powder for oral solution based on a phase 4 drug-drug interaction study between ciprofloxacin and Videx®.

The changes requested to the **Information to Patients** subsection of the **PRECAUTIONS** section includes a statement suggesting that patients should notify their physician before taking levofloxacin in there is a history of convulsions.

The **WARNINGS** section and the **Pediatric Use** section change the words "children" to "pediatric patients".

*MO comment: The Sponsor's proposed changes to the **CLINICAL TRIAL** section of the label is acceptable.*

All other changes requested by the Division in the letters dated May 28, 1998 and July 27, 1998 were made in the Sponsor's revised labeling. These changes are considered acceptable.

Recommendations

The proposed label should not be approved as written. The sponsor's proposal to _____ should not be allowed. All other changes to the label not relating to the geriatric population (as previously reviewed by Dr. Leonard Sacks) are acceptable.

**APPEARS THIS WAY
ON ORIGINAL**

Labeling Review for NDA 20-677/S-001/S-002

/S/

Robert J. Hopkins M.D., M.P.H. & T.M.

Concurrence

HFD-590/DivDir/GoldbergerM

/S/

10/19/97

CC:

NDA 20-013

Division files

HFD-590/DepDiv Dir/Renata Albrecht

HFD-590/DivDir/Mark Goldberger

HFD-590/MO/Leonard Sacks

HFD-590/PM/Mary Dempsey

HFD-590/PM/Robin Anderson

HFD-880/BiopharmTL/Funmi Ajayi

**APPEARS THIS WAY
ON ORIGINAL**