CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-634/S-015, S-021, S-022
20-635/S-012, S-019, S-020

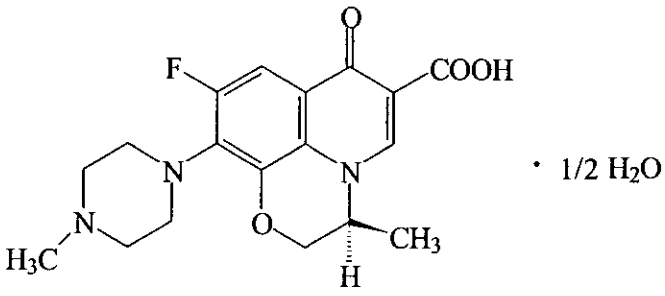
PHARMACOLOGY REVIEW

PHARMACOLOGY / TOXICOLOGY REVIEW AND EVALUATION

NDA#:	20-634 & 20-635
Serial Number:	SLR-015/021/022 & SLR-012/019/020
Type:	Supplement Letter & Labelling Change
Submission Dates:	12/11/01
Review Division:	Special Pathogen and Immunologic Drug Products HFD – 590
Reviewer:	Stephen G. Hundley, Ph.D., Pharmacologist
Review Completion Date:	3/5/02
Sponsor:	The R.W. Johnson Pharmaceutical Research Institute Route 202, P.O. Box 300 Raritan, NJ 08869 – 0602
Phone:	908-704-4198

Drug Information

Name:	Levofloxacin
Drug Name:	Levaquin®
Chemical Name:	S-(-)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl) -7-oxo-7H-pyrido [1,2,3-de] 1,4-benzoxazine-6-carboxylic acid hemihydrate
CAS #:	100986-85-4
Molecular Formula:	$C_{18}H_{20}FN_3O_4 \cdot ½ H_2O$
Molecular Weight:	370.4
Molecular Structure:	



Drug Category: Antimicrobial – Fluoroquinolone

Related Submissions: IND 36,627 and IND 38,368

Current Indications: Complicated Skin and Skin Structure Infections; Acute Exacerbation of Chronic Bronchitis; Sinusitis; Community Acquired Pneumonia; Uncomplicated Urinary Tract Infection; Uncomplicated Skin and Skin Structure Infections

BACKGROUND

Levofloxacin (Levaquin®) is a fluoroquinolone with broad-spectrum antimicrobial activity. The sponsor included proposed labelling changes to the Carcinogenesis, Mutagenesis, Impairment of Fertility section of the label. The proposed changes reflected the elevation of the highest daily human dose from 500 to 750 mg and results from a photo-carcinogenicity study conducted with albino mice. There are no reviewable pharmacology/toxicology studies in the submissions.

EVALUATIONS AND CONCLUSIONS

The photo-carcinogenicity study entitled "12-Month Oral (Gavage) Photocarcinogenicity Study of RWJ-25213-097 (Levofloxacin) in Hairless Mice (Doc. ID 461649:2)" was submitted and reviewed under IND's 36,627 (384), and 38,368 (308). The Pharmacology/Toxicology Review and Evaluation was issued on 2/22/99. The sponsor submitted a labelling change proposal to reflect the results of the photo-carcinogenicity study in March, 2000.

Proposed Language:

[

]

The proposed language of the sponsor was changed by the Pharmacology/Toxicology Reviewer

[ ]

The following language was proposed by the Pharmacology/Toxicology Reviewer in a Facsimile Transmission dated 11/30/01.

FDA Recommended Language:

Levofloxacin did not shorten the time to tumor development of UV-induced skin tumors in hairless albino (Skh-1) mice at any levofloxacin dose level and was therefore non photo-carcinogenic under conditions of this study. Dermal

levofloxacin concentrations in the hairless mice ranged from 25 to 42 μg/g at the highest levofloxacin dose level (300 mg/kg/day) used in the photo-carcinogenicity study. By comparison, dermal levofloxacin concentrations in human subjects receiving 750 mg of levofloxacin (contained in Levaquin® tablets) averaged 11.8 μg/g at Cmax.

Subsequently, the sponsor and the Pharmacology/Toxicology Reviewer agreed upon the following language that will appear in the Carcinogenesis, Mutagenesis, Impairment of Fertility section of the label.

Approved Language:

Levofloxacin did not shorten the time to tumor development of UV-induced skin tumors in hairless albino (Skh-1) mice at any levofloxacin dose level and was therefore non photo-carcinogenic under conditions of this study. Dermal levofloxacin concentrations in the hairless mice ranged from 25 to 42 μg/g at the highest levofloxacin dose level (300 mg/kg/day) used in the photo-carcinogenicity study. By comparison, dermal levofloxacin concentrations in human subjects receiving 750 mg of levofloxacin averaged 11.8 μg/g at Cmax.

The labelling changes for Levaquin Tablets (NDA 20-634) and Levaquin Injection (NDA 20-635) were approved by the FDA on 12/18/01, [Labeling, Clinical, Pharmacology, and Biopharmaceutics Review of Supplemental Labeling Revisions (SLRs)].

There are no pharmacology/toxicology issues associated with the proposed 750 mg dose routine to human subjects.

KEYWORDS: Labelling Changes, Photo-carcinogenicity Study, Levofloxacin

Stephen G. Hundley, Ph.D.

Concurrences:
HFD-590 / R. Albrecht / DDDir
HFD-590 / K. Hastings / TL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Steve Hundley
4/15/02 02:40:45 PM
PHARMACOLOGIST

Kenneth Hastings
4/17/02 02:55:53 PM
PHARMACOLOGIST

Renata Albrecht
5/24/02 01:28:21 PM
MEDICAL OFFICER