CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-634/S-008, S-009

20-635/S-007, S-008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

HFD 540
FAXSCN

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA:	**20-634, Supplement S-008**
Submission Date:	March 31, 1999
Drug Product:	Levofloxacin 250 mg and 500 mg Tablets
Trade Name:	LEVAQUIN®
Sponsor:	R.W. Johnson Pharmaceutical Research Institute Raritan, NJ
Submission Type:	Efficacy Supplement – Treatment of Community Acquired Pneumonia due to Penicillin-Resistant *Streptococcus pneumoniae* (PRSP-CAP)
Category:	1S
OCPB Reviewer:	Philip M. Colangelo, Pharm.D., Ph.D.

MAR 17 2000

I. BACKGROUND / INTRODUCTION

This supplement to NDA 20-634 for levofloxacin tablets and NDA 20-635 for levofloxacin injection was submitted to allow use of levofloxacin for the treatment of levofloxacin-susceptible strains of penicillin-resistant *Streptococcus pneumoniae* in patients with community acquired pneumonia (PRSP-CAP) at a dosage regimen of 500 mg orally or IV Q24 hrs for 7-14 days. This indication and treatment regimen for PRSP-CAP was subsequently approved by the Division of Special Pathogen and Immunologic Drug Products (HFD-590) on February 2, 2000.

II. SUBMISSION SYNOPSIS

This submission contained only clinical trial information in the treatment of PRSP-CAP with levofloxacin. There was no human pharmacokinetics / bioavailability information provided. Thus, there is no formal review from the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). However, the OCPB reviewer was consulted by the HFD-590 Clinical Review Team to provide input/guidance for the design of Phase IV studies to evaluate the effect(s) of levofloxacin on the QT-interval of the electrocardiogram (ECG). These Phase IV commitments were discussed with the sponsor and included in the February 2, 2000 approval letter for PRSP-CAP. The considerations for the design of such Phase IV studies, as outlined by the OCPB reviewer and provided to the Clinical Review Team, are provided below.

WITHHOLD 1 PAGE(S)

/S/ 3/17/2000

Philip M. Colangelo, Pharm.D., Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation 3

RD/FT signed by Funmi Ajayi, Ph.D (TL) /S/ 3/17/00

cc:
Div. File (HFD-590): NDA 20-634, S-008
HFD-590 (J. Fritsch, PM/CSO)
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HFD-205 (FOI)
HFD-880 (F. Ajayi, TL)

APPEARS THIS WAY
ON ORIGINAL

HFD 590
FRITSCH

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA:	**20-635, Supplement S-007**
Submission Date:	March 31, 1999
Drug Product:	Levofloxacin 25 mg/mL and 5 mg/mL Injection
Trade Name:	LEVAQUIN®
Sponsor:	R.W. Johnson Pharmaceutical Research Institute Raritan, NJ
Submission Type:	Efficacy Supplement – Treatment of Community Acquired Pneumonia due to Penicillin-Resistant *Streptococcus pneumoniae* (PRSP-CAP)
Category:	1S
OCPB Reviewer:	Philip M. Colangelo, Pharm.D., Ph.D.

MAR 17 2000

I. BACKGROUND / INTRODUCTION

This supplement to NDA 20-634 for levofloxacin tablets and NDA 20-635 for levofloxacin injection was submitted to allow use of levofloxacin for the treatment of levofloxacin-susceptible strains of penicillin-resistant *Streptococcus pneumoniae* in patients with community acquired pneumonia (PRSP-CAP) at a dosage regimen of 500 mg orally or IV Q24 hrs for 7-14 days. This indication and treatment regimen for PRSP-CAP was subsequently approved by the Division of Special Pathogen and Immunologic Drug Products (HFD-590) on February 2, 2000.

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CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA:	**20-634, Supplement S-009**
Submission Date:	April 1, 1999
Drug Product:	Levofloxacin 250 mg and 500 mg Tablets
Trade Name:	LEVAQUIN®
Sponsor:	R.W. Johnson Pharmaceutical Research Institute Raritan, NJ
Submission Type:	Labeling Supplement – Combined Label for Levofloxacin Tablets and Injection
Category:	1S
OCPB Reviewer:	Philip M. Colangelo, Pharm.D., Ph.D.

I. BACKGROUND / INTRODUCTION

This supplement to NDA 20-634 for levofloxacin tablets and NDA 20-635 for levofloxacin injection was submitted to provide a combined label for LEVAQUIN Tablets and Injection. This combined label was subsequently approved by the Division of Special Pathogen and Immunologic Drug Products (HFD-590) on February 2, 2000.

II. SUBMISSION SYNOPSIS

This submission contained only labeling information for levofloxacin and was also linked to the supplement for the use of levofloxacin in the treatment for the treatment of penicillin-resistant *Streptococcus pneumoniae* in patients with community acquired pneumonia (PRSP-CAP). There was no human pharmacokinetics / bioavailability information provided with this supplement. Thus, there is no formal review from the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). However, the OCPB reviewer was consulted by the HFD-590 Clinical Review Team to provide input/guidance for the design of Phase IV studies to evaluate the effect(s) of levofloxacin on the QT-interval of the electrocardiogram (ECG). These Phase IV commitments were discussed with the sponsor and included in the February 2, 2000 approval letter for PRSP-CAP. The considerations for the design of such Phase IV studies, as outlined by the OCPB reviewer and provided to the Clinical Review Team, are provided below.

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volunteers. The age of study subjects should cover a broad range, i.e., 18 years and older, and should also include elderly subjects (i.e., 65 years and older). The sponsor should consider the inherent variability in the PD parameter, QTc, and also in the pharmacokinetics (PK) of levofloxacin when assessing the number of subjects required needed to make adequate statistical comparisons. It is expected that at least 30 to 40 subjects should be evaluated in each study.

Single doses of levofloxacin and comparator drugs should be at the recommended doses and/or escalated to several multiples of the recommended doses. There should be a sufficient washout period between the doses and between each of the treatments (i.e., at least 5 half-lives).

Serial blood sampling for pharmacokinetic (PK) analysis should cover the time period of the actual occurrence of Cmax for each subject, i.e., from predose (0 hrs) through 8 to 12 hours postdose.

Measurement of the QTc (using Bazzett's correction) should be performed using 12-lead ECG readings at baseline (i.e., mean of 3 ECG readings at predose) and at the same time as each PK sample. ECG's should be read manually by an experienced cardiologist. The change in QTc from baseline, based on the QTc obtained at each individual subject's actual Cmax obtained with each dose and each drug, should be determined. In addition, changes in QTc should be determined as the difference between the maximum QTc observed over the first 8 to 12 hours after dosing and placebo. The primary analysis that would be expected is regression of QTc and/or change in QTc from either baseline or placebo with the actual Cmax for each subject and from each treatment.

Suggested Studies

Study 1: Noncomparative Single Dose Escalation Study
All subjects would receive the following levofloxacin oral doses and placebo in a randomized, blinded, crossover fashion:

Levofloxacin Tablets – 250 mg, 1000 mg, and 2000 mg

Placebo Tablets

Study 2: Comparative Single Dose Escalation Study
All subjects would receive the following doses of the following drugs and placebo in a randomized, blinded, crossover fashion:

Levofloxacin Tablets – 1000 mg

Moxifloxacin Tablets – 800 mg

Ciprofloxacin Tablets – 1500 mg

Placebo Tablets

B. *In Vitro* IK, Comparative Studies – Considerations

- Two cell lines – AT-1; HERG
- Include positive control, i.e., a Type III antiarrhythmic, e.g., sotalol, dofetilide, (others).
- Comparative anti-infectives should include the same as those evaluated *in vivo* in Study 2, i.e., moxifloxacin, ciprofloxacin, and sparfloxacin, but do not necessarily need to be

limited only to these. For example, may also want to include gatifloxacin and/or erythromycin.

- Drug concentrations need to bracket as well as exceed those that are observed/expected clinically with recommended doses.

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