

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 020635

Trade Name : LEVAQUIN INJECTION

Generic Name: Levofloxacin Injection

Sponsor : R. W. Johnson Pharmaceutical

Approval Date: December 20, 1996



Food and Drug Administration
Rockville MD 20857

DEC 20 1996

NDA 20-635

R.W. JOHNSON, Pharmaceutical Research Institute
Attention: Heather Jordan, Associate Director, Regulatory Affairs
920 Route 202
P.O. Box 300
Raritan, New Jersey 08869-0602

Dear Ms. Jordan:

Please refer to your December 21, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levaquin® (levofloxacin) Injection.

We acknowledge receipt of your amendments dated January 19, 1996; February 9, 1996; March 20, 1996; April 26, 1996; May 31, 1996; July 17, 1996; August 23, 1996; September 26, 1996; October 3, 28, and 31, 1996; November 7, 11, 20, and 27, 1996; and December 3, 9, and 13, 1996.

We also acknowledge the receipt of your letter dated December 13, 1996, requesting the withdrawal of the

This new drug application provides for the indications of Acute maxillary sinusitis, Acute bacterial exacerbations of chronic bronchitis, Community-acquired pneumonia, Uncomplicated skin and skin structure infections, Complicated urinary tract infections, and Acute pyelonephritis.

We have completed the review of this application, including the submitted draft labeling, 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 December 18, 1996 draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling dated December 18, 1996. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-635. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Anti-Infective Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

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, please contact Ms. Frances LeSane, Project Manager at 301) 827-2125.

Sincerely yours,

 12-20-96

David W. Feigal, Jr., M.D., M.P.H.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE

cc:

Original NDA 20-635

HFD-520/Div. file

HFD-2/M.Lumpkin

HFD-104/TNearing

HFD-101/L.Carter (with labeling)

HFD-830/E.Sheinin

DISTRICT OFFICE

HF-2/Medwatch (with labeling)

HFD-92 (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613 (with labeling)

HFD-735/(with labeling) - for all NDAs and supplements for adverse reaction changes.

HFD-021/J.Treacy*(with labeling)

HFD-520/MO/RHopkins *with 12/19/96*

HFD-520/MO/KFrank *KA 19-Dec-96*

HFD-520/CHEM/BShetty

HFD-520/PHARM/SJoshi

HFD-520/BIOPHARM/FAjayi *PCR*

HFD-520/MICRO/RKing

HFD-520/STAT/NSilliman

HFD-520/PMS/FVLeSane/11-19-96/revised 12-18-96 *FD 12-18-96*

TEAM LEADERS

HFD-520/TLMO/MAIbuerne

HFD-520/Act.TLCHEM/DKatague *12/19/96*

HFD-520/TLPHARM/ROsterberg *12/19/96*

HFD-520/TLBIOPHARM/FPelsor *12/19/96*

HFD-520/TLMICRO/ASheldon

HFD-520/TLSTAT/DLin *12/19/96*

Concurrence Only:

HFD-520/TLMO/MAIbuerne *mda 12/19/96*

HFD-520/CPMS/JBona

APPROVAL

Pharm/Tox

JUL 5 1996

Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

Date CDER Received: 12/22/95
Date Assigned: 12/27/95
Date Review Started: 12/28/95
Date 1st. Draft Completed: 4/15/96
Date Review Accepted by Supervisor: 5/24/96

NDA # 20-635 (Original Submission dated 12/21/95)

Number of Volumes: 3

Drug: ELEQUINTM (levofloxacin) I.V.

Other Drug Names/Codes: RWJ-25213-097

Sponsor: The R.W. Johnson Pharmaceutical Research Institute,
Raritan, NJ

Contact Person: Heather L. Jordan 908/704-4607

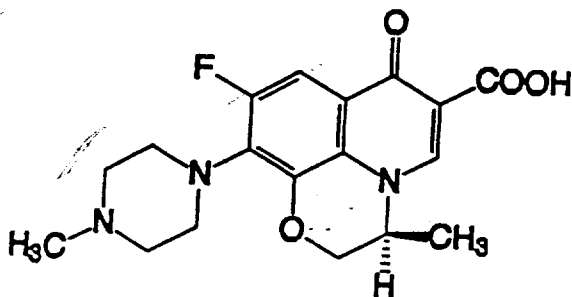
Category: Fluoroquinolone

Dosage Form: Injection, i.v., 5 mg/ml. 25 mg/ml

Indication: Various acute bacterial infections, complicated
UTI, uncomplicated skin and skin structure
infections.

Chemistry: Levofloxacin, a chiral fluorinated
carboxyquinolone, is the pure (-)-(S)-enantiomer
of the racemic drug substance ofloxacin. The
chemical name is:

(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-
piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-
benzooxazine-6-carboxylic acid hemihydrate



.1/2 H₂O

Formulations:

A. Levofloxacin I.V., 25 mg/ml (Single-Use Vial):

Component	Amount/Unit Dose
Levofloxacin(hemihydrate)	mg*
Water for injection	mL

* This quantity is equivalent to _____ mg of levofloxacin anhydrous. The pH adjusted to _____

B. Levofloxacin Injection, 5 mg/ml (Pre-Mixed Flexible Container)

Component	Amount/Unit Dose
Levofloxacin(hemihydrate)	mg*
Dextrose (Monohydrate)	mg
OR	
Dextrose (Anhydrous)	mg
Water for Injection q.s. to	mL

* This quantity is equivalent to _____ mg of levofloxacin anhydrous. The pH adjusted to _____

Related Submissions:

Levofloxacin: INDs' NDA 20-634 (tablets)
Ofloxacin: NDAs 19-735 (tablets) and 20-087 (i.v.)

Review Objectives: Review preclinical data with regard to safety for the proposed marketing of the drug product.

Pharmacology/Toxicology:

All preclinical pharm./tox. data was submitted and reviewed in NDA 20-634. The applicant requests to incorporate this data to their NDA 20-635 by cross-reference. [Please see attached copy of my review of NDA 20-634]

Comments:

1. The new drug substance (NDS), levofloxacin, is a broad-spectrum, synthetic antibacterial agent belonging to the quinolone class of compounds.
2. Chemically, levofloxacin is the l-isomer of the racemate, ofloxacin (FLOXIN[®]). Ofloxacin is currently marketed in the U.S. in both oral and parenteral dosage forms.
3. Toxicologically, levofloxacin is generally comparable to the marketed ofloxacin (see above).
4. 500 mg/kg [equivalent to 10 mg/kg in 50 kg person] is the proposed human clinical oral and intravenous dose. Animal toxicology studies were conducted at multiples of this dose.
5. The nonclinical pharm/tox data submitted in the NDA provide sufficient information to support the safety of this drug.
6. The applicant has initiated a photocarcinogenicity in a rodent and will be reviewed in phase 4.
7. Labelling with regard to carcinogenesis, mutagenesis, impairment of fertility, pregnancy category has been revised. (see attached)

Recommendation: Approval of the drug.

Key Words: levofloxacin, sparfloxacin, enoxacin, arthropathy

S. R. Joshi 7/3/96

ATTACHMENT:

S.R. Joshi, D.V.M., Ph.D.

cc:

Orig.NDA

HFD-340

HFD-520

HFD-520/Pharm/Joshi

HFD-520/MO/~~Medina~~ *Hickins* Concurrance Only HFD-520/Dep.Dir/L.Gavrilovich

HFD-520/Chem/Shetty HFD-520/SPharm/REOsterberg

HFD-520/Micro/King

HFD-520/CSO/Fogarty/LeSane

HFD-520 /rd init. by REOsterberg

R/D/4/15/96/FT/6/3/96/7/3/96/SRJ

N-20-635.001

to 7/5/96

REC 7/3/96

Bio

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20,635
Levofloxacin, IV injection

SUBMISSION DATES: Dec. 21, 1995,
Feb. 5, 1996, Mar. 20, 1996, May 31, 1996,
July 3, 1996, Aug. 2, 1996 & Aug. 23, 1996

R.W. Johnson Pharmaceutical Research Institute **REVIEWER:** Funmilayo O. Ajayi, PhD
920 Route 202 South, P.O. Box 300

Raritan, NJ 08869 **TYPE OF SUBMISSION:** Original NDA **CODE:** 1-S

SYNOPSIS: The application was submitted for levofloxacin which is being proposed for the treatment of adults suffering from infections of the upper and lower respiratory tract, urinary tract, and skin and skin structure caused by susceptible strains of responsible microorganisms.

In support of this application, the sponsor carried out various pharmacokinetic studies that address issues such as drug interactions, systemic availability and disposition of levofloxacin in healthy adults, the elderly, patients with renal impairment, and those with HIV infection. Overall, the pharmacokinetics of levofloxacin is similar to that of the racemic mixture, ofloxacin. There was no evidence of interconversion to the d-isomer (d-ofloxacin) following administration of levofloxacin. The absorption is significantly reduced when administered with aluminum and magnesium containing antacids. Statistically significant increases were observed for AUC_{0-∞} and T_{1/2} following co-administration of a single 500 mg dose of levofloxacin with cimetidine and probenecid; while CL_R were statistically significantly reduced. No significant drug interaction was observed following co-administration with digoxin, cyclosporine, theophylline or warfarin. The elimination of levofloxacin is mainly affected by the degree of renal function. Thus, dosage adjustment is required in subjects with renal impairment.

RECOMMENDATION: The information provided in the Human Pharmacokinetics and Bioavailability section of NDAs 20,634 and 20,635 for levofloxacin tablets and IV injection is acceptable because it meets the requirements set forth in 21 CFR 320. The proposed dissolution method, 900 ml of 0.1N HCl in USP Apparatus I at 100 rpm, and specification of NLT % of label claim dissolved in minutes is acceptable.

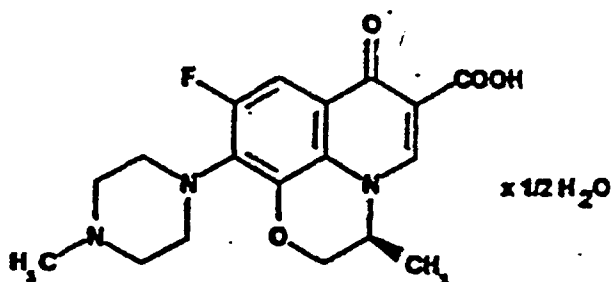
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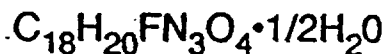
ORGANIZATION OF REVIEW: Following the background is a description of the drug formulation and dissolution method and specification. The summary of the studies is followed by the general comments, labeling comments, and comments to the Firm.

BACKGROUND: Levofloxacin is the levorotatory isomer of the D,L-racemate of ofloxacin and a synthetic, fluorinated carboxyquinolone belonging to the quinolone class of antibacterial agents. Levofloxacin differs from the older generation quinolones such as nalidixic acid by the presence of a fluorine and an N-methylpiperazine substituent. It is chemically distinct from other compounds comprising the newer generation of quinolones with respect to the presence of a benzoxazine ring. Levofloxacin is said to be significantly more soluble than the D-isomer, which should reduce the possibility of crystalluria. It was reported that levofloxacin acts by binding to topoisomerase II (DNA gyrase) and topoisomerase IV which is another enzyme that regulates the superhelicity of DNA, with much greater affinity than the dextro (D-) rotatory species. Levofloxacin has also been shown to be a broad spectrum antibacterial agent, which is active against both conventional and atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. As at the time of submission of this NDA, levofloxacin is marketed in 4 countries namely Japan, Hong Kong, China, and Korea.

Structure of Levofloxacin



Molecular Formula



Molecular Weight

370.38

FORMULATION: The Tables below shows the components for the 250 mg and 500 mg tablets as well as that for the IV formulation.

Levofloxacin Tablet Strength/Components	mg/Tablet
250 mg: FD-25213-097-AB-22	
✓ Levofloxacin hemihydrate (RWJ-25213-097)	
✓ Hydroxypropyl Methylcellulose 2910, USP	
✓ Crospovidone, NF	
✓ Microcrystalline Cellulose, NF	
✓ Magnesium Stearate, NF	
✓ Polyethylene Glycol 8000, NF	
500 mg: FD-25213-097-AA-22	
Levofloxacin hemihydrate (RWJ-25213-097)	
Hydroxypropyl Methylcellulose 2910, USP	
Crospovidone, NF	
Microcrystalline Cellulose, NF	
Magnesium Stearate, NF	
Polyethylene Glycol 8000, NF	

^a This excipient is essentially removed during processing.

Ingredient	mg/unit dose	
	FD-25231-097-D-45 ^a (25 mg/mL)	(5 mg/mL)
Levofloxacin (hemihydrate)	25.6 mg	5.0 mg
		mg
	mL	mL

^a Formula FD-25213-097-D-45 is the proposed commercial formulation for Levofloxacin Injection, 25 mg/ mL, which is the subject of NDA 20-635.

DISSOLUTION: The proposed dissolution method for levofloxacin tablets utilizes USP Apparatus I (basket) containing 900 ml of 0.1 N HCl maintained at 37°C and a rotation of 100 rpm. The dissolution specification (Q) of NLT 85% dissolved in 30 minutes is proposed. All through the NDA, the tablets used have all passed the dissolution testing. The sponsor was requested to provide the dissolution of levofloxacin in other media. However, the following response was submitted and constitute the rationale for (a) using the proposed dissolution method and (b) for not making further efforts to evaluate the dissolution profile in other media:

(1) the sponsor prefers the use of similar dissolution method for levofloxacin as for the approved ofloxacin tablets.

(2) the pH-solubility profile for levofloxacin hemihydrate between 0.56 and 5.84 is flat (73 - 108 mg/ml). Thus, dissolution testing at any pH within this range is expected to be similar. The solubility of levofloxacin hemihydrate was observed to increase with further increases in pH to a maximum of 272 mg/ml at pH 6.74 and minimum pH-solubility profile at pH 7 to 8.

(3) the publication by Russell *et. al.*, Pharm. Res., 1993 provided a report of the gastric and duodenal pH levels measured in 79 healthy elderly men and women under fasted and fed condition using the Heidelberg capsule technique. Overall, the reported minimal and maximal pH values were 1.1 and 6.7.

ANALYTICAL METHOD: Two validated high performance liquid chromatographic (HPLC) methods that achieved chiral discrimination between D- and L-ofloxacin were employed in the quantitation of levofloxacin in biologic fluids.

SUMMARY OF STUDIES:

1. **Pharmacokinetics:** Levofloxacin is rapidly and almost completely absorbed following oral administration with an absolute bioavailability of ~ 99% and a mean apparent volume of distribution of ~ 95 L. The peak plasma concentration (C_{max}) in healthy subjects ranges from 7 to 12 $\mu\text{g/ml}$ following a 500 mg oral dose. The mean apparent total clearance and renal clearance following a single or multiple (q.d. or b.i.d) 250 or 500 mg IV or oral dose ranged from 144 - 226 ml/min and 96 - 142 ml/min, respectively. Following the above dosing regimen, the mean terminal elimination half-life ranged from approximately 6 to 8 hours. The renal clearance is in excess of glomerular filtration rate suggesting tubular secretion of levofloxacin in addition to glomerular filtration. The residual intra-subject variability was estimated from the NONMEM analysis of

pooled data to be 25% and 18.6% at plasma concentration of 1 $\mu\text{g/ml}$ and $\geq 7 \mu\text{g/ml}$, respectively. Inter-subject variability (95% CI) for CL, V and KA are: 21.3 (15.3 - 25.9)%, 24.5 (0 - 35.2)% and 268.5 (0 - 443.7)%, respectively. The inter-subject variability around V and KA can not be adequately estimated because of the lack of enough data points.

1.1 Metabolism and disposition: Levofloxacin is mainly bound to human serum albumin. In-vitro, over a clinically relevant serum/plasma concentration of $\mu\text{g/ml}$, levofloxacin is approximately 24 - 38% bound to serum proteins. It undergoes limited metabolism in humans and is mainly excreted as unchanged drug in urine. Approximately 87% of an administered dose was recovered unchanged in urine in 48 hours; while $< 4\%$ of the dose was recovered in 72 hour feces. Desmethyl levofloxacin (M2) and levofloxacin N-oxide (M3) accounted for ~ 1.75 and 1.63% of the dose, respectively. These metabolites were reported to have little relevant pharmacological activity.

1.2 Bioavailability and bioequivalence: The pharmacokinetics of the individual enantiomers of ofloxacin have been compared and reported in the 8/19/94 submission to IND reviewed by Dr. Ette. The results showed similar values for the bioavailability parameters (C_{max} , AUC & Ae) for both levofloxacin and d-ofloxacin.

Following a review of study # M92-035 (RWJPRI) contained in the 7/11/94 submission to IND 36,627 by Dr. Ette, the 500 mg (hemihydrate levofloxacin, RWJPRI) single clinical tablet was found to be bioequivalent to 5x100 mg (488 mg anhydrous levofloxacin - European formulation, DF). The 500 mg market-image tablet (RWJPRI) was compared to the 500 mg clinical tablet (RWJPRI) in study # LOFBO-PHIO-097 contained in the 5/2/95 submission to IND #s

Dr. Sun's review of the data showed that the market image failed the bioequivalence test because the C_{max} exceeded the 90% CI limit.

In study # HR 355/1/GB/103 (LOFBO-PHIO-100), the 500 mg RWJPRI clinical tablet formulation was compared to the 500 mg HAG tablet and IV formulations. Data from this study demonstrated bioequivalence for the two tablet formulations. In study # LOFBO-PHIO-096 bioequivalence was demonstrated for the RWJPRI 250 mg market-image tablet formulation and 2x125 mg RWJPRI clinical tablet formulation. Study # LOFBO-PHI-104 is a repeated study that compared the 500 mg to-be-marketed formulation to the RWJPRI 500 mg clinical tablet formulation. Results from this study showed that the two tablet formulations are bioequivalent.

Although bioequivalence, as defined by similar rate and extent, can not be proven for a 500 mg dose of levofloxacin given via the IV and oral routes, the degree of exposure (AUC) is comparable following both routes of administration.

1.3 Dose proportionality: The AUC and C_{max} of levofloxacin following single and multiple once daily administration increased linearly over a dose range of 50 mg to 600 mg (study # 91/17). Similarly, these parameters increased proportionally following single and multiple 750 mg and 1 gram oral doses (study # LOFBO-PHIO-093).

1.4 Multiple dosing: The pharmacokinetics of levofloxacin following multiple IV doses (500 mg q 12h - study # L91-054 and 500 mg q24h for 9 days - study # L91-053) was evaluated in normal healthy subjects and reported in a 7/22/94 submission to IND reviewed by Dr. Ette. The extent of accumulation as evaluated from the day10/day1 AUC and C_{max} ratios are 1.06 and 1.14

(study # L91-054) and 0.99 & 1.01 (study # L91-053), respectively. These values were close to the predicted/theoretical of 1.47 for the q.d. and 1.11 for the b.i.d. dosing regimens. The disposition parameters were similar following the two multiple dosing regimen. These results are comparable to those following 500 mg multiple oral doses (study #s K90-077 and K90-014).

The pharmacokinetics of levofloxacin were compared after single and multiple daily or b.i.d. 500 mg oral doses and once daily 750 mg or 1 gram doses in healthy subjects (study # LOFBO-PHIO-093). Overall, a modest accumulation that is predictable from the single dose data was observed and the disposition kinetics of levofloxacin are comparable to those following single oral and IV administration.

1.5 Food effect study: Administration of levofloxacin with food resulted in delayed absorption (60% increase in T_{max}), and slight decrease in the C_{max} (14%) and AUC (10%). Overall, these differences are not of such magnitude that preclude administration of levofloxacin tablets with food [study # HR 355/1/USA/105(LOFBO-PHIO-099)].

1.6 Tissue concentration: The tissue:plasma concentration ratios of levofloxacin were evaluated in study #s LOFBO-PHI-095, HR 355/1/USA/104/GP (N93-069), and HR 355/1/USA/103/GP (N93-070). The tissue:plasma ratio varies from 0.11 to ~ 3 in the cortical and spongiosa bone tissue, blister fluid exudate, and lung tissue.

2. Drug interaction studies:

2.1 Calcium, Aluminum and Magnesium containing antacids: The sponsor proposed identical labeling for levofloxacin dosage and administration as for ofloxacin with respect to interaction with aluminum and magnesium containing antacids in the 8/19/94 submission to IND reviewed by Dr. Ette. This labeling request was found acceptable following a review of submitted information. However, a review of the literature indicated lack of significant effect of ranitidine (H₂ receptor antagonist) and calcium carbonate on the bioavailability of levofloxacin (Shiba *et al.*, Antimicrobial Agents and Chemotherapy, 1992; 36, 2270 - 2274). Hence, the proposed labeling should be made to reflect this finding by removing calcium containing antacids from the list of antacids referred to in the labeling.

2.2 Theophylline: The effect of multiple oral dose of levofloxacin (500 mg q12h x 9 doses), at steady-state, on the kinetics of a single 4.5 mg/kg 30-minute I.V. infusion of theophylline was evaluated in 14 healthy males who completed the study (study # LOFBO-PHI-101). The results showed that the pharmacokinetics of a single 4.5 mg/kg I.V. infusion of theophylline were not significantly altered by steady-state levels of levofloxacin. The steady state kinetics of levofloxacin were similar to those observed in studies where multiple 500 mg oral doses of levofloxacin were administered. A similar result was obtained in another study that evaluated the effect of multiple oral doses of 97.6 mg levofloxacin, q8h Days 5 through 9 on the pharmacokinetics of multiple oral doses of 200 mg theophylline administered twice daily on Days 1 - 9 (study # 3355J-MET038; not reviewed).

2.3 Warfarin: The effect of multiple oral dose of levofloxacin (500 mg q12h x 9 doses), at steady-state, on the kinetics of a single 30 mg oral dose of racemic warfarin was evaluated in 16 healthy

male subjects (study # LOFBO-PHI-098). The results showed that the steady-state levels of levofloxacin had no significant effect on the disposition and anticoagulant effect of R- or S-warfarin.

2.4 Cyclosporine: The effect of multiple oral dose of levofloxacin (500 mg q12h x 11 doses), at steady-state, on the kinetics of a single 10 mg/kg oral dose of cyclosporine was evaluated in 14 healthy men and women (N93-059). The results showed that the pharmacokinetics of a single 10 mg/kg oral dose of cyclosporine were not significantly altered by steady-state levels of levofloxacin.

2.5 Digoxin: The effect of multiple oral dose of levofloxacin (500 mg q12h x 11 doses), at steady-state, on the kinetics of a single 0.4 mg oral dose of digoxin was evaluated in 12 healthy men and women (study # LOFBO-PHI-094). The results showed that the pharmacokinetics of a single 0.4 mg oral dose of digoxin were not significantly altered by steady-state levels of levofloxacin. The steady state kinetics of levofloxacin, with and without concomitant digoxin administration, were similar.

2.6 Cimetidine and probenecid: The effect of multiple oral dose of cimetidine (400 mg q12h x 7 days) or probenecid (500 mg q6h x 7 days) on the kinetics of a single 500 mg of levofloxacin, given on Day 4, was evaluated in 12 healthy male subjects (study # HR 355/1/GB/101). There was no statistically significant changes in the C_{max} and T_{max} of levofloxacin following co-administration with cimetidine or probenecid; indicating little or no changes in the rate of absorption. However, statistically significant increases were observed for $AUC_{0-\infty}$ (27% cimetidine, 38% probenecid) and $T_{1/2}$ (~ 30%). The reductions seen in CL_R were also statistically significant and are 119 ml/min, 91 ml/min and 77 ml/min for levofloxacin alone, with cimetidine and with probenecid, respectively. In general, the observed reductions in CL/F can be attributed to the reductions in CL_R when levofloxacin was co-administered with cimetidine or probenecid.

3. Special population:

3.1 Elderly: The effect of age on the pharmacokinetics of a single 500 mg oral dose of levofloxacin was evaluated in study # N93-024. There was a trend for increased C_{max} and $AUC_{0-\infty}$ with age. The C_{max} , $AUC_{0-\infty}$, Vd/F , T_{max} , CL_R , and CL/F were statistically significantly altered in the elderly. However, differences in total amount excreted (A_e) and T_{max} were not significant. These observed differences were attributable to the differences in renal function. This conclusion is supported by the data from the NONMEM analysis. Thus, dosage adjustment based on age considerations alone is not deemed necessary.

3.2 HIV Patients: The pharmacokinetics of single and multiple oral dosage regimens of levofloxacin was evaluated in HIV seropositive subjects. In study # N93-032, a 750 mg once daily oral dose administered for 14 days followed by 750 mg or 1 gm thrice weekly (t.i.w.) oral doses administered for 2 weeks was evaluated in parallel in patients with CD4 cell counts < 250 and \geq 250. The differences observed in the kinetics of levofloxacin in the 2 groups was attributed to the differences in the renal function [mean CL_{CR} (range) = 83 (50 - 140) ml/min for patients with CD4 cell count < 250; 108 (81 - 182) ml/min for patients with CD4 cell count \geq 250]. The results indicate a linear relationship in the kinetics of levofloxacin following the 750 mg (q.d. & t.i.w.)

and 1 gm (t.i.w.) doses. Also, there was a reasonable degree of accumulation following the multiple oral doses. Two other studies (K90-024 & K90-086) evaluated the pharmacokinetics of levofloxacin following single and multiple (t.i.d.) 350 mg oral doses for 10 days in HIV patients with and without concurrent therapy with AZT. Results from both studies indicate attainment of steady-state plasma levels within 3 days with minimal accumulation upon multiple dosing. There was an agreement in the observed data points and the simulated plasma concentration profile. The kinetics of levofloxacin does not appear to be affected by concomitant administration of AZT. The kinetics of levofloxacin in the HIV patients are similar to that of healthy subjects. No dosage adjustment is thus necessary in this patient population with or without concomitant therapy with AZT.

3.3 Renal disease: The pharmacokinetics of a single 500 mg oral dose of levofloxacin was evaluated in subjects with varying degrees of renal impairment (study # M92-046). There was a good linear correlation between the degree of renal impairment and the plasma clearance as well as the elimination half-life. Overall, less than 15% of the administered dose of levofloxacin (maximum observed amount = 64 mg, in 1 individual) was removed by hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Thus, administration of extra dose following hemodialysis is not warranted as these processes do not significantly remove levofloxacin from the body. The following dosage adjustment was recommended for each group following a simulation (superposition method) based on the parameter values obtained in this study:

CrCl > 80 ml/min - 500 mg q12h or q24h

CrCl = 50 - 80 ml/min - 500 mg q24h

CrCl = 20 - 49 ml/min - 500 mg start, followed by 250 mg q24h

CrCl = 10 - 19 ml/min - 500 mg start, followed by 250 mg q48h

Subjects on hemodialysis or CAPD - 500 mg start, followed by 250 mg q48h

3.4 Gender: Results from study # N93-024 revealed statistically significant differences in C_{max} , T_{max} , apparent volume of distribution (Vd/F), $T_{1/2}$, and CL/F but not CL_R and $AUC_{0-\infty}$ between males and females. In general, the C_{max} in females compared to males was 26% higher, T_{max} was increased by 46% (~0.5h), while the Vd/F, $T_{1/2}$ and CL/F were decreased by 15%, 19% and 18%, respectively. The differences in the pharmacokinetic parameters between the genders were no longer statistically significant when the CrCl of each subject was included as a covariate in the ANOVA model. In fact, good correlations were observed between the subject's CrCl and C_{max} , $AUC_{0-\infty}$, CL/F, and CL_R . Although the observed differences between the genders seem unexplainable, it could in part, be attributable to the observed differences in the renal function. This conclusion is supported by the data from the NONMEM analysis which was verified by Dr. Ette. Good correlations were also observed between the C_{max} , Vd/F and each subject's body weight. Data from simulations of the steady-state plasma concentration profiles for females below 50 kg body weight with compromised renal function, using parameter values from NONMEM analysis and the relevant adjusted dosage regimen, indicated a profile within the concentration range (1- 10 $\mu\text{g/ml}$) seen in normal subjects. Similar differences in the pharmacokinetic parameters were observed in data from studies where males and females were enrolled. However, the magnitude are not high enough to warrant different dosing regimen for females.

3.5 Race: The NONMEM analysis of pooled data from 4 studies indicated similar CL/F and Vd/F for non-white (N=24) and white (N=48) subjects. The NONMEM analysis was reviewed and found acceptable by Dr. Ette.

4. Pharmacokinetic / pharmacodynamic (PK/PD) relationship: A recent 4-month safety update submission contained a report of a multi-center multiple dose study where the pharmacokinetics of levofloxacin was evaluated in hospitalized patients with community acquired infection using population kinetics study design. The relationship between the derived PK parameters (AUC, C_{max}) and clinical outcome, adverse events as well as the microbiological (MIC) outcome was evaluated using logistic regression and Classification And Regression Tree (CART) approach. From a preliminary review, the breakpoint for the C_{max} /MIC ratio was reported by the investigator to be 12.2 for both clinical and microbiological outcomes. Hence, for patients that achieve a C_{max} /MIC ratio of ≥ 12.2 , the probability of a successful clinical and microbiological outcome is $> 95\%$. The report will be further analyzed when the requested data files become available.

GENERAL COMMENTS (Need Not Be Sent to Firm):

1. Five study protocols (LOFBO-PHIO-094 - levofloxacin/digoxin drug interaction study, LOFBO-PHIO-097 - BE study, LOFBIV-MULT-001 - pharmacokinetics in patients with bacterial infections, LOFBO-PHIO-099 - food and age effect, LOFBO-PHI-101 - levofloxacin/theophylline drug interaction) were reviewed prior to initiation of the studies. The sponsor utilized the comments made by the reviewers of the protocols.

2. Five studies (M92-035 - 500 mg vs. 1x500 mg BE study, L91-053 & L91-054 - single vs. Multiple IV dosing, LOFBO-PHIO-097 - 500 mg market-image vs. Clinical BE study) were reviewed prior to the submission of the NDA.

3. Overall, reports of 40 studies were submitted. Five of these were reviewed prior to the submission of the NDA, while I reviewed 28 studies that were pertinent to the description of the disposition of levofloxacin in healthy subjects and special population as well as describe its drug-drug interaction potential.

LABELING COMMENTS: The following sections of the labeling should be modified as thus edited (in italics):

Drug Interactions:

Dosage and Administration: The following statement should be added:

Funmilayo O. Ajayi 9/30/96

Funmilayo O. Ajayi, PhD
Div. of Pharmaceutical Evaluation III

(Clin. Pharm. Biopharm. Briefing - 9/27/96: Lesko, Collins, Fleischer, Albuerne, Hopkins, Huang, Mei-Ling Chen, Pelsor, Lazor, Baweja, Sun, LeSane, Ajayi)

RT initialed by Frank Pelsor, PharmD.....*F. Pelsor*.....

cc: NDA 20,635 HFD-520 (Clinical Division)
cc: HFD-880 (DPE3, Pelsor, Ajayi).
cc: HFD-870 (Bott)
cc: HFD-340 (Vish)

micro

AUG 14 1996

~~ORIGINAL~~

REVIEW FOR HFD-520
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

Microbiologist's Review # 1 of NDA 20-635
August 12, 1996

A. 1. APPLICATION NUMBER: 20-635

APPLICANT: The R.W. Johnson Pharmaceutical Research Institute
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869-0602

2. PRODUCT NAMES: Levofloxacin Injection (Elequin I.V.), 50 ml and 100 ml flexible IV containers.

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 5 mg/ml.
Levofloxacin Injection is to be administered intravenously.

4. METHOD(S) OF STERILIZATION: Terminal sterilization

5. PHARMACOLOGICAL CATEGORY: 1S. Proposed indications for use: Acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, complicated urinary tract infections, acute pyelonephritis, uncomplicated skin and skin structure infections and complicated skin and skin structure infections.

B. 1. DATE OF INITIAL SUBMISSION: May 25, 1995

2. AMENDMENT: none

3. RELATED DOCUMENTS: DMF

4. ASSIGNED FOR REVIEW: July 30, 1996

5. DATE OF CONSULT REQUEST: July 29, 1996

C. REMARKS:

Please note that the microbiology consult was requested a month before the desired completion date.

The drug product is contract manufactured by
DMF dated 5/25/96, section E. 18. "Levofloxacin Injection in IV Flexible
Container, (R.W. Johnson Pharmaceutical Research Institute, 1000 Route 202, Raritan,
NJ 08869)" is the subject of this review.

D. CONCLUSIONS:

The heat sterilization data of the drug product are adequate for sterility assurance.
The submission is recommended for approval for issues concerning microbiology.

*Please note that stability program with regard to sterility testings and endotoxin
levels is not included in DMF and is therefore not reviewed here.*

Brenda Uratani 8/12/96

Brenda Uratani, Ph.D.

cc:

NDA 20-635

HFD-520/ Div. File

HFD-805 /Uratani

HFD-/CSO/LeSane

drafted by: Brenda Uratani, 8/12/96

R/D initialed by P.Cooney, 8/12/96

*Pte
8/14/96*

Chem

HPD 520
CSO LESANE

16 1996

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-635	CHEM. REVIEW #: 1	REVIEW DATE: 1/29/96	
		<i>Revision 9/16/96</i>	
SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL: Original Submission	12/21/95	12/22/95	12/27/95

NAME & ADDRESS OF APPLICANT:
 The R.W. Johnson Pharmaceutical
 920 Route 202 South
 P.O. Box 300, Raritan N.J.
 08869-0602

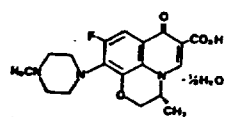
DRUG PRODUCT NAME
 Proprietary: **Levaquin**
 Nonproprietary/USAN: **Levofloxacin injection**
 Code Names/ETs:
 Chemical Type/
 Therapeutic Class: **1 s**

ANDA Suitability Petition/DESI/Patent Status:
 N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION: Quinolone, antibacterial

DOSAGE FORM: Injection
STRENGTHS: 25 mg/mL, 5 mg/mL
ROUTE OF ADMINISTRATION: Intravenous Infusion
DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

- (1) United States adopted name (proposed)
levofloxacin
- (2) International nonproprietary name
levofloxacin
- (3) Code name
DR-3355
- (4) 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
- (5) Chemical abstracts service number
10096-85-4
- (6) Chemical structure

- (7) Molecular formula
C₁₅H₂₀FN₃O₄ · 1/2H₂O
- (8) Molecular weight
370.38

SUPPORTING DOCUMENTS:

The following documents were referenced by the applicant:

IND
IND

DMF
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DMF

RELATED DOCUMENTS (if applicable):

NDA 20-634

CONSULTS:

The labeling & nomenclature committee on 6/20/96 accepted the proposed tradename LEVAQUIN. Earlier proposed tradenames ELEQUIN, ELDOQUIN, ELEGEN and ELOCON were found unacceptable by the LNC.
microbiological consult: approval; Brenda Uratani, Ph.D.

REMARKS/COMMENTS: Levofloxacin is the levorotatory isomer of the D, L-racemate of ofloxacin and a synthetic fluorinated carboxyquinolone. Levofloxacin drug substance, used in the drug product, is hemihydrate (% water content, by weight). However, the concentration of the drug substance in the drug product is expressed in anhydrous form which is theoretically equivalent to % of levofloxacin hemihydrate. Therefore, levofloxacin Injection, 25mg/mL is equivalent to 25.6mg/mL of levofloxacin hemihydrate. Similarly, Levofloxacin Injection, 5mg/mL is equivalent to 5.12mg/mL of levofloxacin hemihydrate.

The Puerto Rico manuf. site (DP) was issued a 483 (date 10/1/96)

NDA 20-635

CHEMIST REVIEW #1

4

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable for manufacturing and controls under section 505 of the Act. Specific items which are not approvable are identified under the following headings: Specifications and Methods, Drug Product Container/Closure, Microbiology, Stability, Environmental Assessment, and Establishment Inspections.

BV Shetty 10/16/96 -

B.Vithal Shetty, Ph.D.
Review Chemist

cc: Orig. NDA 20-635 (other NDA's may be included if appropriate)

HFD-520/Division File

HFD-520/Chem/Shetty

HFD-520/MO/

HFD-520/Pharm/

HFD-520/Micro/King

HFD-520/CSO/ESANE

HFD-805/Micro/Uratani

HFD-830/Chem/Dunn

R/D init. By Supervisor

*BSDunn
10-15-96*

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-635 CHEM. REVIEW #: 2 REVIEW DATE: 12/11/96

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL <i>NO</i>	<i>11/11/96</i>	<i>11/14/96</i>	<i>12/9/96</i>
AMENDMENT/BC <i>YES</i>			

NAME & ADDRESS OF APPLICANT: *The R.W. Johnson Pharmaceutical*
920 Route 202 South
P.O. Box 300, Raritan, N.J
08869-0602

DRUG PRODUCT NAME

Proprietary: *Levaquin*
Nonproprietary/USAN: *Levofloxacin Injection*
Code Names/#'s:
Chemical Type/
Therapeutic Class: *15*

ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOLOGICAL CATEGORY/INDICATION: *Quinolone, antibacterial*

DOSAGE FORM: *Injection*
STRENGTHS: *25 mg/mL, 5 mg/mL*
ROUTE OF ADMINISTRATION: *Intravenous Infusion*
DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

(1) United States adopted name (proposed)

levofloxacin

(2) International nonproprietary name

levofloxacin

(3) Code name

DR-3355

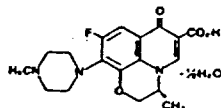
(4) Chemical name

(-)-(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

(5) Chemical abstracts service number

100986-85-4

(6) Chemical structure



(7) Molecular formula

$C_{18}H_{20}FN_3O_4 \cdot 1/2H_2O$

(8) Molecular weight

370.38

NDA 20.635

page 2

SUPPORTING DOCUMENTS:

original NDA

RELATED DOCUMENTS (if applicable):

: none

CONSULTS:

None

REMARKS/COMMENTS: The firm has responded satisfactorily to all the six deficiencies.

CONCLUSIONS & RECOMMENDATIONS:

The NDA original amendment is acceptable.

BVShetty 12/11/96

YOURNAME, Review Chemist

cc: Orig. NDA 20-635
HFD-520/Division File
HFD-520/ Reviewer/Shetty
HFD-520/MO/ Hopkins
HFD-520/Pharm/ Joshi
HFD-520/Micro/ King
HFD-520/CSO / LeSane
HFD-520/SUPERVISOR Acting TL/ Katague
HFD-102/
R/D Init by: SUPERVISOR Team Leader: DBK 12/11/96
filename: