

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-744

MEDICAL REVIEW(S)

Team Leader Review

Application Type	NDA
Submission Number	21-744
Submission Code	N
Letter Date	July 18, 2004
PDUFA Goal Date	May 19, 2005
Established Name	ciprofloxacin hydrochloride (extended release)
(Proposed) Trade Name	PROQUIN®XR
Therapeutic Class	antibacterial
Applicant	Depomed Inc.
Priority Designation	S
Formulation	500 mg tablets
Dosing Regimen	one 500 mg tablet orally taken with a _____ meal _____, preferably the evening meal, once daily for three days
Indication	treatment of uncomplicated urinary tract infection
Intended Population	adult women

RECOMMENDATION:

The Division recommends approval of PROQUIN®XR for the treatment of uncomplicated urinary tract (uUTI) infections in adult females. The Agency has determined that the product is both safe and effective at the recommended dose regimen for this indication based on the review of a double blind study demonstrating that a 3-day regimen of PROQUIN®XR 500 mg po once daily taken with a substantial meal is not inferior to ciprofloxacin intermediate release 250 mg po 12-hourly, for the same treatment duration, in females with uUTI infection. Pediatric studies are waived for this indication.

BACKGROUND: Regulatory

Nalidixic acid was the first member of the quinolone class of antibiotics approved for urinary tract infections. Although the drug achieves therapeutic concentrations in urine, its rapid systemic clearance limits its usefulness for infections outside the urinary tract. Ciprofloxacin, or Cipro® [referred to in this document as ciprofloxacin intermediate release or Cipro IR] was the first fluoroquinolone antimicrobial developed for systemic infections. The drug was approved in 1987 (NDA 19-537) as 250, 500 and 1000 mg as 8 to 12-hourly tablets and is also available in suspension and intravenous solution for injection. More recently, an extended release once-daily formulation of ciprofloxacin has gained regulatory approval (Cipro XR®, NDA 21-473, approved in January 3, 2003). In negotiations with the innovator Bayer, the Agency raised its concern that Cipro XR would be confused with the Cipro IR, which has demonstrated efficacy and is approved for the treatment of a variety of serious respiratory, gastrointestinal, intraabdominal, cutaneous, and musculoskeletal infections. Cipro IR is also approved for several genitourinary indications other than uUTI, including complicated urinary tract infections (cUTI) and pyelonephritis in adults and pediatric patients, bacterial prostatitis, cervical and urethral gonorrhea. In addition, Cipro IR has demonstrated efficacy in inhalational anthrax (post-

exposure) and is part of the strategic national stockpile. Other fluoroquinolones found to have efficacy in serious systemic infections but not in uUTI include moxifloxacin and trovafloxacin.

To support approval of Cipro XR, the Division required that Bayer demonstrate that Cipro XR was noninferior to Cipro IR in uUTI, contingent upon

- a) demonstration of noninferior efficacy of Cipro XR to Cipro IR in cUTI and pyelonephritis in an adequate and well controlled study (approved in August 29, 2003)
- b) evidence that patients and health care providers recognized the distinction between the indications of use for Cipro XR and Cipro IR in a label comprehension study.

Additionally, the Division also stated that should the efficacy of the XR formulation be lower than the anticipated 90% in uUTI, that the Division would not be comfortable with a noninferiority limit of -15%. The studies required by the Division were to ensure that the Cipro XR formulation was distinguishable from the Cipro IR formulation, and that Cipro XR would be efficacious were it used in more severe urinary tract infection (see review of NDA 21-473 -uUTI by Dr. R. Alivisatos and NDA 21-554 CUTI by Dr. J. Meyer for additional detail). The Agency provided similar advice to the applicant of this NDA (August 13, 2001, to PIND 62,386), however, the demonstrated efficacy rates of their 500 mg formulation in uUTI were lower than expected (78% in the pivotal, and 58% in the supportive study) where the efficacy rates are anticipated to be in the range of 90%. The lower efficacy rates were similarly noted in the comparator and the difference in point estimates between PROQUIN[®]XR [also known as Cipro GR or gastro retentive, while in development] and Cipro IR did not exceed the preset -10% limit of noninferiority. The Division concluded that the lower than expected efficacy rates in uUTI did not warrant further development of the 500 mg dosage formulation in the more severe cUTI and pyelonephritis treatment indications, and negotiated wording in the label that specifies the lack of demonstrated efficacy in these indications.

Whereas the applicant had originally intended to submit this NDA as a 505(b)(2), their completion of a preclinical development program in addition to two clinical efficacy and safety studies in uUTI infections in female adults qualified their submission as a 505(b)(1). As such, the applicant cannot rely on Cipro IR data to support the Divisions' finding of efficacy for this indication. The applicant did not compare their product against the Cipro XR formulation as the protocols for the pivotal studies for PROQUIN[®]XR were developed prior to the market availability of the Bayer Cipro XR formulation. Nonetheless, the new product exclusivity granted Bayer's Cipro XR formulation would have blocked the approval of a 505(b)(2) application for the same change in dosing, regardless of whether Depomed conducted any clinical studies, and the applicant chose to apply as a 505(b)(1).

The applicant submitted the NDA as a 505(b)(1) application on the following basis:

- 1) that the scientific information provided to support the application was derived from studies conducted and/or owned by the applicant. The development program should consist of a complete preclinical program (microbiology, chemistry, clinical pharmacology biopharmaceutics, etc) which would serve as the basis for product labeling as well as a clinical program that fulfills the statutory requirements of two adequate and well controlled clinical trials with microbiologic, human pharmacokinetic and pharmacodynamic data. The preclinical and clinical studies performed by the applicant are summarized in Tables 1 and 2.

- 2) that the extent to which the general scientific knowledge is referred to is not essential for approval, although may be referred to in labeling product safety.

The applicant presents efficacy and safety data from one small phase II study and a much larger Phase III study that, together with the completion of additional studies of the clinical pharmacology, toxicology, and microbiology of PROQUIN[®]XR, led the Division to conclude that Depomed Inc.'s New Drug Application ("NDA") for PROQUIN[®]XR for the treatment of uncomplicated urinary tract infections fulfilled the requirements of a 505(b)(1) NDA. These preclinical and clinical studies and the applicant's conclusions are summarized in the following table. Additional carcinogenicity studies were not required given the 3 day duration of human treatment for bladder infections. Please refer to the reviews of the co-locate disciplines for additional detail.

In its review of this NDA, the Division has consulted with the Division of Surveillance, Research, and Communication Support (DSRCS) to evaluate the Label Comprehension Study for PROQUIN[®]XR. DSRCS in its April 8, 2005 memorandum concludes that the study did not achieve its intended communications, that the patients and providers are unlikely to distinguish between PROQUIN[®]XR and Cipro IR and recommended that the sponsor should consider a 3-tablet unit-of-use package that includes the patient package insert, also reviewed by DSRCS. Because the Bayer product Cipro XR is not packaged as unit-of-use package, the applicant has opted for retain traditional bulk packaging, in addition to the unit of use package. The applicant's risk management plan was deemed suitable by the Office of Drug Safety. The negotiated label bears wording that PROQUIN[®]XR has not demonstrated efficacy in pyelonephritis and cUTI, and that the drug needs to be taken with a — meal ————, preferably the evening meal. The Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety recommended labeling revisions to minimize error and that the proprietary name PROQUIN[®]XR did not require any modifier referring to a dose interval in the absence of an alternate PROQUIN[®]XR formulation, based on prescription analysis studies. The applicant similarly cited the precedent set in naming the competitors' extended release formulation, a position that the review team subsequent chose to support, there being no regulatory basis for denying the name.

Table I Preclinical Program

Type of Study	Title	Study #	Conclusions
Repeat dose	A 28-Day Oral (Tablet) Toxicity Study of PROQUIN® XR in Beagle Dogs	3530-2 80-0002	At 23-92 mg/kg (males), 37-144 mg/kg (females) no gastrointestinal, ophthalmological (with fundoscopy exam) and cardiac events due to oral PROQUIN.
	<i>Salmonella-Escherichia coli</i> /Mammalian-Microsome Reverse Mutation Assay with Confirmatory Assay with Ciprofloxacin Hydrochloride Monohydrate	7439-106 80-0004	Ciprofloxacin hydrochloride monohydrate was negative in the <i>Salmonella-Escherichia coli</i> /Mammalian-Microsome Reverse Mutation Assay
Genotoxicity	Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells for Ciprofloxacin Hydrochloride Monohydrate	7439-107 80-0005	PROQUIN induced chromosomal aberrations.. at >300X human plasma levels achieved w/500mg
	In Vivo Rat Micronucleus Assay with Ciprofloxacin HCl	7439-108 80-0006	PROQUIN was non clastogenic as a single high dose to 2000mg/kg
Reproductive & Developmental	Fertility and Early Embryonic Development to Implantation (general toxicity, gonadal function, mating, implantation, fertility) in Rats w/ Ciprofloxacin HCl	7439-105 80-0011	NOAEL (males), NOEL (females), NOEL (fertility, early embryonic development) was 600mg/kg/day
	Dose Range-finding Developmental Toxicity Study of ciprofloxacin HCl in Rats with Toxicokinetics	7439-101 80-0007	NOAEL (maternal toxicity, in-utero and developmental toxicity) = 600 mg/kg/day
	Rat Developmental Toxicity Study with Ciprofloxacin HCl	7439-102 80-0009	NOAEL of 600 mg/kg/day (NOEL50 mg/kg/day for maternal toxicity; NOEL for in-utero and developmental toxicity is 300 mg/kg/day)
	Dose Range-finding Developmental Toxicity Study of ciprofloxacin HCl in Rabbits with Toxicokinetics	7439-100 80-0008	Ciprofloxacin at 30mg/kg/day is recommended as the high dose for the definitive rabbit study
	Rabbit Developmental Toxicity Study with Ciprofloxacin HCl	7439-103 80-0010	maternal tox NOEL/NOAEL=3 /10mg/kg/day, teratogenicity/NOEL/NOAEL=10/30mg/kg/day, embryofetal viability/growth/NOEL=10mg/kg/day
Pre- and Postnatal Development, Including Maternal Function, in the Rat with Ciprofloxacin HCl	7439-104 80-0012	Fo maternal NOEL=50 mg/kg/day. maternal NOAEL=600 mg/kg/day. F1 embryo/fetal survival, F2 development to parturition (incl learning, memory, reproduction) NOEL = 600 mg/kg/day.	

a. First number is testing facility and second is Depomed designations.

Table II Clinical Program

Clinical studies and human biomaterials studies undertaken by the applicant are summarized below. The reader is referred to the reviews of the relevant disciplines for greater detail.

Type of Study	Study	Objective(s) of Study	Study Design & Type of Control	Test Product; Dosage Regimen; Route of Administration	# of Subjects Enrolled/ Treated	Diagnosis	Treatment Duration
Safety & Efficacy	81-0005 Phase II	Compare safety & efficacy of PROQUIN [®] XR & C-IR	R, DB, active-controlled	PROQUIN XR [™] 1 x 500 mg tablets; oral	58/58 29/29 C-GR 29/29 C-IR	Uncomplicated UTI	3 days
	81-0015 Phase III	Compare safety & efficacy of PROQUIN [®] XR & C-IR	R, DB, active-controlled	PROQUIN XR [™] 1 x 500 mg tablets; oral	1037/1027 524/518 C-GR 513/509 C-IR	Uncomplicated UTI	3 days
Bioavailability	81-0026	Compare steady-state PK of PROQUIN [®] XR & C-IR	R, OL, cross-over	PROQUIN XR [™] 1 x 500 mg tablets; oral	28/28	Healthy subjects	3 days
	81-0027	Effect of omeprazole on PK of PROQUIN [®] XR	R, OL, cross-over	PROQUIN XR [™] 2 x 500 mg tablets; oral	28/27	Healthy subjects	2 x 1 day
Bioavailability Bioequivalence	81-0025	Compare single dose PK of PROQUIN [®] XR & C-IR	R, OL, cross-over	PROQUIN XR [™] 1 x 500 mg tablets; oral	28/28	Healthy subjects	Single dose
	81-0029	In vivo-in vitro correlation of 3 PROQUIN [®] XR formulations	Cross-over, OL, fed	3 PROQUIN XR [™] tablet formulations 500 mg; oral	16/16	Healthy subjects	3 x 1 day
Healthy Subjects PK	00-07	Compare PK of PROQUIN [®] XR & C-IR	R, OL, cross-over	2 PROQUIN XR [™] tablet formulations 500 mg; oral	15/15	Healthy subjects	2 x 1 day
	81-0024	Compare PK of PROQUIN [®] XR under fed & fasted conditions	OL, cross-over	PROQUIN XR [™] 1 x 500 mg tablets; oral	28/28	Healthy subjects	2 x 1 day
Intrinsic factor PK	81-0028	Compare PK of PROQUIN [®] XR with & without antacids	R, OL, cross-over	PROQUIN XR [™] 2 x 500 mg tablets; oral	28/28	Healthy subjects	3 x 1 day
	81-0033	Compare PK of PROQUIN [®] XR with & without antacids	R, OL, cross-over	PROQUIN XR [™] 2 x 500 mg tablets; oral	30	Healthy subjects	3 x 1 day
Human Biomaterials	81-0032	PK of PROQUIN [®] XR in elderly subjects	Single dose, one-way, fed	PROQUIN XR [™] 1 x 500 mg tablets; oral	16	Healthy, elderly subjects	Single dose
	84-0001	Evaluate the extent of protein binding of ciprofloxacin in human plasma	In vitro protein binding by ultrafiltration	Ciprofloxacin HCl monohydrate; 0.9, 3, 9, & 30 µM	>3 subjects provided plasma	Healthy subjects	N/A
Human Biomaterials	84-0002	Determine the potential of ciprofloxacin to inhibit human cytochrome P450	In vitro inhibition of cytochrome P450 isoenzymes	Ciprofloxacin HCl monohydrate; 0.3, 0.9, 3, 9, 30, & 90 µM	15 subjects provided hepatocytic microsomes	Healthy subjects	N/A

The applicant also completed 4 Microbiological studies evaluating the *in vitro* susceptibilities of PROQUIN XR™ against clinical urinary tract isolates. The aggregate number of species tested for MICs were > 100 in all these studies, but the number of isolates were no more than 50 per strain (please refer to Dr. Peter Dionne's microbiology review). Additionally the applicant performed PK/PD analyses on data gathered from the phase II and phase III clinical studies, and present the information as 4 additional studies in support of their 505b1 application.

Type of Study	Study	Objective(s) of Study	Study Design & Type of Control	Test Product; Dosage Regimen; Route of Administration
Microbiology	83-0001	Variation in ciprofloxacin MICs as a function of media pH (5 clinical strains, 3 ATCC strains)	Microdilution susceptibility testing	Ciprofloxacin 0.002-32 µg/mL
	83-0002	Variables affecting ciprofloxacin activity (5 clinical strains, 4 ATCC strains)	In vitro MICs under varying environmental conditions	Ciprofloxacin 0.002-32 µg/mL
	83-0003	Anti-microbial susceptibility testing of ciprofloxacin against micro-organisms from putative UTIs (800 isolates)	In vitro MICs by microdilution & disk diffusion methods (NCCLS methodology)	Ciprofloxacin 0.0004-128 µg/mL Levofloxacin 0.008-128 µg/mL
	83-0004	Ciprofloxacin in vitro potency compared to levofloxacin & establishment of disc diffusion break points (862 isolates)	In vitro MICs (broth micro dilution & disc diffusion tests (NCCLS methods))	Ciprofloxacin 0.008-16 µg/mL Levofloxacin 0.008-16 µg/mL
	85-0001	Establishment of a Level A in vitro-in vivo correlation	Develop in vitro-in vivo correlation & correlate in vivo profiles with in vitro profiles	
PK/PD	85-0002	Prediction of bioavailability for in vitro release specifications	Calculation of release specifications from in vitro-in vivo correlation	
	85-0004	Determine ratios of single-dose PK parameters to MICs	Calculation of AUC/MIC, C _{max} /MIC & A _e /MIC ratios from 81-0025 & 83-0003	
	85-0005	Determine ratios of steady-state PK parameters to MICs	Calculation of AUC/MIC, C _{max} /MIC & A _e /MIC ratios from 81-0026 & 83-0001	

The Division also agreed to review additional studies not completed at the time of NDA submission. The following were submitted within the review cycle and are reviewed by the relevant disciplines:

- (1) a study of the PK of PROQUIN® XR in renally impaired patients – submitted 12/24/2004
- (2) a single-dose PK study with warfarin – submitted 11/11/2004
- (3) a mass balance study – submitted 2/9/2005
- (4) the evaluation of CYP450 induction on primary human hepatocyte cultures – 11/11/2004

EFFICACY OF PROQUIN®XR IN UNCOMPLICATED URINARY TRACT INFECTIONS IN FEMALE ADULTS

Dr. Joette Meyers' review summarizes the findings from the phase III study (Study 81-0015) that compares the safety and efficacy of PROQUIN®XR (500 mg once daily for 3 days) with 12-hourly ciprofloxacin (CIPRO® 250 mg twice daily for 3 days). In this single pivotal study 524 randomly received PROQUIN®XR and 513 were randomly assigned to the control group. Approximately half of the randomized patients were excluded from the population of interest; 272 (52%) patients in the PROQUIN®XR group and 252 (49%) in the control group were evaluable for efficacy in the Per-Protocol population. The primary efficacy variable was bacteriologic eradication of the baseline organism(s) with no persistence, and no new infection at the test-of-cure (Day 4 to 11 post-therapy) and was similar for both treatment groups, with a lower bound around the treatment difference of -5.8%, fulfilling the prespecified boundary for noninferiority. The eradication and clinical success rates and their corresponding 95% confidence intervals for the differences between rates (PROQUIN®XR minus control group) are given in the following table:

Primary and Selected Secondary Efficacy Analyses in Study 81-0015 (Per Protocol Population)		
Outcomes at Test of Cure (95% CI around the difference)	PROQUIN®XR 500 mg QD x 3 Days	CIPRO IR 250 mg BID x 3 Days
Randomized Patients	524	513
Per Protocol Patients [@]	272 (52%)	251 (49%)
Bacteriologic Eradication * (Primary efficacy analysis)	212 / 272 (78%)	193 / 251 (77%)
	(-6.2%, 8.2%)	
Clinical Response ** (Secondary Efficacy Analysis)	233 / 272 (85.7%)	216 / 251 (86.1%)
	(-6.4%, 5.6%)	
By Pathogen Bacteriologic Eradication ***		
<i>E. coli</i>	211 / 222 (95%)	184 / 202 (91%)
<i>K. pneumoniae</i>	11 / 12 (92%)	10 / 13 (77%)

[@] The protocol specified analytic population was the Per Protocol population

*Number of patients with baseline organism(s) eradicated and no new infections or superinfections / Total number of per-protocol patients

**Number of patients with clinical success / Total number of per-protocol patients

***Number of patients with specified baseline organism eradicated / Number of per-protocol patients with specified baseline organism

There were insufficient numbers of *P. mirabilis* and *S. saprophyticus* to evaluate efficacy of PROQUIN®XR for these pathogens.

In the applicant's analysis based on the population available for evaluation at the specified timepoint, the microbiologic outcome at TOC favored the study drug, whereas the clinical endpoint at both TOC and late post treatment favored the comparator. None of these numerical differences were statistically significant, and the 95% CI around the numerical difference fell within the prespecified -10% points bound for non inferiority. The difference in point estimates between PROQUIN®XR and Cipro IR for both microbiological and clinical outcomes at the TOC and the late Post -Treatment evaluation were smaller in the Divisions' analysis, based on the evaluable population, and supports the overall conclusion of noninferior efficacy.

Clinical Cure and Microbiologic Eradication in Study 81-0015						
Timing of evaluation in Study 81-0015	APPLICANT ANALYSIS			FDA ANALYSIS		
	PROQUIN® XR	Cipro IR	(PROQUIN®XR-CIPRO IR) 95% CI	PROQUIN® XR	Cipro IR	(PROQUIN®XR-CIPRO IR) 95% CI
Microbiological Eradication						
Test-of-Cure Visit (Day 4 to 11)	254 /272 (93.4%)	225/251 (89.6%)	3.8 (-1.0%, 8.6%)	212/272 (78%)	193/251 (77%)	1.0 (-6.2%, 8.2%)
Late Post-Treatment Visit (PP)(Day 28 to 42)	182/221 (82.4%)	168/202 (83.2%)	-0.8 (-8.0%, 6.4%)	182/272 (66.9%)	168/251 (66.9%)	0 (-8.1%, 8.1%)
Clinical Cure						
Test-of-Cure Visit (Day 4 to 11)	233/281 (82.9%)	216/255 (84.7%)	-1.8 (-8.0%, 4.4%)	233/272 (86%)	216/251 (86%)	0 (-6.4%, 5.6%)
Late Post-Treatment Visit(Day 28 to 42)	196/259 (75.7%)	175/222 (78.8%)	-3.1 (-10.6%, 4.4%)	196/272 (72.1%)	175/251 (69.7%)	2.4 (-5.5%, 10.1%)

The efficacy of the Cipro IR in uncomplicated UTI in this study differed from the expected success rates for this formulation. In prior studies on the efficacy of the Cipro IR formulation in uncomplicated UTI, the efficacy rates based on the same study endpoint consistently show a 90% efficacy in sustained bacterial eradication, although the point estimates suggest a trend for greater efficacy with higher doses and longer treatment courses. The clinical studies section of Bayer's Cipro® labels shows the following efficacy rates for the Cipro IR formulation and the Cipro XR® formulation:

Bayer's ciprofloxacin formulation	Dose (mg)	Duration (days)	Successful Bacteriological Response	
			N	(%)
Cipro IR	100 BID	3	70	91.0
Cipro IR	250 BID	3	223	93.7
Cipro IR	250 BID	7	69	97.0
Cipro XR®	500 BID	3	199	94.5

To determine whether the difference in efficacy could be attributable to the pharmacokinetics of the various formulations of ciprofloxacin, we compared the steady state PK parameters for PROQUIN®XR from the applicant's submission to the reference CIPRO IR from the same study and from the Cipro XR NDA submission (see following table, modified from Dr. Geiser's CPBP review).

Steady State Plasma PK Parameters of PROQUIN®XR vs Cipro® XR, Relative to the Reference Cipro® IR

Dosage Form	Fasted/ Fed	Tmax,ss (hr)	Cmax,ss (ng/mL)	% of Cmax,ss ^b Cipro IR 250 mg BID (Fed or Fasted)	AUC _{0-24h,ss} (ng*h/mL)	% of AUC _{0-24h,ss} of Cipro IR 250 mg BID (Fed or Fasted)
PROQUIN®XR 500 mg QD	Fed high-fat meal	5.0 (median)	820	55% of Cipro IR (Fed)	7667	98% of Cipro IR 250 mg BID (Fed)
Cipro IR 250 mg BID ^a	Fed (high-fat meal)	2.0 (median)	1502		7835	
Cipro XR 500 mg QD ^a	Fasted	1.5 (median)	1500	134% of Cipro IR (Fasted)	7770	97% of Cipro IR 250 mg BID (Fasted)
Cipro IR 250 mg BID ^a	Fasted	1.0 (median)	1120		7990	

^a values from Cipro XR® Package Insert ^bC_{max,1} + C_{max,2}

The steady state pharmacokinetics for the CiproXR™ and Cipro IR, derived from the label of the CiproXR™, are shown for comparison. The C_{max} and AUC parameters of the Cipro IR in the applicant's studies were similar to the PK parameters obtained in the Cipro XR NDA, and therefore could not account for the difference in point estimates obtained in Depomed's pivotal study.

Based on the data obtained above, the maximum plasma concentrations of PROQUIN®XR are expected to exceed the MIC of 88% of the *E. coli* isolates derived from this pivotal study, whereas the minimum concentrations would exceed the MIC of a smaller proportion (86.6%) of the *E. coli* isolates (please see Dr. Pete Dionne's microbiology review).

The AUC_{ss}/MIC ratios for PROQUIN XR™ were greater than 100 and the C_{max,ss}/MIC ratios were greater than 10 for the following microbial strains: *E. coli* strain 1, *E. coli* strain 4, *K. pneumoniae*, and *P. mirabilis*. For the same microorganisms, the C_{min,ss}/MIC values were at least equal to 1 whereas for the pathogens *E. faecalis*, *S. aureus*, and *S. saprophyticus*, the minimum concentrations of ciprofloxacin in urine would fall below 1.

Ratios for Ciprofloxacin AUC/MIC, C_{max}/MIC, C_{min}/MIC and 24-h C_{urine}/MIC
Following a 3-Day Regimen of PROQUIN®XR 500 mg Once Daily in Study 81-0015

ORGANISM	MIC ₉₀ (mcg/mL)	Ciprofloxacin AUC _{0-24h} (7905 ng*h/mL)	Ciprofloxacin C _{max} (857 ng/mL)	Ciprofloxacin C _{min} (67.7 ng/mL)	Ciprofloxacin C _{urine(0-24h)} (65.91 mcg/mL)
<i>E. coli</i> ATCC 25922 (strain 1)	0.016	494	54	4	4119
<i>E. faecalis</i> ATCC 29212 (strain 2)	1	8	1	0.1	65.91
<i>S. aureus</i> ATCC 29213 (strain 3)	0.5	16	2	0.1	131.8
<i>E. coli</i> N9688 (strain 4)	0.045	176	19	2	1465
<i>K. pneumoniae</i> N9189 (strain 5)	0.016	494	54	4	4119
<i>E. faecalis</i> ST12,296 (strain 6)	>32	<0.25	<0.03	<0.002	<2.06
<i>S. saprophyticus</i> , SP8822 (strain 7)	0.5	16	2	0.1	131.8
<i>P. mirabilis</i> N9287 (strain 8)	0.045	176	19	2	1465

$$C_{urine(0-24h)} = A_{e0-24h} / \text{volume of urine in 24 h}$$

The review team could not attribute the lower than expected cure rates for this pivotal study to increased resistance of *E. coli* uropathogens or demographic differences in the populations studied. A review of the shifts in laboratory urinalysis findings at the test of cure indicates that several urine samples may not have been midstream sample and the cultures that accompanied these specimens may have reflected colonization rather than true infection. As noted in Dr. Meyer's review and reflected in the label, enterococci were the predominant pathogen identified as new infections, and the investigator did not deem treatment necessary for these positive cultures.

The findings in the phase III trial were similar to that seen in the phase II supportive study (study 81-0005) of virtually the same study design, although only 20 patients in the PROQUIN®XR group and 21 patients in the Cipro IR group were evaluable, based on a positive urine microbiology and uropathogen susceptibility test results, and completed 3 days of dosing. One notable difference in the patient population in this study is that the mean age of the patients studied was 44 years, compared to 39 in the pivotal study. Nonetheless, the small number of

patients limits the conclusions derived from this study. The Division review team's analysis based on the Per Protocol and Modified Intent to Treat population are shown below.

Outcome at Test of Cure In Study 81-0005	Per Protocol		Modified Intent to treat	
	PROQUIN [®] XR 500 mg QD x 3 days	Cipro IR 250 mg BID x 3 days	PROQUIN [®] XR 500 mg QD x 3 days	Cipro IR 250 mg BID x 3 days
Bacteriologic Eradication* (primary analysis)	10/15 (66.7%)	8/13 (61.5%)	13/22 (59.1%)	14/22 (63.6%)
Clinical Response (secondary analysis)	10/15 (66.7%)	11/13 (84.6%)	14/22 (63.6%)	16/22 (72.7%)

* Eradication = Urine culture showed that all uropathogens present at study enrollment at $\geq 10^3$ CFU/mL were reduced to $<10^4$ CFU/mL AND no new infections

SAFETY OF PROQUIN[®]XR IN UNCOMPLICATED URINARY TRACT INFECTIONS IN FEMALE ADULTS

The safety of PROQUIN[®]XR was evaluated in 1,095 patients enrolled in the two active-controlled studies (Phase II study 81-0005 and Phase III study 81-0015), in which patients received either PROQUIN[®]XR 500 mg once daily or Cipro IR 250 mg twice daily for 3 days. In the safety evaluable population, there were numerically more premature treatment discontinuation in the PROQUIN[®]XR study group compared to the Cipro IR group. Of patients who discontinued treatment, more patients in the PROQUIN[®]XR treated group discontinued due to an adverse event or were lost to follow-up.

Table 6 Reasons for Discontinuation of Study Medication: All Patients Randomized in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total (n = 1095)
	C-GR (n=553)	C-IR (n=542)	
	Number (%) of Patients		
Randomized	553	542	1095
Received Assigned Randomized Treatment	546	538	1084
Received Non-randomized Treatment	1	0	1
Received Treatment for Safety Data Analysis	547 (100%)	538 (100%)	1085 (100%)
Completed the Study Medication	519 (94.9%)	521 (96.8%)	1040 (95.9%)
Discontinued the Study Medication Prematurely	28 (5.1%)	17 (3.2%)	45 (4.1%)
Reason for Discontinuation			
Adverse event	7 (1.3%)	3 (0.6%)	10 (0.9%)
Withdrawal of consent	2 (0.4%)	2 (0.4%)	4 (0.4%)
Lost to follow-up	16 (2.9%)	12 (2.2%)	28 (2.6%)
Other reason	3 (0.5%)	0 (0.0%)	3 (0.3%)

An adverse event occurred in 461 (42.5%) of the safety evaluable population, with similar proportions of patients in the PROQUIN[®]XR and Cipro IR reporting an adverse event [230 (42.0%) in the PROQUIN[®]XR and 231 (42.9%) Cipro IR patients, respectively]. There were no deaths in the entire study program. Most AEs in both studies were mild or moderate in severity and unrelated to study drug treatment. In the small subset of patients [9 (0.9%)] that developed serious adverse events, 3 received PROQUIN[®]XR, whereas 6 patients received Cipro IR. These adverse events included chest pain (PROQUIN[®]XR, 1 patient; Cipro IR 2 patients), anemia and papillary thyroid cancer (PROQUIN[®]XR 1 patient) and intestinal obstruction, pyelonephritis, nephrolithiasis, and ovarian cyst in the Cipro IR group. None of these were considered by the investigators to be drug-related. Treatment-related AEs in the PROQUIN[®]XR arm leading to discontinuation were hypersensitivity in two patients; and dyspnea, urticaria, and suprapubic pain, each in one patient.

Overall, 7.6% reported gastrointestinal adverse events. The applicant postulates that the PROQUIN[®]XR formulation would result in a distinct gastrointestinal adverse event profile of less nausea and diarrhea. Within the gastrointestinal system, the most common AE was nausea (1.9% of all patients), and the incidence of this adverse events was not significantly different between treatment arms. The applicant's analysis points to a difference in rates of diarrhea that occurred in a greater number of patients that received the Cipro IR. Given the number of comparisons made for adverse events, it is likely that this difference in diarrhea and dysuria, which was more common with PROQUIN[®]XR, may have been due to chance alone, given that analyses for each individual event were not adjusted for multiple comparisons.

Applicant's Table 14.1.3-2

	Treatment Group		
	PROQUIN [®] XR	CiproIR	p-value
Number of Patients Randomized in the Study	524	513	--
Number (%) of Patients Received Treatment	518 (100%)	509 (100%)	--
Number (%) of Patients w/ at Least One AE	213 (41.1%)	216 (42.4%)	NS
Number (%) of <u>Patients</u> w/ AEs occurring >1%			
Urinary tract infection NOS	56 (10.8%)	50 (9.8%)	NS
Escherichia infection NOS	2 (0.4%)	0	NS
Klebsiella infection NOS	1 (0.2%)	0	NS
Streptococcal infection NOS	1 (0.2%)	0	NS
Suprapubic pain	7 (1.4%)	3 (0.6%)	NS
Micturition urgency	10 (1.9%)	5 (1.0%)	NS
Urinary frequency	7 (1.4%)	5 (1.0%)	NS
Dysuria	8 (1.5%)	1 (0.2%)	0.038
Diarrhoea NOS	2 (0.4%)	9 (1.8%)	0.036
Nausea	7 (1.4%)	11 (2.2%)	NS
Abdominal pain NOS	9 (1.7%)	6 (1.2%)	NS
Chest pain	2 (0.4%)	5 (1.0%)	NS
Nasopharyngitis	14 (2.7%)	7 (1.4%)	NS
Pharyngitis	6 (1.2%)	5 (1.0%)	NS
Nasal congestion	6 (1.2%)	1 (0.2%)	NS
Fungal infection NOS	14 (2.7%)	9 (1.8%)	NS

Upper respiratory tract infection NOS	7 (1.4%)	15 (2.9%)	NS
Vaginosis fungal NOS	4 (0.8%)	8 (1.6%)	NS
Sinusitis NOS	4 (0.8%)	7 (1.4%)	NS
Back pain	9 (1.7%)	8 (1.6%)	NS
Headache	12 (2.3%)	20 (3.9%)	NS
Dizziness	6 (1.2%)	1 (0.2%)	NS

One notable observation, however is that overall, approximately one in five (19.6%) patients in the study reported infections as adverse events. Investigators report that approximately 1 in 10 (10.5%) developed urinary tract infections as adverse events. The number of investigator reports of urinary tract infections as adverse events that occurred during study were numerically more frequent in the PROQUIN[®]XR arm, although the numbers were small overall.

Modified from Applicant's Table 14.1.3-3

Summary of Incidences of Adverse Events

Number of <u>Adverse Events</u>	PROQUIN [®] XR N=518 (100%)	Cipro IR N=509 (100%)	TOTAL 1027 (100%)
Urinary tract infection	61	52	113
Pyelonephritis NOS	1	2	3
Escherichia infection NOS	3	0	3
Klebsiella infection NOS	1	0	1

No additional clinical detail is available for these patients, as none of them were categorized as serious adverse events.

The safety of PROQUIN[®]XR was evaluated in nine open-label normal volunteer pharmacokinetic (PK) studies that included 216 healthy adults; four of the PK studies included treatment with PROQUIN[®]XR and Cipro IR and five included treatment with PROQUIN[®]XR only. No additional safety issues were noted in these studies.

LABELING REVIEW

Dr. Meyer's review describes the following perspectives that guided the labeling negotiations:

- 1) Data necessary for approval of PROQUIN[®]XR is derived from the applicant's studies
- 2) The resolution of labeling issues prioritize patient safety
- 3) Class labeling for the fluoroquinolones would apply to relevant sections of the label.
- 4) In the absence of confirmatory data that PROQUIN[®]XR would be efficacious in pyelonephritis or complicated urinary tract infections, nor of confirmation that the provider and patient could distinguish this product from the Cipro IR, the lack of evidence of PROQUIN[®]XR efficacy in complicated UTI and pyelonephritis is prominently labeled. In the setting of persistent symptoms or symptoms suggestive of pyelonephritis, alternative therapy to PROQUIN[®]XR is suggested.

5)



- 6) The plasma pharmacokinetics, and ultimately, the effective urinary concentrations of PROQUIN[®]XR are highly dependent on the increased absorption of this drug when taken in the fed state. The label describes the need to take the daily dose with a "the main meal of the day,

preferably at bedtime".

The applicant disclosed their plan to

Natural history studies of UUTI find that spontaneous resolution occurs in 20-40% of untreated patients, and the 67-78% PROQUIN[®]XR efficacy estimates in the two clinical studies submitted to support the indication claim are clearly better than the no treatment rate. However, equivalence becomes difficult to assess when the efficacy estimates approach the spontaneous cure rates. The Division is unable to fully explain the overall lower efficacy in UUTI in this study for both the study drug and comparator, which cannot be entirely explained by the early emergence of enterococcus as a new infection, nor by an increase in the ciprofloxacin MICs for *E.coli*, compared to recent uUTI studies. Furthermore, in the applicant's PKPD analysis, the minimum concentrations of ciprofloxacin in the urine appear to be a discriminant for efficacy, implying that in uUTI a threshold minimum concentration can influence microbiologic outcome in fluoroquinolone treated patients. If further validated as a predictor of clinical outcomes, this correlation is particularly important for a drug such as PROQUIN[®]XR, whose absorption is heavily dependent on dosing with a substantial meal. If the drug is not taken as designed, with a substantial meal, uUTI treatment failures may occur if PROQUIN[®]XR urinary concentrations do not exceed *E coli* MICs. Epidemiologic evidence from the surveillance studies undertaken by Focus technologies for the FDA show a trend for increasing ciprofloxacin MICs in *E. coli* urine and bloodstream isolates. Published literature supports this trend, with increased *E. coli* resistance to ciprofloxacin reported in patients previously treated with fluoroquinolones. The Division recommended that the applicant

and that they monitor the use for PROQUIN[®]XR following its market availability.

Eileen Navarro, MD
Medical Team Leader
HFD 590
April 29, 2005

Dr. Renata Albrecht
Division Director
HFD 590

Cc: Yon Yu - PM
NDA 21-744 files
Review team, NDA 21-744

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

/s/

Eileen Navarro
5/19/05 01:02:40 PM
MEDICAL OFFICER

Renata, The numbers in this document are consistent with
stats and Joette's reviews, and exclude the one
patient (252 vs 251) that was in contention.

Renata Albrecht
5/19/05 03:57:34 PM
MEDICAL OFFICER
NDA 21-744

CLINICAL REVIEW

Application Type NDA 21-744
Submission Number 000
Submission Code N

Letter Date July 18, 2004
Stamp Date July 19, 2004
PDUFA Goal Date May 18, 2004

Reviewer Name Joette M. Meyer, Pharm.D.
Review Completion Date May 17, 2005

Established Name Ciprofloxacin Hydrochloride
Extended-Release Tablets
(Proposed) Trade Name Proquin XR™
Therapeutic Class fluoroquinolone antimicrobial
Applicant DepoMed, Inc.

Priority Designation S

Formulation Extended-release tablets
Dosing Regimen 500 mg once daily for 3 days
Indication Uncomplicated urinary tract
infection
Intended Population Adult Women

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Of the patients with their baseline pathogen eradicated, new infections were detected in 42/254 (16.5%) Proquin XR patients and 32/225 (14.2%) Cipro IR patients at the TOC visit. Of the patients with new infections, gram-negative rods were responsible for new infections in 10/42 (24%) patients in the Proquin XR group and 7/32 (22%) patients in the Cipro IR group.

Clinical cure at the TOC visit, a secondary endpoint, was also similar between the two groups (86% in both groups; 95% CI of the difference [-6.4%, 5.6%]).

Safety data from the Phase II and Phase III studies were combined. One or more treatment-emergent AEs during the 5-week study period occurred in 230 (42.0%) patients treated with Proquin XR and 231 (42.9%) patients treated with Cipro IR. The incidence of common adverse events (reported for at least 1% of patients treated with Proquin XR) is: fungal infection (2.6%), nasopharyngitis (2.6%), headache (2.4%), micturition urgency (2.0%), abdominal pain (1.6%), back pain (1.6%), dysuria (1.6%), upper respiratory tract infection (1.6%), suprapubic pain (1.5%), nausea (1.3%), pharyngitis (1.3%), urinary frequency (1.3%), hematuria (1.1%), dizziness (1.1%), nasal congestion (1.1%), and vaginosis fungal (1.1%). Overall, the incidence and types of AEs seen in these studies were generally similar for the two treatment groups and consistent with what is expected for ciprofloxacin. No new safety concerns were raised.

In summary, Proquin XR (ciprofloxacin extended-release 500 mg tablets) demonstrated efficacy and safety in the treatment of uncomplicated urinary tract infection in adult women and should be approved for this indication. The recommended dose is 500 mg orally once daily for 3 days. Proquin XR should be given with a main meal of the day, preferably the evening meal.

1.2 Recommendation on Postmarketing Actions

There are no recommendations for risk management activity. The Division requests two Phase 4 commitments from the applicant.

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

1. Track ciprofloxacin-resistance to baseline and treatment emergent isolates of *E. coli* prospectively in patients with uncomplicated urinary tract infection for the first two years of Proquin XR availability:
Protocol Submission: January 1, 2006
Study Start: July 1, 2006
Final Report Submission: December 31, 2008
2. Provide an annual update on Proquin XR usage patterns, noting patient demographics, setting of practice, indication for use, and treatment regimen prescribed for the first two years of product availability; with the submission dates being no later than _____ respectively.

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1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The applicant conducted one Phase II (Study 81-0005) and one Phase III (Study 81-0015) in adult women with uncomplicated urinary tract infection. Both studies were both prospective, multicenter, double-blind, randomized, parallel-group, studies that compared the safety and efficacy of Proquin XR to Cipro IR. Cipro IR was chosen as the active control because it is an approved treatment for acute, uncomplicated UTI. The study design was in accordance with the 1998 draft Guidance for Industry: *Uncomplicated Urinary Tract Infections -- Developing Antimicrobial Drug for Treatment on clinical studies of uncomplicated UTI.*

Patients received either Proquin XR 500 mg once daily or Cipro IR 250 mg twice daily for 3 days. Patients were evaluated at a Test-of-Cure Visit (4 - 11 days after the end of treatment) and at a Late Post-Treatment Visit (5 weeks \pm 7 days after the end of treatment).

The primary efficacy endpoint was microbiological eradication at the Test-of-Cure (TOC) Visit. Clinical cure at the TOC visit was a secondary efficacy endpoint. Microbiological eradication was defined as eradication of the baseline pathogen(s) and no new infection. The primary efficacy analysis in the Phase III study was the construction of the 95% confidence interval of the difference in the one-week microbiological eradication rates at the Test-of-Cure Visit between the two treatment groups (Proquin XR minus Cipro IR). If the lower boundary of the confidence interval of the difference in the microbiological eradication rate at Test-of-Cure Visit was not less than -10%, Proquin XR would be considered non-inferior to the Cipro IR treatment.

The FDA's modified intent-to-treat (MITT) population included evaluable patients (i.e., randomized patients who met the enrollment criteria for a baseline pathogen(s) and susceptibility to ciprofloxacin). Patients missing microbiological data at the Test-of-Cure Visit were considered to be cases of microbiological persistence at that visit for the MITT analysis. Patients missing clinical response data at Test-of-Cure Visit were considered to be clinical failures at that visit for the MITT analysis.

The FDA's Per Protocol (PP) population included evaluable patients randomized in this study who had microbiological data at Test-of-Cure Visit. The PP population was used for the analysis of all primary and secondary efficacy parameters.

In the Phase II study, 29 patients were randomly assigned to the Proquin XR group and 29 were randomly assigned to the Cipro IR group. Of the total enrolled, 28 patients (15 in the Proquin XR group and 13 in the Cipro IR group) were evaluable for efficacy and included in the Per-Protocol population.

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In the Phase III study, 524 patients were randomly assigned to Proquin XR and 513 were randomly assigned to Cipro IR. Of the total enrolled, 272 (52%) patients in the Proquin XR group and 251 (49%) in the Cipro IR group were evaluable for efficacy and included in the Per-Protocol population.

1.3.2 Efficacy

Microbiological and clinical outcome at the TOC visit for both studies is provided in the table below. The 95% confidence intervals for the treatment differences (Proquin XR minus Cipro IR group) for the Phase III study are also provided in the table. The lower bound of the 95% confidence interval for the treatment difference in microbiological eradication rates is above -10% (95% CI [-6.2%, 8.2%]), indicating Proquin XR is non-inferior to Cipro IR.

Microbiological and Clinical Outcome at the Test-of-Cure (TOC) Visit Studies 81-0005 (Phase 2) and 81-0015 (Phase 3)

	Proquin XR 500 mg qd x 3 Days	Cipro IR 250 mg bid x 3 Days
Phase II Study		
Randomized Patients	29	29
Per Protocol Patients	15	13
Microbiological Eradication with no new infection at TOC*	10/15 (66.6%)	8/13 (61.5%)
Clinical Response at TOC*	10/15 (66.7%)	11/13 (84.6%)
Microbiological Eradication by organism**		
<i>E. coli</i>	8/10 (80.0%)	11/12 (93.8%)
Phase III Study		
Randomized Patients	524	513
Per Protocol Patients	272 (52%)	251 (49%)
Microbiological Eradication with no new infection at TOC	212 / 272 (78%)	193 / 251 (77%)
	(-6.2%, 8.2%)	
Clinical Response at TOC	233 / 272 (86%)	216 / 251 (86%)
	(-6.4%, 5.6%)	
Microbiological Eradication by organism*		
<i>E. coli</i>	211 / 222 (95%)	184 / 202 (91%)
<i>K. pneumoniae</i>	11 / 12 (92%)	10 / 13 (77%)

* 95% confidence intervals not calculated, the study was not powered to demonstrate non-inferiority

** Number of patients with specified baseline organism eradicated / Number of per-protocol patients with specified baseline organism.

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The microbiological eradication rates for baseline organisms at TOC were 93% (254/272) for the Proquin XR group and 90% (225/251) for the Cipro IR group. Of the patients with their baseline pathogen eradicated, new infections were detected in 42/254 (16.5%) Proquin XR patients and 32/225 (14.2%) Cipro IR patients at the TOC visit. Of the patients with new infections, gram-negative rods were responsible for new infections in 10/42 (24%) patients in the Proquin XR group and 7/32 (22%) patients in the Cipro IR group.

1.3.3 Safety

There were no deaths during the studies. Ten patients (4 Proquin XR patients; 6 patients Cipro IR patients) experienced one or more serious adverse events (SAEs) during the Phase II and Phase III studies. The most common SAE was chest pain (2 Proquin XR patients; 2 patients, Cipro IR patients). All other types of SAE were reported for one patient each; these events were: anemia and papillary thyroid cancer in the Proquin XR patients and intestinal obstruction, pyelonephritis, nephrolithiasis, and ovarian cyst in the Cipro IR patients. None of the SAEs were considered to be related to study drug.

Seven of 547 patients (1.3%) treated with Proquin XR group and three of 538 patients (0.6%) treated with Cipro IR experienced AEs causing discontinuation of study drug. These were not statistically different. One Proquin XR patient and one Cipro IR patient experienced hypersensitivity that caused discontinuation of study drug. No other AEs causing discontinuation of study drug were experienced by more than one patient. Five patients (3 Proquin XR patients and 2 Cipro IR patients) experienced AEs causing discontinuation that were considered related to study drug in Study 81-0015. Treatment-related AEs leading to discontinuation were hypersensitivity in two patients; and dyspnea, urticaria, and suprapubic pain each in one patient.

Five patients (3 Proquin XR patients and 2 Cipro IR patients) experienced AEs causing discontinuation that were considered related to study drug in Study 81-0015. Treatment-related AEs leading to discontinuation were hypersensitivity in two patients; and dyspnea, urticaria, and suprapubic pain each in one patient. None of these events raised any new safety concerns.

One or more treatment-emergent AEs during the 5-week study period occurred in 230 (42.0%) Proquin XR patients and 231 (42.9%) Cipro IR patients. The incidence of common adverse events (reported for at least 1% of patients treated with Proquin XR) is: fungal infection (2.6%), nasopharyngitis (2.6%), headache (2.4%), micturition urgency (2.0%), abdominal pain (1.6%), back pain (1.6%), dysuria (1.6%), upper respiratory tract infection (1.6%), suprapubic pain (1.5%), nausea (1.3%), pharyngitis (1.3%), urinary frequency (1.3%), hematuria (1.1%), dizziness (1.1%), nasal congestion (1.1%), and vaginosis fungal (1.1%).

The incidence of adverse events, judged by investigators to be at least possibly drug-related, occurring any time during the study in at least 1% of Proquin XR patients was fungal infection (1.6%).

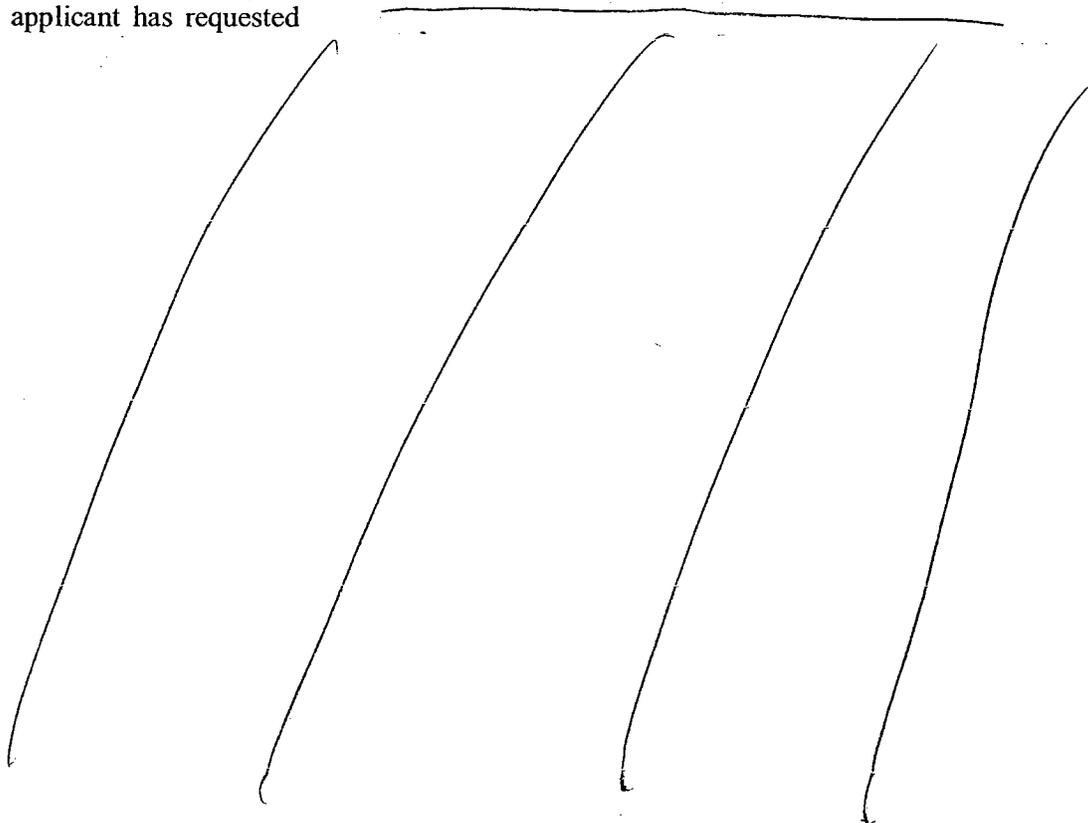
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Overall, the incidence and types of AEs seen in these studies were generally similar for the two treatment groups and consistent with what is expected for ciprofloxacin. No new safety concerns were raised.

1.3.4 Dosing Regimen and Administration

The applicant has requested



Upon review of the data provided by the applicant, the Division has concluded that there is not sufficient data to support

As discussed in Section 7.1.5: "*Common Adverse Events*", the incidence of nausea in the clinical studies was lower in the Proquin XR group, but not significantly different from the Cipro IR group (1.3% and 2.8%, respectively; $p = 0.088$). The incidence of diarrhea was statistically lower in the Proquin XR group (0.4%) compared to Cipro IR (1.9%) ($p=0.021$). However, the overall incidence of any type of gastrointestinal adverse event was not statistically different between the two products (6.2% and 8.9%, respectively, nor was the overall incidence of adverse events (42.0% and 42.9%, respectively). The rate of discontinuation from study drug was numerically higher in the Proquin XR group (1.3%) compared to the Cipro IR group (0.6%).

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1.3.5 Drug-Drug Interactions

Ciprofloxacin is involved in drug-food and drug-drug interactions. These are summarized below.

1.3.5.1 Drug-Food Interactions

Several published studies have shown that oral multivitamin and mineral supplements fortified with multivalent cations such as calcium, iron or zinc, calcium-fortified orange juice, and dairy products like milk and yogurt, interact with the fluoroquinolones, including other formulations of ciprofloxacin, by chemical complexation with the multivalent cations thereby reducing the serum and urine concentrations of ciprofloxacin.

Therefore, fortified oral multivitamins and mineral supplements should not be administered concomitantly with Proquin XR. Proquin XR should not be taken alone with dairy products (like milk or yogurt) or calcium-fortified juices, since the absorption of ciprofloxacin may be significantly reduced. However, Proquin XR may be taken with a meal that contains these products.

1.3.5.2 Drug-Drug Interactions

1.3.5.2.1 *Caffeine*

Some quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its serum half-life.

1.3.5.2.2 *Cyclosporine*

Concomitant administration of other formulations of ciprofloxacin to patients receiving cyclosporine maintenance therapy has resulted in increased risk of nephrotoxicity including acute renal failure with transient elevations in serum creatinine. The mechanism of this interaction is not known but is thought could involve synergistic effects of the drug and/or interference by ciprofloxacin with cyclosporine metabolism. Therefore, Proquin XR should be administered cautiously to patients on cyclosporine maintenance therapy.

1.3.5.2.3 *Glyburide*

There are published case reports that concomitant administration of other formulations of ciprofloxacin with glyburide therapy has, on rare occasions, resulted in severe hypoglycemia. Therefore, concomitant administration of Proquin XR and glyburide should be avoided or blood glucose levels should be monitored very closely.

1.3.5.2.4 *Methotrexate*

Concomitant administration of other formulations of ciprofloxacin and methotrexate has been reported to result in inhibition of renal tubular transport of methotrexate potentially resulting in increased plasma levels and associated toxic reactions. Therefore, patients on methotrexate therapy should be carefully monitored when concomitant Proquin XR is required.

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1.3.5.2.5 Multivalent Cation-Containing Products

Concurrent administration of oral quinolones, including other oral formulations of ciprofloxacin, with multivalent cation-containing products such as magnesium or aluminum antacids, sucralfate, VIDEX chewable/buffered tablets or pediatric powder, or products containing calcium, iron, or zinc may substantially decrease the absorption of ciprofloxacin, resulting in serum and urine levels considerably lower than desired.

The interaction of Proquin XR and magnesium/aluminum-containing antacids was evaluated in healthy volunteers. To minimize the effect of antacids on the absorption of ciprofloxacin, Proquin XR should be given either 2 hours after or at least 4 hours before antacids. This time window for Proquin XR is different than for other oral formulations of ciprofloxacin.

1.3.5.2.6 Non-steroidal anti-inflammatory drugs (but not aspirin)

Published studies in animals have reported that fluoroquinolones decrease the receptor binding of gamma-amino-butyric acid (GABA) leading to CNS excitation. This decreased binding may be potentiated by simultaneous administration of certain non-steroidal anti-inflammatory drugs (NSAIDs). There have been recent reports from Japan of convulsions in patients receiving the NSAID, fenbufen, and the fluoroquinolone, enoxacin. Therefore, concomitant administration of Proquin XR with a NSAID could result in increased risk of CNS stimulation (e.g., seizures).

1.3.5.2.7 Omeprazole

The rate and extent of absorption of ciprofloxacin was not substantially different when Proquin XR was given alone or when Proquin XR was given 2 hours after omeprazole at the dose that maximally suppresses gastric acid secretion. Proquin XR should be taken with the main meal of the day, preferably the evening meal, and should be taken at least 2 hours after omeprazole

1.3.5.2.8 Phenytoin

There are reports in the literature that other formulations of ciprofloxacin interacted with phenytoin in rare instances resulting in altered (increase or decrease) serum levels of phenytoin. Therefore, the concomitant administration of Proquin XR with phenytoin should be avoided and if it must be given concomitantly, plasma phenytoin concentrations should be monitored.

1.3.5.2.9 Probenecid

Concomitant administration of probenecid has been reported in the literature to interfere with renal tubular secretion of other formulations of ciprofloxacin resulting in a reduction in renal clearance, an increase in systemic concentration, and a prolonged serum half-life of ciprofloxacin. Therefore, patients should be monitored for an increased incidence of adverse events if Proquin XR and probenecid are to be administered concomitantly.

1.3.5.2.10 Theophylline

As with some other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use of Proquin XR and theophylline cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

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1.3.5.2.11 Warfarin

Administration of fluoroquinolones, including other formulations of ciprofloxacin, to patients on the oral anticoagulant, warfarin, or its derivatives, has resulted in published reports of an increased anticoagulant effect and an increased risk of bleeding.

The co-administration of single doses of Proquin XR and Coumadin® (7.5 mg) did not result in significant changes in the pharmacokinetics of ciprofloxacin nor did it significantly affect the pharmacodynamics of S-warfarin and R-warfarin. Although the C_{max} and AUC of the two warfarin enantiomers and the elimination $t_{1/2}$ of S-warfarin were not significantly altered by ciprofloxacin co-administration, the $t_{1/2}$ of R-warfarin was statistically significantly prolonged ($P=0.029$). Therefore, Proquin XR should be administered with caution in patients receiving coumarin anticoagulant therapy and prothrombin time and international normalized ratio (INR) should be monitored very closely.

1.3.6 Special Populations

The patient populations studied in the clinical trials did not include pregnant or nursing women, pediatric patients, or patients with renal or hepatic impairment.

1.3.6.1 Pregnant Women or Nursing Mothers

There are no adequate and well-controlled studies of Proquin XR in pregnant women or nursing mothers. An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS – the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data = fair), but the data are insufficient to state that there is no risk.

Ciprofloxacin is excreted into breast milk and could result in the potential for serious adverse effects of ciprofloxacin in the nursing infant. Therefore, in lactating mothers, if Proquin XR treatment is indicated, a decision should be made either to discontinue the drug or discontinue breastfeeding.

1.3.6.2 Renal Impairment

In severe renally impaired patients ($CL_{cr} < 30$ mL/min); the recommended maximum daily dose of ciprofloxacin has been determined to be 400 mg IV or 500 mg orally once daily. Since the maximum daily dose of ciprofloxacin for uncomplicated UTI is 500 mg orally, no dosage adjustment is required for patients with severe renal impairment with uncomplicated UTI receiving Proquin XR.

1.3.6.3 Hepatic Impairment

No dosage adjustment is required for patients with stable chronic cirrhosis, since hepatic dysfunction appears to have little effect on the disposition and elimination of ciprofloxacin.

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Thus, the exclusion of these patients from the clinical studies should not impact the predicted safety of this product in the marketplace. Other formulations of ciprofloxacin have been marketed worldwide for over 15 years, and the safety profile of ciprofloxacin is well established.

1.3.6.4 Pediatrics

Ciprofloxacin, like most other fluoroquinolones, causes arthropathy in immature animals of various species. The safety and effectiveness of Proquin XR in patients < 18 years of age has not been established.

1.3.6.5 Age (< 65 years or ≥ 65 Years)

Microbiological eradication rates were similar for patients 65 years or older and younger patients in the Phase III study. No clinically relevant differences in safety were observed between older patients and patients less than 65 years old. Dosage adjustments based upon age are not warranted.

1.3.6.6 Race (Caucasian and non-Caucasian)

Microbiological eradication rates were similar for Caucasian and non-Caucasian patients. No clinically relevant differences in safety were observed between Caucasian and non-Caucasian patients. Dosage adjustments race are not warranted.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Established Name: ciprofloxacin hydrochloride extended-release tablets
Proposed Trade Name: Proquin XR™
Therapeutic Class: fluoroquinolone antimicrobial
Applicant: DepoMed, Inc.
Strength: 500 mg
Dosing Regimen: 500 mg once daily for 3 days
Active Ingredient: ciprofloxacin hydrochloride, USP
Inactive ingredients: film coating (Opadry® Blue), magnesium stearate, polyethylene oxide, and povidone.
Indication: uncomplicated urinary tract infection
Intended Population: adult women

2.2 Currently Available Treatment for Indications

The oral fluoroquinolone antimicrobials approved for the treatment of uncomplicated urinary tract infection include:

Cipro XR® ciprofloxacin hydrochloride and ciprofloxacin extended release): for uncomplicated urinary tract infection caused by *Escherichia coli*, *Proteus mirabilis*, *Enterococcus faecalis*, or *Staphylococcus saprophyticus*^a

^a Treatment of infections due to this organism in the organ system was studied in fewer than 10 patients.

Ciprofloxacin: For uncomplicated urinary tract infection caused by *Escherichia coli* or *Staphylococcus saprophyticus*.

Floxin®: For uncomplicated urinary tract infection caused by *Citrobacter diversus*, *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* or *Pseudomonas aeruginosa*.

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Maxaquin®: For uncomplicated urinary tract infection caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Staphylococcus saprophyticus*.

Noroxin®: For uncomplicated urinary tract infection caused by *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Proteus vulgaris*, *Streptococcus agalactiae*.

Penetrex®: For uncomplicated urinary tract infection caused by *Escherichia coli*, *Staphylococcus epidermidis* and *Staphylococcus saprophyticus*.

Tequin®: Uncomplicated UTI (cystitis) due to *Escherichia coli*, *Proteus mirabilis*, or *Klebsiella pneumoniae*. (single dose)

2.3 Availability of Proposed Active Ingredient in the United States

Ciprofloxacin has been marketed worldwide since 1988 and is approved to treat mild/moderate to severe/complicated UTI. The recommended dosage regimen for immediate ciprofloxacin tablets or oral suspension is 250 to 500 mg BID for 7 to 14 days. Cipro XR® (ciprofloxacin hydrochloride and ciprofloxacin extended release) has been approved since December 12, 2002 and is indicated for both uncomplicated (500 mg once daily for 3 days) and complicated (1000 mg once daily for 7 to 14 days).

2.4 Important Issues With Pharmacologically Related Products

Ciprofloxacin and other quinolones are associated with absorption-based drug interactions with magnesium and/or aluminum-containing products resulting in reduced systemic exposure to ciprofloxacin and the potential for lack of efficacy.

Ciprofloxacin inhibits the metabolism of theophylline resulting in elevated serum theophylline levels and the potential for theophylline-associated toxicities.

Other adverse events associated with ciprofloxacin and the quinolones include: CNS toxicities, hypersensitivity reactions, pseudomembranous colitis, peripheral neuropathy, and tendon rupture.

All of these potential adverse events are included, along with class labeling, when appropriate, in the Proquin XR package insert.

2.5 Presubmission Regulatory Activity

One regulatory issue arose during the pre-NDA period: whether the proposed NDA would be a "stand alone" [505(b)1] application under the FD&C Act; or whether the applicant could rely on information from the scientific literature pertaining to other formulations of ciprofloxacin [505(b)2].

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A teleconference between the Division and the applicant was held on January 27, 2003 which outlined the Division's requirements and the studies needed to support future approval of Proquin XR as a 505(b)1 NDA. The complete minutes from that meeting are included below:

Clinical Reviewer's Comment: Ciprofloxacin GR is the same as Proquin XR

Background:

DepoMed had originally planned to file an NDA under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. On August 16, 2002, they submitted a letter requesting the Division's concurrence with their decision to submit a 505(b)(1) new drug application (NDA) for Ciprofloxacin GR for the treatment of uncomplicated urinary tract infection. The purpose of this teleconference is to discuss the requirements and the studies needed in order to submit a 505(b)(1) new drug application.

Discussion items:

After reviewing the package which will be submitted as a 505(b)(1), the Division expressed concern that this will not be a complete NDA and that the applicant will be relying on data they do not own or have a right of reference to. Additional studies are needed in order for their application to be considered under a 505(b)(1) application.

The 28-day dog study is acceptable for submission, but additional studies are required. These studies should include genotoxicity studies, reproductive toxicity studies, and teratogenicity in rats and rabbits. Carcinogenicity studies are not required. DepoMed will propose a schedule for the toxicology studies and will submit to the Division for concurrence.

DepoMed inquired about any ADME studies or any additional clinical pharmacology studies needed for a 505(b)(1) application.

The Division will communicate to DepoMed any clinical pharmacology studies needed in the submission. Including any drug interaction studies.

The Division recommends that a labeling comprehension study be done regardless of whether it is a 505(b)(1) or 505(b)(2) application.

Clinical Reviewer's Comment The applicant submitted a "proposed outline" for Stage 2 of a Label Comprehension Study as an amendment to the NDA (dated November 23, 2004), which was reviewed by DSRCs (review date April 8, 2005). Results from the study were not included in the submission. DSRCs concluded the majority of the questions asked as part of the Stage 2 study were aimed at healthcare providers, not patients, and therefore, and appear to be targeted for marketing purpose, as opposed to achieving patient understanding of directions for use.

The microbiology section is adequate and will not be affected by a switch to a 505(b)(1). A single clinical trial with 500 evaluable patients in uncomplicated UTI is adequate to support a 505(b)(1) application.

Following the January 27, 2003 teleconference, an additional request from the Division was sent to the applicant (dated April 3, 2003) which specifies in addition to the genetic and reproductive toxicology studies proposed by the applicant to support a 505(b)1 application, a Segment I male and female rat fertility study should also be conducted, which is a standard study outlined in the ICH Guidance Documents.

A Pre-NDA Meeting with the applicant was held on March 5, 2004. Meeting minutes from that meeting are included below:

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Clinical Reviewer's Comment: The discussion pertaining to clinical and 505(b)1 issues with the proposed NDA have been abstracted below by the Reviewer from the complete meeting minutes, which can be found in DFS under IND 62,386.

BACKGROUND:

This meeting is being held as a result of Depomed's request for a face-to-face Pre-NDA meeting to discuss their NDA submission plans for Ciprofloxacin GR. Depomed had originally planned to submit a 505(b)(2) NDA for Ciprofloxacin GR. However, post-EOP II meeting, on August 16, 2002, the sponsor submitted a letter requesting the Division's comments on their decision to submit a 505(b)(1) NDA for Ciprofloxacin GR for the treatment of uncomplicated urinary tract infection. On January 27, 2003, the Division discussed with Depomed via teleconference the requirements for a 505(b)(1) NDA and informed the sponsor of additional studies necessary for their application to be considered under a 505(b)(1) approval. In preparation for the Pre-NDA meeting, Depomed has provided synopses of completed Phase II and Phase III studies along with a list of questions in a Briefing Package, submitted on January 2, 2004, seeking the Division's comments on the information to be included in the planned NDA submission. The sponsor proposes to cite literature to support some of the statements in the proposed draft labeling for Ciprofloxacin GR. Depomed is of the position that some literature studies may be referred to in support of a 505(b)(1) NDA.

MEETING SUMMARY:

It was stated at the onset of the meeting that the Division's review of Depomed's planned NDA submission for Ciprofloxacin GR as outlined in the Briefing Package found it to not meet the criteria for a 505(b)(1) application. The Division stated that a discussion on the classification of the sponsor's planned NDA submission (i.e. 505(b)(1) vs. 505(b)(2)) will require the participants of the Agency's legal counsel. Therefore, it was recommended that the regulatory discussion of 505(b)(1) vs. 505(b)(2) will be tabled for another time. It was agreed that the meeting will focus on the scientific discussion of the drug product. After an induction of all the attendees, Depomed provided a presentation on Ciprofloxacin GR describing its mechanism of action, PK profile, adverse events as well as a brief summary of Phase III study. Following the presentation, the sponsor facilitated the discussion by requesting the Division's response to their questions listed in the Briefing Package. The Division's responses are summarized below.

QUESTIONS FOR DISCUSSION WITH THE AGENCY'S RESPONSES:

(The sponsor's questions are reproduced in italicized type below in the order they were asked during the meeting.)

Microbiology

3. The proposed labeling for the microbiology subsection will be based upon the data obtained from the clinical trials and medical literature. Depomed has provided a draft package insert for the proposed application. Does the Division concur that the layout of the Microbiology section is acceptable for approval of the 505(b)(1) NDA application?

A 505(b)(1) NDA relies exclusively on studies that you conducted, that were conducted for you, or for which you have the right of reference. Therefore, any information required for the labeling in the microbiology subsection must come from studies you have conducted or were conducted for you or for which you have right of reference. To include organisms in the *in vitro* activity listing (list #2) in the labeling, you will need to conduct 2 separate studies (2 different laboratories) that show MIC 90 values for each species below susceptibility breakpoints. Usually at least 100 isolates of each species must be tested. You may need to establish breakpoints on your own data if you can not refer to other studies. This would require more than 100 isolates. Since NCCLS documents are public you may be able to reference these documents to establish breakpoints.

The sponsor asked if multi-center study is acceptable.

We recommend 2 separate studies (i.e. 2 different laboratories). However, if you choose to do a multi-center study, it must be a well established reputable center.

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The PK package as discussed at the End of Phase II meeting and the 505(b)(1) teleconference with reference to referred PK articles in journals is intended to be the complete PK package to support the labeling for Ciprofloxacin GR. Depomed is utilizing this approach based on the understanding that the other 505(b)(1) NDA applications for approved — dosage forms may have utilized only PK literature references to define the labeling for the basic pharmacokinetics and ADME of their products. Does the Division concur with this approach?

No, the requisite for a 505(b)(1) NDA consideration is that the application relies exclusively on studies that you conducted, that were conducted for you, or for which you have the right of reference.

4. The clinical program is comprised of one Phase II Study and one Phase III Study. In addition, safety data from 7 pharmacokinetic studies will be included in the clinical safety summary. The Phase II (81-0005) and Phase III (81-0015) studies were conducted to determine safety and efficacy of Ciprofloxacin GR for the treatment of uncomplicated urinary tract infections (UTI) in adult females. Both studies were randomized, double-blind, parallel-group studies that compared Ciprofloxacin GR to immediate release (IR) ciprofloxacin (CIPRO). Does the Division concur that these studies meet the requirements for a 505(b)(1) NDA filing?

One Phase III study with supportive Phase II study is acceptable.

5. Approximately 294 patients were included in the efficacy population and 544 patients were included in the safety population in the overall clinical program with treatment with 500 mg Ciprofloxacin GR once daily for 3 days. Is this extent of exposure adequate to support this 505(b)(1) filing?

Yes.

Biostatistics

6. The efficacy results generated from 2 clinical studies, Phase II Study 81-0005 and Phase III study 81-0015 will be presented individually for each study in section 2.7.3.2 Summary of Results from Individual Studies. This section will include tables for the primary and secondary efficacy parameters. Tables included will be the same format as those in the study reports. Is this acceptable?

Yes.

7. The efficacy data from these 2 individual studies will not be pooled for data analysis. Visual integration of key efficacy data will be 2.7.3.3. We will compare and analyze results across studies by presenting results from these 2 studies within the same table as side-by-side columns with no statistical comparisons being made across studies. Is this acceptable?

Yes, we find it acceptable.

8. Are there any additional analyses of efficacy data required for this NDA submission?

Not at this time. However, we may request additional analyses during the NDA review.

The sponsor then inquired about the adequacy of the use of a per-protocol analysis group in the primary efficacy analysis.

It is Division policy to consider the results of the modified intent-to-treat group (i.e., including all patients enrolled who had documented baseline infection) of at least as much importance as that of the per-protocol group. Subjects in the modified intent-to-treat group with missing efficacy evaluations should be considered failures for this analysis. The sponsor is not obligated to include this modified intent-to-treat analysis for submission of the NDA; however, the Division would like to inform the sponsor that this analysis will be conducted and considered in the Division's evaluation of the study.

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9. The baseline demographics, termination and adverse event data collected for patients from 2 clinical studies (81-005 and 81-0015) will be pooled for the integrated safety data presentations. Is this acceptable? Are there any other safety parameters for which data must be pooled across these studies

Pooling the safety data is acceptable.

ADDITIONAL COMMENTS:

Questions regarding the definition of common knowledge and prior scientific knowledge and how they relate to 505(b)ness of a NDA were raised. It was agreed that for a further discussion on the issue of literature support for a 505(b)(1) NDA, Depomed will first provide the Agency with their position statement that delineates and supports their opinion.

Clinical Reviewer's Comment: At the time of filing the Division agreed that the application submitted was a "stand alone" NDA under 505(b)1 of the FD&C Act. The applicant submitted a position paper regarding the rationale for designating their product as a 505(b)1, as opposed to 505(b)2, application. The executive summary of their document can be found under Section 8.8: "Other Relevant Materials" and the complete document can be found in the NDA submission of July 18, 2004

In the submission, the applicant has supplied study reports for a number of clinical pharmacology studies, which they conducted at the request of the Division. The animal pharmacology studies mentioned in the February 28, 2003 meeting minutes (i.e., genotoxicity studies, reproductive toxicity studies, and teratogenicity in rats and rabbits) have also been completed and submitted by the applicant.

Pertinent sections of the applicant's NDA cover letter are included below which describes additional clinical pharmacology data collected by the applicant, at the Division's request, which is included in the NDA submission and why additional studies are not necessary (remaining pertinent data is part of the general scientific literature). The animal pharmacology studies discussed with the applicant (i.e., genotoxicity studies, reproductive toxicity studies, including Segment I male and female rat fertility study, and teratogenicity in rats and rabbits) have also been completed and submitted by the applicant as part of the NDA.

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In correspondence dated 28 February 2003, DSPIDP requested that Depomed conduct a number of additional pharmacology studies to support Depomed's 505(b)(1) NDA application for Proquin™. Depomed has made every effort to complete nearly all of the additional clinical pharmacology studies requested by DSPIDP, or to commit to complete them as part of Phase IV commitments. The four remaining requests, i.e., a study of the pharmacokinetics of Proquin™ in hepatic-impaired patients, and pharmacodynamic drug interaction studies with warfarin and theophylline, are considered redundant for acceptance of this NDA for filing, and should not be necessary for approval. Instead, Depomed provides references to the scientific literature to supply information helpful to the prescriber. These references do not make this NDA a 505(b)(2) application. Such information is not essential to the DSPIDP's determination that Proquin™ (1) is safe and (2) has the effect it purports to have in its proposed labeling.

With regard to hepatic-impaired patients, this NDA includes data on urine recovery of metabolites. Depomed's data, as well as the scientific literature, demonstrate that the majority of ciprofloxacin is eliminated in urine. Thus, no dose adjustments should be required for hepatic impaired patients. For the same reason, a study in this patient population is not essential to the filing or approval of the application. With regard to drug interaction studies with warfarin and theophylline, Depomed submits that Class labeling for quinolones apply. The Class warnings would appear in the labeling of Proquin™ regardless of the results of such studies. Thus, the information is both common prior scientific knowledge and unnecessary for filing or approval to have separately provided for in full reports of studies conducted by Depomed. In addition, Depomed is willing to commit to conducting a single-dose pharmacokinetic study with warfarin in healthy volunteers as part of the Phase IV studies.

We characterize the pharmacology issues raised by DSPIDP at the 28 February 2003 meeting as either "formulation independent issues" (i.e., issues that address questions pertaining to ciprofloxacin itself, regardless of formulation or route of administration) or "formulation dependent issues" (i.e., how the formulation performs in the population of interest before ciprofloxacin is absorbed). For those issues we identify as being formulation independent, we believe there is sufficient evidence in the peer reviewed literature to address DSPIDP's concerns such that additional in vitro and ex vivo studies are unnecessary. Specifically, the

issues of in vitro metabolism, the potential for inhibition or induction of CYP isoenzymes, ciprofloxacin protein binding, and the potential for in vivo drug-drug interactions are formulation independent issues that should not require full reports from additional studies. Omitting studies the results of which the scientific community (including DSPIDP reviewers) already know does not convert this 505(b)(1) NDA to a 505(b)(2) application. Instead, Depomed references the scientific literature to supply information helpful to the prescriber and reviewer on these issues, as well as to meet Depomed's obligation to include in the NDA all pertinent information from any source. The issues of mass balance, dose-proportionality, and effect of gender and race on ciprofloxacin pharmacokinetics from CGR have been addressed by Depomed in Phase I studies already completed. Please refer to the position paper, titled "Evaluation of Additional Pharmacokinetic Studies, PK White Paper", appended to the "505(b)(1) Position Paper". This PK White Paper addresses each DSPIDP request.

2.6 Other Relevant Background Information

DSRCS was consulted regarding the Label Comprehension Study (amendment to the NDA, submitted on November 23, 2004). See discussion in Section 2.5: "Presubmission Regulatory Activity" above. The complete review (dated April 8, 2005) can be found in DFS.

DSCRCS was also consulted on the applicant's Patient Package Insert, included as part of the Package Insert (submitted with the NDA on July 18, 2004). See discussion in Section 9.4 "Labeling Review." The complete review (dated April 4, 2005) can be found in DFS.

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ODS was consulted on the applicant's Risk Management Plan (submitted with the NDA on July 18, 2004). ODS concluded that the proposed plan did not differ substantially from typical new product labeling and routine passive post-marketing safety surveillance. The complete review (dated March 24, 2005) can be found in DFS.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The application is approvable from the Chemistry, Manufacturing, and Controls (CMC) perspective. Below is a summary of the CMC review.

Clinical Reviewer's Comment: For more information, see the complete CMC Review by Balajee Shanmugam, Ph.D. filed with this NDA.

The DMF for the drug substance was reviewed previously and found to be adequate. The inactive ingredients used in the drug product are mostly compendial except Opadry® Blue for which the company has provided adequate information in the NDA submission. In addition, the firm also provided reference to a DMF for Opadry Blue. The manufacturing process for the drug product has been adequately described.

All issues regarding the drug product specifications have been adequately negotiated with the applicant. The applicant will continue to monitor the stability of the drug substance and drug product. The manufacturing and testing facilities have acceptable cGMP status and the Office of Compliance has issued an Overall Recommendation of Acceptable for the NDA.

3.2 Animal Pharmacology/Toxicology

The application is approvable from the Pharmacology/Toxicology perspective. Below is a summary of the Pharmacology/Toxicology review.

Clinical Reviewer's Comment: For more information, see the complete Pharmacology/Toxicology Review by Steven Hundley, Ph.D. filed with this NDA.

Pharmacologic Activity:

The pharmacologic activity of ciprofloxacin and the fluoroquinolone class is well documented. Additional discussion of the pharmacological activity and antibacterial mechanism of action of ciprofloxacin is not needed for this review.

Nonclinical Findings Overview:

Restatement of the overall nonclinical toxicological profile for ciprofloxacin is not needed for the current Pharmacology/Toxicology Review and Evaluation. The sponsor conducted a bridging repeat-dose general toxicity in beagle dogs that compared the toxicological effects of the Proquin XR™ gastro-retentive tablets to Cipro® tablets (500 mg). None of the dosing regimens resulted

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in compound-related toxicity. The NOAEL for the study was 1000 mg ciprofloxacin (two 500 mg Proquin XR™ gastro-retentive tablets) at average dose levels of 92 and 144 mg/kg (male and female dogs, respectively).

The sponsor conducted genetic toxicology and reproductive toxicology studies to comply with labeling requirements for a drug product submitted as a 505 (b)(1) application. Ciprofloxacin was negative for mutagenic activity with or without an S-9 enzymatic metabolic activation system in *Salmonella* strains TA98, TA100, TA1535, and TA1537 and in the *E. coli* strain WP2uvrA. Ciprofloxacin induced chromosomal aberrations in the CHO mammalian cell culture system in the presence and absence of an S-9 enzymatic metabolic activation system. Ciprofloxacin did not cause elevated levels of micronucleus formation in the *in vivo* rat micronucleus assay at any dose level including the highest dose level of 2,000 mg/kg.

Embryo/fetal developmental toxicity studies were conducted in pregnant rats and rabbits. No embryo/fetal lethality was observed in the study with pregnant rats at any ciprofloxacin dose level (highest dose = 600 mg/kg). Skeletal variations were observed in fetuses at the maternally toxic highest dose level (reduced body weight gain), whereas no evidence of visceral or skeletal malformations was observed. Pregnant rabbits exhibited a 10 percent reduction in mean body weight and a 2-fold reduction in body weight gain at the highest dose level of ciprofloxacin, 30 mg/kg. Eight of the 22 pregnant rabbits aborted at the 30 mg/kg dose and two of 22 aborted at the 10 mg/kg dose level. The 30 mg/kg dose level resulted in embryo/fetal lethality and fetal developmental effects (lower mean fetal weight and increased skeletal variations). No embryo/fetal effects were observed at the other two ciprofloxacin dose levels (3 and 10 mg/kg). Compound related visceral and skeletal malformations were not observed at any ciprofloxacin dose level.

The effects upon male and female rat fertility were examined at ciprofloxacin dose levels as high as 600 mg/kg. No compound-related effect was observed on fertility rates. No compound-related gross pathological effects were observed in the epididymis, testis, seminal vesicles, and prostate of male rats. No compound-related effects were observed for sperm count, morphology, and motility. The peri/postnatal reproductive toxicity study in pregnant rats also resulted in minimal effects. The F0 pregnant female rats exhibited a slight reduction in mean body weight during gestation (Day 6 through Day 20) at the two highest ciprofloxacin dose levels (300 and 600 mg/kg). No compound related developmental effects were observed in the F1 pups from F0 pregnant dams dosed with ciprofloxacin. F1 males and females were mated upon reaching sexual maturity and no effects were observed in the fertility and reproduction indices. The NOAEL for ciprofloxacin-dosed pregnant rats was 50 mg/kg and the NOAEL for developmental effects to the F1 pups was 600 mg/kg.

Nonclinical Safety Issues:

There are no nonclinical safety issues with Proquin XR™ (ciprofloxacin HCl).

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4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The applicant conducted one Phase 2 (Study 81-0005) and one Phase 3 (Study 81-0015) in adult women with uncomplicated urinary tract infection.

The clinical study reports and electronic datasets used in this review can be found at:

\\Cdsub1\21744\N_000\2004-07-18

\\Cdsub1\21744\N_000\2005-02-17

4.2 Tables of Clinical Studies

A summary of the two clinical studies conducted by the applicant can be found in Table 1.

TABLE 1
Summary of Clinical Studies

Study ID	No. of Study Centers Location(s)	Study Start Enrollment Status/Date Total enrollment/enrollment goal	Design Control Type	Study & Control Drugs, Dose, Route, & Regimen	Study Objective	#Subjects by Arm Entered/ Completed	Duration of Treatment	Mean Age (range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
81-0005 Phase II	6 United States	Start: Oct 2001 Completed: April 2002 58/50	Randomized, double-blind, active-controlled, parallel group, non-inferiority safety and efficacy study in female patients with uncomplicated UTI	C-GR 500 mg qd, oral C-IR 250 mg bid, oral	Establish safety and efficacy of C-GR by comparison to C-IR	C-GR 29/29 C-IR 29/27	3 days	44 yrs (19-81)	Uncomplicated UTI. Females with clinical signs and symptoms and at least 1 positive ($\geq 10^5$ CFU/mL) pretreatment urine culture	Micro Eradication and Clinical Cure at 4 - 11 days posttreatment
81-0015 Phase III	70 United States	Start: June 2003 Completed: Dec 2003 1037/960	Randomized, double-blind, active-controlled, parallel group, non-inferiority safety and efficacy study in female patients with uncomplicated UTI	C-GR 500 mg qd, oral C-IR 250 mg bid, oral	Establish safety and efficacy of C-GR by comparison to C-IR	C-GR: 524/471 C-IR: 513/458	3 days	39 yrs (18-89)	Uncomplicated UTI. Females with clinical signs and symptoms and at least 1 positive ($\geq 10^5$ CFU/mL) pretreatment urine culture	Micro Eradication and Clinical cure at 4 - 11 days posttreatment

C-GR = ciprofloxacin gastric-release tablets (also known as Proquin XR)

C-IR = ciprofloxacin immediate release tablets (Cipro®)

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4.3 Review Strategy

The Phase 3 study (Study 81-0015) was considered pivotal and the Phase 2 study (Study 81-0005) was considered supportive.

4.4 Data Quality and Integrity

A DSI audit was performed for the 3 investigator sites listed below. These sites were selected for inspection because they were the highest enrolling sites into the Phase 3 study (Study 81-0015).

No major deficiencies were noted by DSI in any of the sites inspected that could compromise the integrity of the data. They recommended no subsequent actions or follow-up inspections.

Site #24 (49 patients enrolled)

L. Scott Larsen, MD, FACEP
EMO Medical Care
2 Kings Highway
Middletown, NJ 07748

Site #39 (N=47 patients enrolled)

Robert D. Rosen, MD, FAAFP
Ardmore Family Practice
2805 Lyndhurst Avenue
Winston-Salem, NC 27103

Site #27 (46 patients enrolled)

Frank Mazzone, MD
Coastal Medical Research Group, Inc.
2146 Parker Street, Suite B-3
San Luis Obispo, CA 93401

A 10% random sample of subjects (N=103) enrolled in Study 81-0015 was generated by the FDA Statistical Reviewer. The applicant was requested to submit the CRFs for these subjects for review. The FDA Clinical Reviewer examined the CRFs for inclusion/exclusion criteria, dates of visits, clinical signs and symptoms, concomitant medications and indications, and evaluability determinations. The data in the CRFs was compared to the electronic datasets generated by the applicant. The Reviewer found agreement between the random sample of CRFs and the electronic datasets.

4.5 Compliance with Good Clinical Practices

No specific issues with informed consent, protocol violations, or any site-specific issues were identified in this review.

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4.6 Financial Disclosures

The applicant obtained certification from each investigator and sub-investigator who enrolled patients in the Phase III study. No investigator or sub-investigator had any disclosable information to reveal.

5 CLINICAL PHARMACOLOGY

The application is approvable from the Clinical Pharmacology/Biopharmaceutics perspective. Below is a summary of the Clinical Pharmacology/Biopharmaceutics review.

5.1 Pharmacokinetics

Clinical Reviewer's Comment: For more information, see the complete Clinical Pharmacology/Biopharmaceutics Review by Gerlie Gieser, Ph.D. filed with this NDA.

Proquin XR™ is an extended release tablet containing 500 mg of ciprofloxacin hydrochloride. Proquin XR™ differs from currently marketed ciprofloxacin immediate-release and modified-release solid oral dosage forms because of its distinct absorption profile, as well as its unique interaction with food and drugs that alter ciprofloxacin absorption (e.g., antacids, omeprazole).

Patients should not substitute Proquin XR™ for other ciprofloxacin dosage forms unless they are properly counseled by their physician and/or pharmacist. Proquin XR™ should be given with the main meal of the day, preferably the evening meal. The recommended timing of Proquin XR™ co-administration with antacids and omeprazole are different from the usual time of dosing recommendations for currently marketed ciprofloxacin oral dosage forms. Despite these differences, the total systemic ciprofloxacin exposure and the cumulative urinary excretion of ciprofloxacin and its active metabolites from Proquin XR™ 500 mg once-daily appear to be comparable to that achieved from the reference ciprofloxacin treatment (Cipro® 250 mg BID).

For the treatment of uncomplicated urinary tract infections (uUTI), the proposed Proquin XR™ dosing regimen is one (500 mg) tablet once daily (with a meal) for 3 consecutive days. Based on the calculated AUC/MIC and C_{max}/MIC ratios, adequate plasma exposures, as well as urinary concentrations of ciprofloxacin are achieved from Proquin XR™ that during the 3-day dosing period would sustain antimicrobial activity against susceptible strains of at least the following microbes commonly encountered in uncomplicated urinary tract infections: *Escherichia coli*, *Klebsiella pneumoniae*. (For more details See Section 5.3: "Exposure-Response Relationships")

Age, body weight, height, gender, and race were not significant covariates of ciprofloxacin exposure from Proquin XR™ 500 mg once daily for 3 days. Thus dosing adjustments based on these factors are not warranted. Furthermore, based on the findings of the PK studies conducted in special populations, as well as on existing literature PK information, dosage adjustments do not appear to be necessary for elderly patients and patients with renal impairment

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Although the *in vitro* study conducted to investigate the inhibitory effects of ciprofloxacin on selected CYP450 enzymes was not able to definitively demonstrate the potential of this drug to inhibit the metabolism of CYP1A2 substrates at test concentrations covering relevant plasma exposure, the label will contain a precautionary statement regarding the drug interactions of ciprofloxacin that result in decreased clearance of CYP1A2 substrates (e.g. theophylline, caffeine). Likewise, despite the inability to show a PK and/or PD interaction between single-doses of Proquin XR™ and warfarin (Coumadin®) in healthy volunteers, the label will indicate the potential of ciprofloxacin to increase the anticoagulant effect of warfarin, as stated in the labels of other ciprofloxacin products.

Based on a Level A IVIVC, the proposed release specifications for dissolution testing of Proquin™ extended-release tablets are acceptable.

5.2 Pharmacodynamics

No applicable.

5.3 Exposure-Response Relationships

Clinical Reviewer's Comment: For more information, see the complete Clinical Pharmacology/Biopharmaceutics Review by Gerlie Gieser, Ph.D. filed with this NDA.

Like other fluoroquinolones, ciprofloxacin shows concentration-dependent killing of bacteria *in vitro*. *In vivo* studies in animals and humans demonstrated that a 24-hour AUC/MIC ratio of at least 100 and a C_{max}/MIC ratio of at least 10 are often associated with maximal clinical and bactericidal effect in the treatment of (uncomplicated) urinary tract infections caused by gram-negative microbes. Based on the sponsor's PK/PD analysis, the administration of Proquin XR™ 500mg once daily with a high-fat meal for three consecutive days produces the following AUC/MIC and C_{max}/MIC values in Table 21 (measured on Day 3 of therapy) for the pathogens commonly found in uncomplicated urinary tract infections (uUTI). Based on these calculated surrogate PK/PD parameters, i.e., AUC/MIC and C_{max}/MIC, the proposed dosage regimen for Proquin XR™ appears to produce sufficient systemic exposures to ciprofloxacin to successfully treat urinary tract infections caused by microbes that are similar in susceptibility to *E. coli*, *K. pneumoniae*. The trough ciprofloxacin concentrations (C_{min}) achieved at steady state following 3 daily doses of Proquin XR™ 500mg were at least equivalent to the MIC₉₀ of these susceptible microbial strains. Furthermore, it was observed that the measured mean urinary concentrations of ciprofloxacin were substantially higher in urine than in plasma, suggesting that exposure to ciprofloxacin at the organ sites involved in uncomplicated urinary tract infection (uUTI) will also be adequate, at least when the four susceptible microbial strains are involved.

TABLE 21
Ratios for Ciprofloxacin AUC/MIC, C_{max}/MIC, C_{min}/MIC and 24-h C_{urine}/MIC
Following a 3-Day Regimen of Proquin™ 500 mg Once Daily

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ORGANISM	MIC ₉₀ (mcg/mL)	Ciprofloxacin AUC _{0-24h} (7905 ng*h/mL)	Ciprofloxacin C _{max} (857 ng/mL)	Ciprofloxacin C _{min} (67.7 ng/mL)	Ciprofloxacin C _{urine(0-24h)} (65.91 mcg/mL)
<i>E. coli</i> ATCC 25922 (strain 1)	0.016	494	54	4	4119
<i>E. faecalis</i> ATCC 29212 (strain 2)	1	8	1	0.1	65.91
<i>S. aureus</i> ATCC 29213 (strain 3)	0.5	16	2	0.1	131.8
<i>E. coli</i> N9688 (strain 4)	0.045	176	19	2	1465
<i>K. pneumoniae</i> N9189 (strain 5)	0.016	494	54	4	4119
<i>E. faecalis</i> ST12,296 (strain 6)	>32	<0.25	<0.03	<0.002	<2.06
<i>S.</i> <i>saphrophyticus</i> , SP8822 (strain 7)	0.5	16	2	0.1	131.8
<i>P. mirabilis</i> N9287 (strain 8)	0.045	176	19	2	1465

$$C_{urine(0-24h)} = A_{c0-24h} / \text{volume of urine in 24 h}$$

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

6.1.1 Methods

The study design of the Phase 2 and Phase 3 studies were similar. However, the primary efficacy endpoint in the Phase 2 study was not powered for non-inferiority (defined as a lower bound of the 95% confidence interval above -10% for the difference in microbiological eradication rates at the Test-of-Cure Visit between the two treatment groups). Therefore, the

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results of the two studies were not pooled and only results from the Phase 3 study were considered pivotal.

6.1.2 General Discussion of Endpoints

In the analysis of microbiological eradication, patients experiencing new infections at the test-of-cure visit were considered failures in the FDA's analysis, but not the applicant's analysis.¹ Although not specifically stated as such in the 1998 draft Guidance for Industry (Uncomplicated Urinary Tract Infection – Developing Antimicrobial Drugs for Treatment), it has historically been the position of the Agency, for trials of uncomplicated urinary tract infections, to consider patients to be microbiological successes if there is eradication of the baseline pathogen and no new infection.

6.1.3 Study Design

The Phase II (Study 81-0005) and Phase III (Study 81-0015) studies were both prospective, multicenter, double-blind, randomized, parallel-group, studies that compared the safety and efficacy of Proquin XR to Cipro IR. Cipro IR was chosen as the active control because it is an approved treatment for acute, uncomplicated UTI.

Patients received either Proquin XR 500 mg once daily (qd) or Cipro IR 250 mg twice daily (bid). The duration of treatment was 3 days. The total daily dose of ciprofloxacin and the duration of treatment were chosen to be consistent with the regimen included in the Cipro IR package insert. Patients were evaluated at a Test-of-Cure Visit (4 - 11 days after the end of treatment) and at a Late Post-Treatment Visit (5 weeks \pm 7 days after the end of treatment).

In the Phase II study, the pre-specified primary efficacy endpoints were microbiological and clinical outcomes at the Test-of-Cure Visit. The secondary efficacy endpoints were the microbiological and clinical outcomes at the Late-Post-Treatment Visit. The designation of primary and secondary efficacy endpoints was changed in the statistical analysis plan (prior to study unblinding) to be consistent with those in the Phase III study (i.e., microbiological eradication at the Test-of-Cure Visit was the only primary efficacy endpoint; all other outcomes were secondary endpoints).

In the Phase III study, the primary efficacy endpoint was microbiological eradication at the Test-of-Cure Visit. Secondary efficacy endpoints included additional microbiological outcomes (persistence and new infection) at the Test-of-Cure Visit; clinical outcomes (cure or failure) at the Test-of-Cure Visit; microbiological outcomes (long-term sustained eradication, persistence, or new infection) at the Late Post-Treatment Visit; and clinical outcomes (sustained cure, relapse, or failure) at the Late Post-Treatment Visit.

¹ New infection is defined as a microorganism found at baseline at a level of $\leq 10^5$ CFU/mL, which is present at the level of $\geq 10^5$ CFU/mL any time after completion of therapy.

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The primary efficacy analysis in the Phase III study was the construction of the 95% confidence interval of the difference in the one-week microbiological eradication rates at the Test-of-Cure Visit between the two treatment groups (Proquin XR minus Cipro IR). If the lower boundary of the confidence interval of the difference in the microbiological eradication rate at Test-of-Cure Visit was not less than -10%, the Proquin XR treatment was considered non-inferior to the Cipro IR treatment.

The FDA's modified intent-to-treat (MITT) population included evaluable patients (i.e., randomized patients who met the enrollment criteria for positive urine microbiology and uropathogen susceptibility. Patients missing microbiological data at the Test-of-Cure Visit were considered to be cases of microbiological persistence at that visit for the MITT analysis. Patients missing clinical response data at Test-of-Cure Visit were considered to be clinical failures at that visit for the MITT analysis.

The FDA's Per Protocol population included evaluable patients randomized in this study who had microbiological data at Test-of-Cure Visit. The efficacy population was used for the analysis of all primary and secondary efficacy parameters.

The study design was in accordance with the 1998 draft Guidance for Industry: *Uncomplicated Urinary Tract Infections -- Developing Antimicrobial Drug for Treatment on clinical studies of uncomplicated UTI*.

6.1.4 Efficacy Findings

6.1.4.1 Phase II study (Study 81-0005)

Of the 58 patients enrolled, 29 were randomly assigned to the Proquin XR group and 29 were randomly assigned to the Cipro IR group. A total of 28 patients (15 in the Proquin XR group and 13 in the Cipro IR group) were evaluable for efficacy and included in the Per-Protocol population. The primary efficacy variable was microbiological eradication of the baseline organism(s) with no new infection at the Test-of-Cure visit (Day 4 to 11 post-therapy).

The microbiological eradication and clinical success rates were similar for both treatment groups. The eradication and clinical success rates are given in Table 2.

Clinical Reviewer's Comment: This small Phase II study was not powered to determine non-inferiority of the two treatment groups, therefore, confidence intervals of the treatment differences were not calculated.

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TABLE 2
Microbiological and Clinical Outcome at the Test-of-Cure (TOC) Visit
Study 81-0005 (Phase 2 Study)

	Proquin XR 500 mg qd x 3 Days	Cipro IR 250 mg bid x 3 Days
Randomized Patients	29	29
Per Protocol Patients	15	13
Microbiological Eradication with no new infection at TOC	10/15 (66.6%)	8/13 (61.5%)
Clinical Response at TOC	10/15 (66.7%)	11/13 (84.6%)
Microbiological Eradication by organism*		
<i>E. coli</i>	8/10 (80.0%)	11/12 (93.8%)

*Number of patients with specified baseline organism eradicated / Number of per-protocol patients with specified baseline organism.

6.1.4.2 Phase III Study (81-0015)

Of the 1,037 patients enrolled, 524 were randomly assigned to the Proquin XR group and 513 were randomly assigned to the Cipro IR group (ciprofloxacin immediate-release). A total of 272 (52%) patients in the Proquin XR group and 251 (49%) in the Cipro IR group were evaluable for efficacy and included in the Per-Protocol population. The primary efficacy variable was microbiological eradication of the baseline organism(s) with no new infection at the Test-of-Cure visit (Day 4 to 11 post-therapy).

The microbiological eradication and clinical success rates were similar for both treatment groups. The eradication and cure rates and their corresponding 95% confidence intervals for the differences between rates (Proquin XR minus Cipro IR group) are given in Table 3.

The 95% confidence interval for the treatment difference in microbiological eradication rates at the Test-of-Cure visit (-6.2%, 8.2%) lies above -10%, indicating the non-inferiority of Proquin XR compared to Cipro IR.

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TABLE 3
Microbiological and Clinical Outcome at the Test-of-Cure (TOC) Visit
Study 81-0015 (Phase 3 Study)

	Proquin XR 500 mg qd x 3 Days	Cipro IR 250 mg bid x 3 Days
Randomized Patients	524	513
Per Protocol Patients	272 (52%)	251 (49%)
Microbiological Eradication with no new infection at TOC	212 / 272 (78%)	193 / 251 (77%)
	(-6.2%, 8.2%)	
Clinical Response at TOC	233 / 272 (86%)	216 / 251 (86%)
	(-6.4%, 5.6%)	
Microbiological Eradication by organism*		
<i>E. coli</i>	211 / 222 (95%)	184 / 202 (91%)
<i>K. pneumoniae</i>	11 / 12 (92%)	10 / 13 (77%)

*Number of patients with specified baseline organism eradicated / Number of per-protocol patients with specified baseline organism.

6.1.5 Clinical Microbiology

The application is approvable from the microbiological viewpoint when changes are made to the MICROBIOLOGY subsection of the package insert. The required microbiology revisions are listed as recommendations below.

Clinical Reviewer's Comment: Information in the section below was abstracted from the Microbiology Review. The complete Microbiology Review by Peter Dionne, M.S., is filed with this NDA.

Recent surveillance studies, which evaluated uropathogens associated with uncomplicated urinary tract infections (uUTI), showed that over 90% of *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus saprophyticus* isolates were susceptible to ciprofloxacin. Approximately 50% of enterococci and 76% of *Proteus mirabilis* isolates were susceptible to ciprofloxacin.

The frequency distribution of MICs of ciprofloxacin obtained during the Phase III clinical trial was similar to data provided in preclinical studies to assess interpretive criteria. The preclinical data and the subsequent analyses of the Phase III clinical trial data indicated that the appropriate MIC susceptibility breakpoints should be Susceptible = ≤ 1 $\mu\text{g/mL}$; Intermediate = 2 $\mu\text{g/mL}$; and Resistant = ≥ 4 $\mu\text{g/mL}$. Corresponding breakpoints for disk diffusion were Susceptible = ≥ 21 mm; Intermediate = 16-20 mm; and Resistant = ≤ 15 mm. These criteria, however, are established based on serum levels of ciprofloxacin and are not appropriate for uncomplicated UTI infections.

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The [applicant] is requesting an indication of uncomplicated urinary tract infections (acute cystitis) caused by *Escherichia coli*, *Klebsiella pneumoniae*, _____

As usual in urinary tract infections, most of the pathogens [in the Phase III clinical trial] were *Escherichia coli*. There were very few of the other pathogens detected in the clinical trial. Some organisms, such as Group D streptococci and coagulase negative staphylococci, were not speciated as they should have been. Eradication rates were good for *Escherichia coli* and *Klebsiella pneumoniae* and *Proteus mirabilis*, but were not as good for Group D streptococci or coagulase negative staphylococci.

Microbiology Reviewer's Comments to the Applicant Regarding the Proposed Package Insert:

1. _____
_____ must be deleted from the label.
2. There were very few isolates of *Proteus mirabilis* in the clinical trials. _____

_____. This organism may be allowed into the label in list #2.
3. _____
_____ this organism will not be allowed into list #2.
4. Since Susceptibility Testing criteria are based on serum drug levels and not levels of the drug in urine they are not appropriate for drugs indicated for uncomplicated urinary tract infections only. These criteria may be more appropriate if complicated urinary tract infections are also indicated. The Susceptibility Testing Section of the label should state that interpretive criteria for urinary tract infections have not been established and that criteria established for systemic infections may not be appropriate for uncomplicated urinary tract infections.

Clinical Reviewer's Comment: The applicant has requested _____

_____ The applicant's rationale and supporting data are included below.

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A summary of microbiological eradication and clinical cure rates of *P. mirabilis* at the Test-of-Cure Visit is presented in Table 4.

TABLE 4
Eradication and Clinical Cure Rates of *Proteus mirabilis* at the Test-of-Cure Visit

	Microbiological Eradication Rate		Clinical Cure Rate	
	Proquin XR 500 mg qd	Cipro IR 250 mg bid	Proquin XR 500 mg qd	Cipro IR 250 mg bid
≥10⁵ CFU/mL				
Phase III Trial	7/7 (100%)	8/9 (88.9%)	6/7 (85.7%)	6/10 (60%)
Phase II Trial	1/2 (50%)	1/1 (100%)	0/2 (0%)	0/1 (0%)
Combined	8/9 (88.9%)	9/10 (90%)	6/9 (66.7%)	6/11 (54.5%)
≥10⁴ CFU/mL				
Phase III Trial	7/8 (87.5%)	8/9 (88.9%)	7/8 (87.5%)	6/10 (60%)
Phase II Trial	1/2 (50%)	1/1 (100%)	0/2 (0%)	0/1 (0%)
Combined	8/10 (80%)	9/10 (90%)	7/10 (70%)	6/11 (54.5%)

Clinical Reviewer's Comment: The number of P. mirabilis organisms ≥ 10⁵ cfu/mL at baseline in the Proquin XR groups in the Phase II and III studies is < 10, which is fewer than the Division recommends for labeling (N=9). To be considered a urinary pathogen, the Division usually requires that organisms be present in the urine in a concentration of at least 10⁵ cfu/mL (with the exception of S. saprophyticus, which is considered to be a urinary pathogen at ≥ 10⁴ cfu/mL). Therefore, the presence of P. mirabilis at a concentration of ≥ 10⁴ cfu/mL is not adequate and this additional organism should not be pooled with those present in the urine ≥ 10⁵ cfu/mL.

However, P. mirabilis may be included in the second list in the MICROBIOLOGY section of the label. See Section 9.4: "Labeling Review."

6.1.6 Efficacy Conclusions

Proquin XR was evaluated for the treatment of uncomplicated urinary tract infections (uUTI) in two randomized double-blind, controlled trials comparing Proquin XR (500 mg once daily for 3 days) with ciprofloxacin immediate-release tablets (Cipro IR 250 mg twice daily for 3 days).

The pivotal Phase III study enrolled 1,037 patients. The primary efficacy variable was microbiological eradication of the baseline organism(s) with no new infection at the Test-of-Cure visit (Day 4 to 11 post-therapy). In the FDA's analysis, microbiological eradication in the efficacy (Per Protocol) population is 212/272 (78%) in the Proquin XR group and 193/251 (77%) in the Cipro IR group. The 95% confidence interval for the treatment difference in

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microbiological eradication rates at the Test-of-Cure visit (-6.2%, 8.2%) lies above -10%, indicating the non-inferiority of Proquin XR compared to Cipro IR.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety of Proquin XR in female patients with uncomplicated UTIs was evaluated in two clinical studies (one Phase II, 81-0005, and one Phase III, 81-0015). The safety of Proquin XR was also evaluated in healthy male and female subjects during nine Phase I, pharmacokinetic studies.

The Phase II and Phase III studies included female patients, at least 18 years of age, with clinical signs and symptoms of an acute, uncomplicated lower UTI. The safety database included elderly patients (≥ 65 years of age) and substantial numbers of both Caucasian and non-Caucasian patients. All patients in the Phase II and III studies were female, but male and female subjects were included in the pharmacokinetic studies.

The Phase II and Phase III studies compared Proquin XR treatment (500 mg qd for 3 days) to Cipro IR treatment (250 mg bid for 3 days). A total of 547 patients received one or more doses of Proquin XR and 538 patients received one or more doses of Cipro IR during the safety and efficacy studies. The average duration of exposure to Proquin XR was 3 days (range 1 to 3 days) and all patients received the same dose (500 mg qd). The average duration of exposure to Cipro IR was 4 days (range 1 to 4 days) and all patients received the same dose (250 mg bid). The average duration of exposure to active study drug appears longer for Cipro IR-treated patients because the final dose was taken on the morning of the 4th day, whereas the final dose for Proquin XR-treated patients was taken on the evening of the 3rd day.

The pharmacokinetic studies included 216 healthy male and female subjects who received Proquin XR 500 mg or 1000 mg for 1 day or 500 mg qd for 3 days. Four of these studies also included dosing with Cipro IR (250 mg bid for 1 or 3 days, or 500 mg bid for 1 day).

7.1.1 Deaths

There were no deaths in any of the Phase I, Phase II, or Phase III studies.

7.1.2 Other Serious Adverse Events

There were no serious adverse events (SAEs) during the Phase I studies. Details of SAEs occurring during the Phase II and Phase III studies are presented in Table 5.

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Ten patients (Proquin XR, 4 patients; C-IR, 6 patients) experienced one or more SAEs during the Phase II and Phase III studies. The most common SAE was chest pain (Proquin XR, 2 patients; Cipro IR, 2 patients). All other types of SAE were reported for one patient each; these events were: anemia and papillary thyroid cancer in the Proquin XR group and intestinal obstruction, pyelonephritis, nephrolithiasis, and ovarian cyst in the Cipro IR group.

None of the SAEs were considered to be related to study drug. Five of the SAEs were considered severe, three were moderate, and two were mild. Two patients permanently discontinued study drug due to the SAE. All SAEs were resolved, usually within a few days, except for one SAE where the outcome was unknown. None of these SAEs raised any new safety concerns.

Narratives for patients who had SAEs can be found in the individual study reviews of Study 81-0005 and 81-0015 found in Section 10: "Appendices."

TABLE 5
Listing of Serious Adverse Events Other than Death: Safety Population
Clinical Studies 81-0015 and 81-0005

Tx Group/ Patient ID	Age/ Race	MedDRA Preferred Term	Relation- ship to Study Drug	Why Serious	Severity	Duration	Change in Study Drug	Outcome
Phase III (81-0015)								
GR/1026	39/Caucasian	Anaemia	Not related	Hospitalization	Severe	4 days	Discontinued	Resolved
C-GR/4215	24/Caucasian	Papillary thyroid cancer	Not related	Other	Severe	67 days	None	Resolved
C-GR/6812	74/Caucasian	Chest pain	Not related	Hospitalization	Moderate	4 days	None	Resolved
C-IR/1006	29/Caucasian	Intestinal obstruction	Not related	Hospitalization	Moderate	8 days	None	Resolved
C-IR/1009	77/Caucasian	Chest pain	Not related	Hospitalization	Severe	4 days	None	Resolved
C-IR/1013	38/Caucasian	Pyelonephritis	Not related	Hospitalization	Severe	3 days	Discontinued	Resolved
C-IR/2004	76/Caucasian	Chest pain	Not related	Hospitalization	Moderate	4 days	None	Resolved
C-IR/3710	46/Caucasian	Ovarian cyst	Not related	Hospitalization	Severe	2 days	None	Resolved
C-IR/7004	18/Caucasian	Nephrolithiasis	Not related	Hospitalization	Mild	Ongoing	None	Unknown
Phase II (81-0005)								
C-GR/604	61/Caucasian	Chest pain	Not related	Hospitalization	Mild	4 days	None	Resolved

C-GR = Proquin XR tablets; C-IR = Cipro® immediate release tablets

Source: Table 17 in the applicant's Summary of Clinical Safety in the NDA submission

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7.1.3 Dropouts and Other Significant Adverse Events

There were no adverse events (AEs) causing discontinuation of study drug during the Phase I studies. Adverse events (AEs) causing discontinuation of study drug during the Phase II and Phase III studies are presented in Table 6.

Seven of 547 patients (1.3%) in the Proquin XR group and three of 538 patients (0.6%) in the Cipro IR group experienced AEs causing discontinuation of study drug. These were not statistically different. One Proquin XR-treated patient and one Cipro IR-treated patient experienced hypersensitivity that caused discontinuation of study drug. No other AEs causing discontinuation of study drug were experienced by more than one patient.

Five patients (3 patients in the Proquin XR group and 2 patients in the Cipro IR group) experienced AEs causing discontinuation that were considered related to study drug in Study 81-0015. Treatment-related AEs leading to discontinuation were hypersensitivity in two patients; and dyspnea, urticaria, and suprapubic pain each in one patient. None of these events raised any new safety concerns.

Clinical Reviewer's Comment: Table 6 has been reproduced from a larger table in the applicant's submission.

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TABLE 6
Adverse Events Causing the Discontinuation of Study Drug: Safety Population of Clinical Studies 81-0005 and 81-0015

System Organ Class Preferred Term	Treatment Group	
	C-GR	C-IR
	(n=547)	(n=538)
With at least one AE causing discontinuation	7 (1.3%)	3 (0.6%)
Blood and lymphatic system disorders	1 (0.2%)	0
Anemia NOS	1 (0.2%)	0
General disorders and administration site conditions	0	1 (0.2%)
Suprapubic pain	0	1 (0.2%)
Immune system disorders	1 (0.2%)	1 (0.2%)
Hypersensitivity NOS	1 (0.2%)	1 (0.2%)
Infections and infestations	0	1 (0.2%)
Pyelonephritis NOS	0	1 (0.2%)
Nervous system disorders	1 (0.2%)	0
Dizziness	1 (0.2%)	0
Renal and urinary disorders	2 (0.4%)	0
Cystitis NOS	1 (0.2%)	0
Nephrolithiasis	1 (0.2%)	0
Respiratory, thoracic and mediastinal disorders	1 (0.2%)	0
Dyspnoea NOS	1 (0.2%)	0
Skin and subcutaneous tissue disorders	1 (0.2%)	0
Urticaria NOS	1 (0.2%)	0

C-GR = Proquin XR tablets; C-IR = Cipro® immediate release tablets

Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

Source: Table 17 in the applicant's Summary of Clinical Safety in the NDA submission

7.1.4 Other Search Strategies

7.1.4.1 Adverse Events During Treatment (and up to 3 days after treatment)

The applicant summarized adverse events in the Phase II and III studies during the entire 5-week study period and while patients were on study drug (i.e., during dosing and within 3 days after

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the end of dosing). A cut-off of 3 days after the last dose of study drug was used by the applicant to ensure that drug and metabolites had been completely eliminated.

AEs which occurred while patients were on study drug are presented in Table 7.

The overall frequency of AEs while patients were on study drug was low; 71 patients (13.0%) in the Proquin XR group and 83 patients (15.4%) in the Cipro IR group experienced one or more AEs while on study drug. The most common AEs were gastrointestinal disorders (4.2% of all patients). Within the gastrointestinal system, the most common AE was nausea (1.5% of all patients). Only two types of AEs (nausea and headache) were reported for more than 1% of all patients.

There was no significant difference between treatment groups for the proportion of patients with AEs while on study drug. The types of AEs were generally similar for the two treatment groups. However, the proportion of patients with gastrointestinal disorders, nausea/nausea aggravated, and diarrhea were significantly lower in the Proquin XR group than in the Cipro IR group: GI disorders, Proquin XR 16/547 (2.9%), Cipro IR 30/538 (5.6%) ($p=0.035$); nausea/nausea aggravated, Proquin XR 3/547 (0.5%), Cipro IR 14/538 (2.6%) ($p=0.007$); diarrhea, Proquin XR 1/547 (0.2%), Cipro IR, 7/538 (1.3%) ($p=0.037$). In addition, the proportion of patients with psychiatric disorders was significantly lower in the Proquin XR group (0/547, 0%) than in the Cipro IR group (4/538, 0.7%) ($p=0.060$).

The majority of AEs that occurred while patients were on study drug were mild or moderate in severity and considered unrelated to study drug. The proportion of patients with severe AEs and the types of severe AEs were similar for the two treatment groups (data not shown).

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TABLE 7

**Adverse Events Occurring While Patients Were on Study Drug
 (or Within 3 Days of Discontinuation)
 Safety Population of Clinical Studies 81-0005 and 81-0015**

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number of Patients Randomized in the Study	553	542	1095	
Number (%) of Patients Received Treatment	547 (100%)	538 (100%)	1085 (100%)	
Number (%) of Patients without Any Adverse Event While Patients Were on Study Drug	476 (87.0%)	455 (84.6%)	931 (85.8%)	
Number (%) of Patients with at Least One Adverse Event While Patients Were on Study Drug	71 (13.0%)	83 (15.4%)	154 (14.2%)	NS
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Blood and lymphatic system disorders	2 (0.4%)	0	2 (0.2%)	NS
Anaemia NOS	1 (0.2%)	0	1 (0.1%)	NS
Lymphadenopathy	1 (0.2%)	0	1 (0.1%)	NS
Ear and labyrinth disorders	1 (0.2%)	0	1 (0.1%)	NS
Fluid in middle ear	1 (0.2%)	0	1 (0.1%)	NS
Endocrine disorders	1 (0.2%)	0	1 (0.1%)	NS
Goitre	1 (0.2%)	0	1 (0.1%)	NS
Gastrointestinal disorders	16 (2.9%)	30 (5.6%)	46 (4.2%)	0.035
Nausea	3 (0.5%)	13 (2.4%)	16 (1.5%)	0.011
Abdominal pain NOS	5 (0.9%)	3 (0.6%)	8 (0.7%)	NS
Diarrhoea NOS	1 (0.2%)	7 (1.3%)	8 (0.7%)	0.037
Dyspepsia	2 (0.4%)	3 (0.6%)	5 (0.5%)	NS
Abdominal pain lower	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Constipation	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Flatulence	0	2 (0.4%)	2 (0.2%)	NS
Abdominal pain upper	0	1 (0.2%)	1 (0.1%)	NS
Gastritis NOS	1 (0.2%)	0	1 (0.1%)	NS
Haemorrhoidal haemorrhage	1 (0.2%)	0	1 (0.1%)	NS
Haemorrhoids	1 (0.2%)	0	1 (0.1%)	NS
Melaena	1 (0.2%)	0	1 (0.1%)	NS
Nausea aggravated	0	1 (0.2%)	1 (0.1%)	NS
Oral mucosal discolouration	1 (0.2%)	0	1 (0.1%)	NS
Vomiting NOS	0	1 (0.2%)	1 (0.1%)	NS
General disorders and administration site conditions	5 (0.9%)	7 (1.3%)	12 (1.1%)	NS
Chest pain	2 (0.4%)	0	2 (0.2%)	NS
Fatigue	0	2 (0.4%)	2 (0.2%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

Source: Table 13 in the applicant's Summary of Clinical Safety in the NDA submission

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TABLE 7 (continued)
Adverse Events Occurring While Patients Were on Study Drug
(or Within 3 Days of Discontinuation)
Safety Population of Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	547 (100%)	538 (100%)	1085 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
General disorders and administration site conditions: (Continued)				
Pyrexia	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Rigors	0	2 (0.4%)	2 (0.2%)	NS
Axillary pain	1 (0.2%)	0	1 (0.1%)	NS
Discomfort NOS	0	1 (0.2%)	1 (0.1%)	NS
Feeling cold	0	1 (0.2%)	1 (0.1%)	NS
Feeling hot	0	1 (0.2%)	1 (0.1%)	NS
Malaise	0	1 (0.2%)	1 (0.1%)	NS
Suprapubic pain	0	1 (0.2%)	1 (0.1%)	NS
Thirst	1 (0.2%)	0	1 (0.1%)	NS
Immune system disorders	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Hypersensitivity NOS	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Infections and infestations	20 (3.7%)	21 (3.9%)	41 (3.8%)	NS
Urinary tract infection NOS	4 (0.7%)	4 (0.7%)	8 (0.7%)	NS
Vaginosis fungal NOS	3 (0.5%)	4 (0.7%)	7 (0.6%)	NS
Fungal infection NOS	4 (0.7%)	1 (0.2%)	5 (0.5%)	NS
Upper respiratory tract infection NOS	1 (0.2%)	3 (0.6%)	4 (0.4%)	NS
Vaginitis	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Herpes simplex	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Influenza	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Pyelonephritis NOS	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Sinusitis NOS	0	2 (0.4%)	2 (0.2%)	NS
Vaginitis bacterial NOS	0	2 (0.4%)	2 (0.2%)	NS
Oral candidiasis	1 (0.2%)	0	1 (0.1%)	NS
Otitis media NOS	1 (0.2%)	0	1 (0.1%)	NS
Pharyngitis viral NOS	0	1 (0.2%)	1 (0.1%)	NS
Tooth abscess	0	1 (0.2%)	1 (0.1%)	NS
Vaginal candidiasis	0	1 (0.2%)	1 (0.1%)	NS
Vaginal infection NOS	1 (0.2%)	0	1 (0.1%)	NS
Viral infection NOS	1 (0.2%)	0	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

Source: Table 13 in the applicant's Summary of Clinical Safety in the NDA submission

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TABLE 7 (continued)
Adverse Events Occurring While Patients Were on Study Drug
(or Within 3 Days of Discontinuation)
Safety Population of Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin ER		
Number (%) of Patients Received Treatment	547 (100%)	538 (100%)	1085 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Injury, poisoning and procedural complications	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Abrasion NOS	1 (0.2%)	0	1 (0.1%)	NS
Alcohol poisoning	0	1 (0.2%)	1 (0.1%)	NS
Muscle strain	0	1 (0.2%)	1 (0.1%)	NS
Investigations	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Gamma-glutamyltransferase increased	0	1 (0.2%)	1 (0.1%)	NS
Platelet count decreased	1 (0.2%)	0	1 (0.1%)	NS
Metabolism and nutrition disorders	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Anorexia	1 (0.2%)	0	1 (0.1%)	NS
Appetite increased NOS	0	1 (0.2%)	1 (0.1%)	NS
Hypernatraemia	0	1 (0.2%)	1 (0.1%)	NS
Musculoskeletal and connective tissue disorders	9 (1.6%)	5 (0.9%)	14 (1.3%)	NS
Back pain	3 (0.5%)	1 (0.2%)	4 (0.4%)	NS
Arthralgia	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Joint swelling	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Back pain aggravated	1 (0.2%)	0	1 (0.1%)	NS
Chest wall pain	0	1 (0.2%)	1 (0.1%)	NS
Facial pain	1 (0.2%)	0	1 (0.1%)	NS
Flank pain	0	1 (0.2%)	1 (0.1%)	NS
Night cramps	1 (0.2%)	0	1 (0.1%)	NS
Pain in limb	1 (0.2%)	0	1 (0.1%)	NS
Scoliosis	1 (0.2%)	0	1 (0.1%)	NS
Nervous system disorders	12 (2.2%)	18 (3.3%)	30 (2.8%)	NS
Headache	8 (1.5%)	11 (2.0%)	19 (1.8%)	NS
Dizziness	5 (0.9%)	2 (0.4%)	7 (0.6%)	NS
Dysgeusia	0	2 (0.4%)	2 (0.2%)	NS
Hypoaesthesia	0	1 (0.2%)	1 (0.1%)	NS
Migraine NOS	0	1 (0.2%)	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

Source: Table 13 in the applicant's Summary of Clinical Safety in the NDA submission

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TABLE 7 (continued)
Adverse Events Occurring While Patients Were on Study Drug
(or Within 3 Days of Discontinuation)
Safety Population of Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	547 (100%)	538 (100%)	1085 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Nervous system disorders (Continued)				
Paraesthesia	1 (0.2%)	0	1 (0.1%)	NS
Sciatica	0	1 (0.2%)	1 (0.1%)	NS
Syncope	0	1 (0.2%)	1 (0.1%)	NS
Psychiatric disorders	0	4 (0.7%)	4 (0.4%)	0.060
Anxiety	0	1 (0.2%)	1 (0.1%)	NS
Depression aggravated	0	1 (0.2%)	1 (0.1%)	NS
Disorientation	0	1 (0.2%)	1 (0.1%)	NS
Insomnia	0	1 (0.2%)	1 (0.1%)	NS
Renal and urinary disorders	5 (0.9%)	1 (0.2%)	6 (0.6%)	NS
Haematuria	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS
Nephrolithiasis	2 (0.4%)	0	2 (0.2%)	NS
Chromaturia	1 (0.2%)	0	1 (0.1%)	NS
Cystitis NOS	1 (0.2%)	0	1 (0.1%)	NS
Reproductive system and breast disorders	5 (0.9%)	3 (0.6%)	8 (0.7%)	NS
Genital pruritus female	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Vaginal haemorrhage	2 (0.4%)	0	2 (0.2%)	NS
Menstruation irregular	0	1 (0.2%)	1 (0.1%)	NS
Metrorrhagia	1 (0.2%)	0	1 (0.1%)	NS
Ovarian cyst	0	1 (0.2%)	1 (0.1%)	NS
Uterine pain	1 (0.2%)	0	1 (0.1%)	NS
Vaginal burning sensation	0	1 (0.2%)	1 (0.1%)	NS
Respiratory, thoracic and mediastinal disorders	7 (1.3%)	6 (1.1%)	13 (1.2%)	NS
Pharyngitis	3 (0.5%)	1 (0.2%)	4 (0.4%)	NS
Nasopharyngitis	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Dyspnoea NOS	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Bronchitis NOS	1 (0.2%)	0	1 (0.1%)	NS
Cough	0	1 (0.2%)	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

Source: Table 13 in the applicant's Summary of Clinical Safety in the NDA submission

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TABLE 7 (continued)
Adverse Events Occurring While Patients Were on Study Drug
(or Within 3 Days of Discontinuation)
Safety Population of Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin GR	Ciprofloxacin IR		
Number (%) of Patients Received Treatment	547 (100%)	538 (100%)	1085 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Respiratory, thoracic and mediastinal disorders (Continued)				
Epistaxis	1 (0.2%)	0	1 (0.1%)	NS
Nasal congestion	1 (0.2%)	0	1 (0.1%)	NS
Pleurisy	0	1 (0.2%)	1 (0.1%)	NS
Skin and subcutaneous tissue disorders				
Rash NOS	4 (0.7%)	5 (1.1%)	10 (0.9%)	NS
Dermatitis contact	2 (0.4%)	2 (0.4%)	4 (0.4%)	NS
Parapsoriasis	0	1 (0.2%)	1 (0.1%)	NS
Pruritus	0	1 (0.2%)	1 (0.1%)	NS
Rash maculo-papular	1 (0.2%)	0	1 (0.1%)	NS
Sweating increased	0	1 (0.2%)	1 (0.1%)	NS
Urticaria NOS	1 (0.2%)	0	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

Source: Table 13 in the applicant's Summary of Clinical Safety in the NDA submission

7.1.4.2 Adverse Events in the Phase I Studies

A total of 53/216 subjects who received Proquin XR and 21/85 who received Cipro IR had one or more AEs during the pharmacokinetic studies.

The most common AEs during both Proquin XR and IR treatment were headache, dizziness, elevated blood glucose, and WBCs in urine. However, 4/5 subjects in the GR groups and 6/6 subjects in the Cipro IR groups who had AEs of elevated blood glucose were in a single study (81-0026; food effect study). During PK studies, laboratory results were recorded as AEs if they were outside the normal ranges for the testing laboratory, whether or not the Investigator considered them to be clinically significant. All events were mild or moderate in severity and all except one were considered unrelated or unlikely to be related to study drug. One patient who received Proquin XR in Study 81-0032 (food effect study in elderly subjects) had a mild AE of lightheadedness that was considered to be highly probably related to study drug.

7.1.4.3 Adverse Events in Special Populations

Clinical Reviewer's Comment: The following adverse event tables by age and race were provided by the applicant, upon request, and were submitted to the NDA on May 4, 2005.

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7.1.4.3.1 Age

Adverse events were tabulated separately for patients < 65 and ≥ 65 years of age as shown in Tables 8 and 9, respectively. Differences, if any, in rates of particular adverse events between younger and older patients were not clinically meaningful. Dosage adjustments, based upon age alone, are not warranted.

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TABLE 8
Adverse Events:
Patients Who Were Less Than 65 Years Old in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number of Patients Randomized in the Study	519	500	1019	
Number (%) of Patients Received Treatment	515 (100%)	497 (100%)	1012 (100%)	
Number (%) of Patients without Any Adverse Event in the Study	298 (57.9%)	287 (57.7%)	585 (57.8%)	
Number (%) of Patients with at Least One Adverse Event in the Study	217 (42.1%)	210 (42.3%)	427 (42.2%)	NS
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Blood and lymphatic system disorders	4 (0.8%)	2 (0.4%)	6 (0.6%)	NS
Lymphadenopathy	3 (0.6%)	1 (0.2%)	4 (0.4%)	NS
Anaemia NOS	1 (0.2%)	0	1 (0.1%)	NS
Leukopenia NOS	0	1 (0.2%)	1 (0.1%)	NS
Ear and labyrinth disorders	3 (0.6%)	5 (1.0%)	8 (0.8%)	NS
Ear pain	0	2 (0.4%)	2 (0.2%)	NS
Fluid in middle ear	2 (0.4%)	0	2 (0.2%)	NS
Vertigo	0	2 (0.4%)	2 (0.2%)	NS
Cerumen impaction	1 (0.2%)	0	1 (0.1%)	NS
Deafness NOS	0	1 (0.2%)	1 (0.1%)	NS
Endocrine disorders	1 (0.2%)	0	1 (0.1%)	NS
Goitre	1 (0.2%)	0	1 (0.1%)	NS
Eye disorders	0	3 (0.6%)	3 (0.3%)	NS
Conjunctivitis	0	2 (0.4%)	2 (0.2%)	NS
Eye swelling	0	1 (0.2%)	1 (0.1%)	NS
Vision blurred	0	1 (0.2%)	1 (0.1%)	NS
Gastrointestinal disorders	33 (6.4%)	42 (8.5%)	75 (7.4%)	NS
Nausea / Nausea aggravated	6 (1.2%)	13 (2.6%)	19 (1.9%)	NS
Abdominal pain NOS	9 (1.7%)	5 (1.0%)	14 (1.4%)	NS
Diarrhoea NOS	2 (0.4%)	6 (1.2%)	8 (0.8%)	NS
Dyspepsia	2 (0.4%)	3 (0.6%)	5 (0.5%)	NS
Abdominal pain upper	1 (0.2%)	3 (0.6%)	4 (0.4%)	NS
Constipation	2 (0.4%)	2 (0.4%)	4 (0.4%)	NS
Abdominal pain lower	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Abdominal tenderness	3 (0.6%)	0	3 (0.3%)	NS
Gastroesophageal reflux disease	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 31 in the applicant's submission dated May 4, 2005

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TABLE 8 (continued)
Adverse Events:
Patients Who Were Less Than 65 Years Old in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number (%) of Patients Received Treatment	515 (100%)	497 (100%)	1012 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Gastrointestinal disorders (Continued)				
Vomiting NOS	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Abdominal distension	2 (0.4%)	0	2 (0.2%)	NS
Flatulence	0	2 (0.4%)	2 (0.2%)	NS
Haemorrhoids	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Irritable bowel syndrome aggravated	2 (0.4%)	0	2 (0.2%)	NS
Abdominal discomfort	1 (0.2%)	0	1 (0.1%)	NS
Anal discomfort	0	1 (0.2%)	1 (0.1%)	NS
Diverticulum NOS	1 (0.2%)	0	1 (0.1%)	NS
Gastritis NOS	1 (0.2%)	0	1 (0.1%)	NS
Gastroenteritis NOS	1 (0.2%)	0	1 (0.1%)	NS
Gingivitis	0	1 (0.2%)	1 (0.1%)	NS
Haemorrhoidal haemorrhage	1 (0.2%)	0	1 (0.1%)	NS
Intestinal obstruction NOS	0	1 (0.2%)	1 (0.1%)	NS
Lip ulceration	0	1 (0.2%)	1 (0.1%)	NS
Melaena	1 (0.2%)	0	1 (0.1%)	NS
Oesophageal spasm	1 (0.2%)	0	1 (0.1%)	NS
Oral mucosal discolouration	1 (0.2%)	0	1 (0.1%)	NS
Pruritus ani	0	1 (0.2%)	1 (0.1%)	NS
Rectal discharge	0	1 (0.2%)	1 (0.1%)	NS
Toothache	0	1 (0.2%)	1 (0.1%)	NS
General disorders and administration site conditions	21 (4.1%)	16 (3.2%)	37 (3.7%)	NS
Suprapubic pain	7 (1.4%)	3 (0.6%)	10 (1.0%)	NS
Fatigue	3 (0.6%)	4 (0.8%)	7 (0.7%)	NS
Pyrexia	3 (0.6%)	3 (0.6%)	6 (0.6%)	NS
Chest pain	2 (0.4%)	3 (0.6%)	5 (0.5%)	NS
Pain NOS	3 (0.6%)	2 (0.4%)	5 (0.5%)	NS
Rigors	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Asthenia	1 (0.2%)	0	1 (0.1%)	NS
Axillary pain	1 (0.2%)	0	1 (0.1%)	NS
Discomfort NOS	0	1 (0.2%)	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 31 in the applicant's submission dated May 4, 2005

Clinical Review
 Joette M. Meyer, Pharm.D.
 NDA 21-744
 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 8 (continued)
Adverse Events:
Patients Who Were Less Than 65 Years Old in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number (%) of Patients Received Treatment	515 (100%)	497 (100%)	1012 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
General disorders and administration site conditions (Continued)				
Feeling cold	0	1 (0.2%)	1 (0.1%)	NS
Feeling hot	0	1 (0.2%)	1 (0.1%)	NS
Inflammation NOS	0	1 (0.2%)	1 (0.1%)	NS
Lethargy	1 (0.2%)	0	1 (0.1%)	NS
Malaise	0	1 (0.2%)	1 (0.1%)	NS
Tenderness NOS	1 (0.2%)	0	1 (0.1%)	NS
Thirst	1 (0.2%)	0	1 (0.1%)	NS
Hepatobiliary disorders	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Cholelithiasis	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Immune system disorders	2 (0.4%)	5 (1.0%)	7 (0.7%)	NS
Seasonal allergy	0	3 (0.6%)	3 (0.3%)	NS
Hypersensitivity NOS	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Allergy to arthropod sting	1 (0.2%)	0	1 (0.1%)	NS
Drug hypersensitivity	0	1 (0.2%)	1 (0.1%)	NS
Infections and infestations	99 (19.2%)	99 (19.9%)	198 (19.6%)	NS
Urinary tract infection NOS	54 (10.5%)	51 (10.3%)	105 (10.4%)	NS
Upper respiratory tract infection NOS	9 (1.7%)	17 (3.4%)	26 (2.6%)	NS
Fungal infection NOS	14 (2.7%)	9 (1.8%)	23 (2.3%)	NS
Vaginosis fungal NOS	6 (1.2%)	10 (2.0%)	16 (1.6%)	NS
Sinusitis NOS	4 (0.8%)	8 (1.6%)	12 (1.2%)	NS
Vaginitis bacterial NOS	3 (0.6%)	4 (0.8%)	7 (0.7%)	NS
Vaginal candidiasis	2 (0.4%)	3 (0.6%)	5 (0.5%)	NS
Gastroenteritis viral NOS	2 (0.4%)	2 (0.4%)	4 (0.4%)	NS
Herpes simplex	1 (0.2%)	3 (0.6%)	4 (0.4%)	NS
Pyelonephritis NOS	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Tooth abscess	0	3 (0.6%)	3 (0.3%)	NS
Vaginal infection NOS	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS
Vaginitis	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 31 in the applicant's submission dated May 4, 2005

Clinical Review
 Joette M. Meyer, Pharm.D.
 NDA 21-744
 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 8 (continued)
Adverse Events:
Patients Who Were Less Than 65 Years Old in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number (%) of Patients Received Treatment	515 (100%)	497 (100%)	1012 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Infections and infestations (Continued)				
Beta haemolytic streptococcal infection	2 (0.4%)	0	2 (0.2%)	NS
Candidal infection NOS	0	2 (0.4%)	2 (0.2%)	NS
Otitis media NOS	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Escherichia infection NOS	1 (0.2%)	0	1 (0.1%)	NS
Influenza	1 (0.2%)	0	1 (0.1%)	NS
Klebsiella infection NOS	1 (0.2%)	0	1 (0.1%)	NS
Lyme disease	0	1 (0.2%)	1 (0.1%)	NS
Oral candidiasis	1 (0.2%)	0	1 (0.1%)	NS
Otitis externa NOS	0	1 (0.2%)	1 (0.1%)	NS
Otitis media serous acute NOS	0	1 (0.2%)	1 (0.1%)	NS
Pharyngitis streptococcal	1 (0.2%)	0	1 (0.1%)	NS
Pharyngitis viral NOS	0	1 (0.2%)	1 (0.1%)	NS
Pharyngotonsillitis	1 (0.2%)	0	1 (0.1%)	NS
Pneumonia NOS	1 (0.2%)	0	1 (0.1%)	NS
Streptococcal infection NOS	1 (0.2%)	0	1 (0.1%)	NS
Upper respiratory tract infection viral NOS	1 (0.2%)	0	1 (0.1%)	NS
Viral infection NOS	1 (0.2%)	0	1 (0.1%)	NS
Injury, poisoning and procedural complications				
Muscle strain	2 (0.4%)	2 (0.4%)	4 (0.4%)	NS
Thermal burn	0	2 (0.4%)	2 (0.2%)	NS
Abrasion NOS	1 (0.2%)	0	1 (0.1%)	NS
Alcohol poisoning	0	1 (0.2%)	1 (0.1%)	NS
Arthropod bite	0	1 (0.2%)	1 (0.1%)	NS
Heat exhaustion	1 (0.2%)	0	1 (0.1%)	NS
Joint sprain	0	1 (0.2%)	1 (0.1%)	NS
Periorbital haematoma	0	1 (0.2%)	1 (0.1%)	NS
Skin laceration	1 (0.2%)	0	1 (0.1%)	NS
Investigations				
Gamma-glutamyltransferase increased	7 (1.4%)	7 (1.4%)	14 (1.4%)	NS
	0	4 (0.8%)	4 (0.4%)	0.058

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 31 in the applicant's submission dated May 4, 2005

Clinical Review
 Joette M. Meyer, Pharm.D.
 NDA 21-744
 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 8 (continued)
Adverse Events:
Patients Who Were Less Than 65 Years Old in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number (%) of Patients Received Treatment	515 (100%)	497 (100%)	1012 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
<u>Investigations (Continued)</u>				
Blood bilirubin increased	3 (0.6%)	0	3 (0.3%)	NS
Alanine aminotransferase increased	2 (0.4%)	0	2 (0.2%)	NS
Blood potassium increased	0	2 (0.4%)	2 (0.2%)	NS
Abdominal aortic bruit	1 (0.2%)	0	1 (0.1%)	NS
Aspartate aminotransferase increased	1 (0.2%)	0	1 (0.1%)	NS
Body temperature increased	1 (0.2%)	0	1 (0.1%)	NS
Culture urine positive	1 (0.2%)	0	1 (0.1%)	NS
Haematocrit decreased	0	1 (0.2%)	1 (0.1%)	NS
Haemoglobin decreased	0	1 (0.2%)	1 (0.1%)	NS
Platelet count decreased	1 (0.2%)	0	1 (0.1%)	NS
Red blood cell count decreased	0	1 (0.2%)	1 (0.1%)	NS
White blood cell count decreased	0	1 (0.2%)	1 (0.1%)	NS
Metabolism and nutrition disorders	1 (0.2%)	4 (0.8%)	5 (0.5%)	NS
Anorexia	1 (0.2%)	0	1 (0.1%)	NS
Appetite increased NOS	0	1 (0.2%)	1 (0.1%)	NS
Hyperglycaemia NOS	0	1 (0.2%)	1 (0.1%)	NS
Hyperlipidaemia NOS	0	1 (0.2%)	1 (0.1%)	NS
Hypernatraemia	0	1 (0.2%)	1 (0.1%)	NS
Musculoskeletal and connective tissue disorders	21 (4.1%)	21 (4.2%)	42 (4.2%)	NS
Back pain	9 (1.7%)	9 (1.8%)	18 (1.8%)	NS
Arthralgia	2 (0.4%)	2 (0.4%)	4 (0.4%)	NS
Chest wall pain	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Flank pain	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Joint swelling	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Myalgia	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Pain in limb	2 (0.4%)	0	2 (0.2%)	NS
Back pain aggravated	1 (0.2%)	0	1 (0.1%)	NS
Bursitis	0	1 (0.2%)	1 (0.1%)	NS
Costochondritis	0	1 (0.2%)	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.
 A patient may be reported in more than one category.
 The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.
 NS = Not statistically significant at 0.10 level.

Source: Table 31 in the applicant's submission dated May 4, 2005

Clinical Review
 Joette M. Meyer, Pharm.D.
 NDA 21-744
 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 8 (continued)
Adverse Events:
Patients Who Were Less Than 65 Years Old in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number (%) of Patients Received Treatment	515 (100%)	497 (100%)	1012 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Musculoskeletal and connective tissue disorders (Continued)				
Facial pain	1 (0.2%)	0	1 (0.1%)	NS
Groin pain	0	1 (0.2%)	1 (0.1%)	NS
Muscle cramp	0	1 (0.2%)	1 (0.1%)	NS
Muscle spasms	1 (0.2%)	0	1 (0.1%)	NS
Musculoskeletal stiffness	0	1 (0.2%)	1 (0.1%)	NS
Neck pain	1 (0.2%)	0	1 (0.1%)	NS
Night cramps	1 (0.2%)	0	1 (0.1%)	NS
Pain in jaw	0	1 (0.2%)	1 (0.1%)	NS
Scoliosis	1 (0.2%)	0	1 (0.1%)	NS
Spinal osteoarthritis	0	1 (0.2%)	1 (0.1%)	NS
Tendonitis	0	1 (0.2%)	1 (0.1%)	NS
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.4%)	0	2 (0.2%)	NS
Non-Hodgkin's lymphoma NOS	1 (0.2%)	0	1 (0.1%)	NS
Papillary thyroid cancer	1 (0.2%)	0	1 (0.1%)	NS
Nervous system disorders	21 (4.1%)	28 (5.6%)	49 (4.8%)	NS
Headache	13 (2.5%)	19 (3.8%)	32 (3.2%)	NS
Dizziness	4 (0.8%)	2 (0.4%)	6 (0.6%)	NS
Migraine NOS	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS
Dysgeusia	0	2 (0.4%)	2 (0.2%)	NS
Tension headaches	0	2 (0.4%)	2 (0.2%)	NS
Disturbance in attention	1 (0.2%)	0	1 (0.1%)	NS
Hypoaesthesia	0	1 (0.2%)	1 (0.1%)	NS
Radiculopathy NOS	1 (0.2%)	0	1 (0.1%)	NS
Sciatica	1 (0.2%)	0	1 (0.1%)	NS
Sinus headache	1 (0.2%)	0	1 (0.1%)	NS
Syncope	0	1 (0.2%)	1 (0.1%)	NS
Pregnancy, puerperium and perinatal conditions	1 (0.2%)	0	1 (0.1%)	NS
Pregnancy NOS	1 (0.2%)	0	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.
 A patient may be reported in more than one category.
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 NS = Not statistically significant at 0.10 level.

Source: Table 31 in the applicant's submission dated May 4, 2005

Clinical Review
 Joette M. Meyer, Pharm.D.
 NDA 21-744

Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 8 (continued)
Adverse Events:
Patients Who Were Less Than 65 Years Old in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number (%) of Patients Received Treatment	515 (100%)	497 (100%)	1012 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Psychiatric disorders	1 (0.2%)	9 (1.8%)	10 (1.0%)	0.010
Anxiety	0	2 (0.4%)	2 (0.2%)	NS
Depression	0	2 (0.4%)	2 (0.2%)	NS
Insomnia	0	2 (0.4%)	2 (0.2%)	NS
Depression aggravated	0	1 (0.2%)	1 (0.1%)	NS
Disorientation	0	1 (0.2%)	1 (0.1%)	NS
Mood swings	1 (0.2%)	0	1 (0.1%)	NS
Panic attack	0	1 (0.2%)	1 (0.1%)	NS
Renal and urinary disorders	33 (6.4%)	14 (2.8%)	47 (4.6%)	0.007
Micturition urgency	10 (1.9%)	5 (1.0%)	15 (1.5%)	
Dysuria	9 (1.7%)	1 (0.2%)	10 (1.0%)	0.021
Urinary frequency	6 (1.2%)	4 (0.8%)	10 (1.0%)	NS
Haematuria	6 (1.2%)	1 (0.2%)	7 (0.7%)	NS
Cystitis NOS	3 (0.6%)	1 (0.2%)	4 (0.4%)	NS
Nephrolithiasis	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS
Chromaturia	2 (0.4%)	0	2 (0.2%)	NS
Urine odour abnormal	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Bladder pain	1 (0.2%)	0	1 (0.1%)	NS
Bladder spasm	0	1 (0.2%)	1 (0.1%)	NS
Costovertebral angle tenderness	1 (0.2%)	0	1 (0.1%)	NS
Cystitis interstitial	0	1 (0.2%)	1 (0.1%)	NS
Cystocele	1 (0.2%)	0	1 (0.1%)	NS
Incontinence NOS	1 (0.2%)	0	1 (0.1%)	NS
Urethral cyst	1 (0.2%)	0	1 (0.1%)	NS
Urethral spasm	1 (0.2%)	0	1 (0.1%)	NS
Urethral syndrome	0	1 (0.2%)	1 (0.1%)	NS
Reproductive system and breast disorders	15 (2.9%)	12 (2.4%)	27 (2.7%)	NS
Genital pruritus female	2 (0.4%)	4 (0.8%)	6 (0.6%)	NS
Ovarian cyst	1 (0.2%)	3 (0.6%)	4 (0.4%)	NS
Vaginal discharge	3 (0.6%)	1 (0.2%)	4 (0.4%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

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NS = Not statistically significant at 0.10 level.

Source: Table 31 in the applicant's submission dated May 4, 2005

Clinical Review
 Joette M. Meyer, Pharm.D.
 NDA 21-744
 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 8 (continued)
Adverse Events:
Patients Who Were Less Than 65 Years Old in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number (%) of Patients Received Treatment	515 (100%)	497 (100%)	1012 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Reproductive system and breast disorders (Continued)				
Adnexa uteri pain	0	2 (0.4%)	2 (0.2%)	NS
Dysmenorrhoea	2 (0.4%)	0	2 (0.2%)	NS
Vaginal burning sensation	0	2 (0.4%)	2 (0.2%)	NS
Vaginal haemorrhage	2 (0.4%)	0	2 (0.2%)	NS
Amenorrhoea NOS	0	1 (0.2%)	1 (0.1%)	NS
Dyspareunia NOS	1 (0.2%)	0	1 (0.1%)	NS
Endometrial hypertrophy	1 (0.2%)	0	1 (0.1%)	NS
Menstruation irregular	0	1 (0.2%)	1 (0.1%)	NS
Metrorrhagia	1 (0.2%)	0	1 (0.1%)	NS
Pelvic pain NOS	0	1 (0.2%)	1 (0.1%)	NS
Uterine pain	1 (0.2%)	0	1 (0.1%)	NS
Vaginal disorder NOS	1 (0.2%)	0	1 (0.1%)	NS
Vaginal irritation	1 (0.2%)	0	1 (0.1%)	NS
Vulvovaginal dryness	1 (0.2%)	0	1 (0.1%)	NS
Respiratory, thoracic and mediastinal disorders				
Nasopharyngitis	13 (2.5%)	7 (1.4%)	20 (2.0%)	NS
Pharyngitis	7 (1.4%)	6 (1.2%)	13 (1.3%)	NS
Nasal congestion	6 (1.2%)	1 (0.2%)	7 (0.7%)	NS
Bronchitis NOS	1 (0.2%)	5 (1.0%)	6 (0.6%)	NS
Cough	2 (0.4%)	4 (0.8%)	6 (0.6%)	NS
Rhinitis allergic NOS	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS
Sinus congestion	2 (0.4%)	1 (0.2%)	3 (0.3%)	NS
Dyspnoea NOS	0	2 (0.4%)	2 (0.2%)	NS
Postnasal drip	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Rhinitis seasonal	2 (0.4%)	0	2 (0.2%)	NS
Rhinorrhoea	2 (0.4%)	0	2 (0.2%)	NS
Allergic sinusitis	0	1 (0.2%)	1 (0.1%)	NS
Emphysema	0	1 (0.2%)	1 (0.1%)	NS
Epistaxis	1 (0.2%)	0	1 (0.1%)	NS
Haemoptysis	0	1 (0.2%)	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.
 A patient may be reported in more than one category.
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 NS = Not statistically significant at 0.10 level.

Source: Table 31 in the applicant's submission dated May 4, 2005

Clinical Review
 Joette M. Meyer, Pharm.D.
 NDA 21-744
 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 8 (continued)
Adverse Events:
Patients Who Were Less Than 65 Years Old in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number (%) of Patients Received Treatment	515 (100%)	497 (100%)	1012 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Respiratory, thoracic and mediastinal disorders (Continued)				
Pleurisy	0	1 (0.2%)	1 (0.1%)	NS
Pleuritic pain	0	1 (0.2%)	1 (0.1%)	NS
Rhonchi	1 (0.2%)	0	1 (0.1%)	NS
Sinus pain	1 (0.2%)	0	1 (0.1%)	NS
Wheezing	1 (0.2%)	0	1 (0.1%)	NS
Skin and subcutaneous tissue disorders				
Rash NOS	13 (2.5%)	8 (1.6%)	21 (2.1%)	NS
Contusion	3 (0.6%)	2 (0.4%)	5 (0.5%)	NS
Erythema	3 (0.6%)	0	3 (0.3%)	NS
Acne NOS	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Pruritus	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Urticaria NOS	2 (0.4%)	0	2 (0.2%)	NS
Dermatitis contact	2 (0.4%)	0	2 (0.2%)	NS
Eczema	0	1 (0.2%)	1 (0.1%)	NS
Rash maculo-papular	1 (0.2%)	0	1 (0.1%)	NS
Sweating increased	0	1 (0.2%)	1 (0.1%)	NS
Swelling face	0	1 (0.2%)	1 (0.1%)	NS
Surgical and medical procedures				
Nasal cyst removal	1 (0.2%)	0	1 (0.1%)	NS
Vascular disorders				
Hot flushes NOS	1 (0.2%)	2 (0.4%)	3 (0.3%)	NS
Hypertension NOS	1 (0.2%)	0	1 (0.1%)	NS
Hypertension aggravated	0	1 (0.2%)	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 31 in the applicant's submission dated May 4, 2005

Clinical Review
 Joette M. Meyer, Pharm.D.
 NDA 21-744
 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 9
Adverse Events:
Patients Who Were at Least 65 Years Old in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number of Patients Randomized in the Study	34	42	76	
Number (%) of Patients Received Treatment	32 (100%)	41 (100%)	73 (100%)	
Number (%) of Patients without Any Adverse Event in the Study	19 (59.4%)	20 (48.8%)	39 (53.4%)	
Number (%) of Patients with at Least One Adverse Event in the Study	13 (40.6%)	21 (51.2%)	34 (46.6%)	NS
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Blood and lymphatic system disorders	0	1 (2.4%)	1 (1.4%)	NS
Leukopenia NOS	0	1 (2.4%)	1 (1.4%)	NS
Cardiac disorders	1 (3.1%)	0	1 (1.4%)	NS
Ventricular bigeminy	1 (3.1%)	0	1 (1.4%)	NS
Gastrointestinal disorders	1 (3.1%)	6 (14.6%)	7 (9.6%)	NS
Diarrhoea NOS	0	4 (9.8%)	4 (5.5%)	NS
Nausea / Nausea aggravated	1 (3.1%)	2 (4.9%)	3 (4.1%)	NS
Abdominal pain lower	0	2 (4.9%)	2 (2.7%)	NS
Abdominal pain.NOS	0	1 (2.4%)	1 (1.4%)	NS
General disorders and administration site conditions	2 (6.3%)	4 (9.8%)	6 (8.2%)	NS
Chest pain	1 (3.1%)	2 (4.9%)	3 (4.1%)	NS
Suprapubic pain	1 (3.1%)	1 (2.4%)	2 (2.7%)	NS
Oedema peripheral	0	1 (2.4%)	1 (1.4%)	NS
Immune system disorders	0	1 (2.4%)	1 (1.4%)	NS
Drug hypersensitivity	0	1 (2.4%)	1 (1.4%)	NS
Infections and infestations	7 (21.9%)	8 (19.5%)	15 (20.5%)	NS
Urinary tract infection NOS	5 (15.6%)	4 (9.8%)	9 (12.3%)	NS
Beta haemolytic streptococcal infection	0	1 (2.4%)	1 (1.4%)	NS
Escherichia infection NOS	1 (3.1%)	0	1 (1.4%)	NS
Fungal infection NOS	0	1 (2.4%)	1 (1.4%)	NS
Influenza	0	1 (2.4%)	1 (1.4%)	NS
Tooth abscess	1 (3.1%)	0	1 (1.4%)	NS
Vaginosis fungal NOS	0	1 (2.4%)	1 (1.4%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 32 in the applicant's submission dated May 4, 2005

Clinical Review
 Joette M. Meyer, Pharm.D.
 NDA 21-744
 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 9 (continued)
Adverse Events:
Patients Who Were at Least 65 Years Old in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number (%) of Patients Received Treatment	32 (100%)	41 (100%)	73 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Investigations	0	1 (2.4%)	1 (1.4%)	NS
Blood potassium increased	0	1 (2.4%)	1 (1.4%)	NS
Metabolism and nutrition disorders	0	1 (2.4%)	1 (1.4%)	NS
Hypercalcaemia	0	1 (2.4%)	1 (1.4%)	NS
Musculoskeletal and connective tissue disorders	0	2 (4.9%)	2 (2.7%)	NS
Flank pain	0	1 (2.4%)	1 (1.4%)	NS
Joint swelling	0	1 (2.4%)	1 (1.4%)	NS
Nervous system disorders	2 (6.3%)	5 (12.2%)	7 (9.6%)	NS
Dizziness	2 (6.3%)	2 (4.9%)	4 (5.5%)	NS
Headache	0	2 (4.9%)	2 (2.7%)	NS
Paraesthesia	1 (3.1%)	0	1 (1.4%)	NS
Sciatica	0	1 (2.4%)	1 (1.4%)	NS
Syncope	0	1 (2.4%)	1 (1.4%)	NS
Psychiatric disorders	0	1 (2.4%)	1 (1.4%)	NS
Insomnia	0	1 (2.4%)	1 (1.4%)	NS
Renal and urinary disorders	2 (6.3%)	1 (2.4%)	3 (4.1%)	NS
Urinary frequency	1 (3.1%)	1 (2.4%)	2 (2.7%)	NS
Micturition urgency	1 (3.1%)	0	1 (1.4%)	NS
Urethral pain	1 (3.1%)	0	1 (1.4%)	NS
Urine odour abnormal	0	1 (2.4%)	1 (1.4%)	NS
Respiratory, thoracic and mediastinal disorders	2 (6.3%)	0	2 (2.7%)	NS
Dyspnoea NOS	1 (3.1%)	0	1 (1.4%)	NS
Laryngitis NOS	1 (3.1%)	0	1 (1.4%)	NS
Nasopharyngitis	1 (3.1%)	0	1 (1.4%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

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Clinical Review
 Joette M. Meyer, Pharm.D.
 NDA 21-744
 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 9 (continued)
Adverse Events:
Patients Who Were at Least 65 Years Old in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number (%) of Patients Received Treatment	32 (100%)	41 (100%)	73 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Skin and subcutaneous tissue disorders	0	2 (4.9%)	2 (2.7%)	NS
Contusion	0	1 (2.4%)	1 (1.4%)	NS
Parapsoriasis	0	1 (2.4%)	1 (1.4%)	NS
Vascular disorders	0	3 (7.3%)	3 (4.1%)	NS
Aortic aneurysm	0	1 (2.4%)	1 (1.4%)	NS
Hot flushes NOS	0	1 (2.4%)	1 (1.4%)	NS
Hypertension aggravated	0	1 (2.4%)	1 (1.4%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.
 A patient may be reported in more than one category.
 The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.
 NS = Not statistically significant at 0.10 level.

Source: Table 32 in the applicant's submission dated May 4, 2005

7.1.4.3.2 Race

Adverse events were tabulated separately for Caucasian and non-Caucasian patients as shown in Tables 10 and 11, respectively. Differences, if any, in rates of particular adverse events between races were not clinically meaningful. Dosage adjustments, based upon race alone, are not warranted.

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Clinical Review
 Joette M. Meyer, Pharm.D.
 NDA 21-744
 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 10
Adverse Events:
Caucasian Patients in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number of Patients Randomized in the Study	421	438	859	
Number (%) of Patients Received Treatment	418 (100%)	434 (100%)	852 (100%)	
Number (%) of Patients without Any Adverse Event in the Study	235 (56.2%)	243 (56.0%)	478 (56.1%)	
Number (%) of Patients with at Least One Adverse Event in the Study	183 (43.8%)	191 (44.0%)	374 (43.9%)	NS
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Blood and lymphatic system disorders	4 (1.0%)	3 (0.7%)	7 (0.8%)	NS
Lymphadenopathy	3 (0.7%)	1 (0.2%)	4 (0.5%)	NS
Leukopenia NOS	0	2 (0.5%)	2 (0.2%)	NS
Anaemia NOS	1 (0.2%)	0	1 (0.1%)	NS
Cardiac disorders	1 (0.2%)	0	1 (0.1%)	NS
Ventricular bigeminy	1 (0.2%)	0	1 (0.1%)	NS
Ear and labyrinth disorders	3 (0.7%)	3 (0.7%)	6 (0.7%)	NS
Ear pain	0	2 (0.5%)	2 (0.2%)	NS
Fluid in middle ear	2 (0.5%)	0	2 (0.2%)	NS
Cerumen impaction	1 (0.2%)	0	1 (0.1%)	NS
Deafness NOS	0	1 (0.2%)	1 (0.1%)	NS
Endocrine disorders	1 (0.2%)	0	1 (0.1%)	NS
Goitre	1 (0.2%)	0	1 (0.1%)	NS
Eye disorders	0	3 (0.7%)	3 (0.4%)	NS
Conjunctivitis	0	2 (0.5%)	2 (0.2%)	NS
Eye swelling	0	1 (0.2%)	1 (0.1%)	NS
Vision blurred	0	1 (0.2%)	1 (0.1%)	NS
Gastrointestinal disorders	28 (6.7%)	39 (9.0%)	67 (7.9%)	NS
Nausea / Nausea aggravated	6 (1.4%)	12 (2.8%)	18 (2.1%)	NS
Abdominal pain NOS	7 (1.7%)	5 (1.2%)	12 (1.4%)	NS
Diarrhoea NOS	2 (0.5%)	10 (2.3%)	12 (1.4%)	0.038
Abdominal pain lower	0	4 (0.9%)	4 (0.5%)	NS
Dyspepsia	2 (0.5%)	2 (0.5%)	4 (0.5%)	NS
Abdominal pain upper	1 (0.2%)	2 (0.5%)	3 (0.4%)	NS
Gastroesophageal reflux disease	2 (0.5%)	1 (0.2%)	3 (0.4%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 33 in the applicant's submission dated May 4, 2005

Clinical Review
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 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 10 (continued)
Adverse Events:
Caucasian Patients in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number (%) of Patients Received Treatment	418 (100%)	434 (100%)	852 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Gastrointestinal disorders (Continued)				
Abdominal tenderness	2 (0.5%)	0	2 (0.2%)	NS
Constipation	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Haemorrhoids	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Abdominal discomfort	1 (0.2%)	0	1 (0.1%)	NS
Anal discomfort	0	1 (0.2%)	1 (0.1%)	NS
Diverticulum NOS	1 (0.2%)	0	1 (0.1%)	NS
Flatulence	0	1 (0.2%)	1 (0.1%)	NS
Gastritis NOS	1 (0.2%)	0	1 (0.1%)	NS
Gastroenteritis NOS	1 (0.2%)	0	1 (0.1%)	NS
Gingivitis	0	1 (0.2%)	1 (0.1%)	NS
Haemorrhoidal haemorrhage	1 (0.2%)	0	1 (0.1%)	NS
Intestinal obstruction NOS	0	1 (0.2%)	1 (0.1%)	NS
Irritable bowel syndrome aggravated	1 (0.2%)	0	1 (0.1%)	NS
Lip ulceration	0	1 (0.2%)	1 (0.1%)	NS
Melaena	1 (0.2%)	0	1 (0.1%)	NS
Oesophageal spasm	1 (0.2%)	0	1 (0.1%)	NS
Oral mucosal discolouration	1 (0.2%)	0	1 (0.1%)	NS
Pruritus ani	0	1 (0.2%)	1 (0.1%)	NS
Rectal discharge	0	1 (0.2%)	1 (0.1%)	NS
Toothache	0	1 (0.2%)	1 (0.1%)	NS
Vomiting NOS	1 (0.2%)	0	1 (0.1%)	NS
General disorders and administration site conditions				
Suprapubic pain	8 (1.9%)	4 (0.9%)	12 (1.4%)	NS
Chest pain	3 (0.7%)	5 (1.2%)	8 (0.9%)	NS
Fatigue	3 (0.7%)	4 (0.9%)	7 (0.8%)	NS
Pyrexia	3 (0.7%)	3 (0.7%)	6 (0.7%)	NS
Pain NOS	2 (0.5%)	2 (0.5%)	4 (0.5%)	NS
Rigors	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Asthenia	1 (0.2%)	0	1 (0.1%)	NS
Axillary pain	1 (0.2%)	0	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 33 in the applicant's submission dated May 4, 2005

Clinical Review
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 NDA 21-744
 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 10 (continued)
Adverse Events:
Caucasian Patients in Clinical Studies 81-0005 and 81-0015

	Treatment Group			p-value
	Ciprofloxacin	Ciprofloxacin	Total	
	GR	IR		
Number (%) of Patients Received Treatment	418 (100%)	434 (100%)	852 (100%)	
Number (%) of Patients Who Reported Adverse Events by System Organ Class				
General disorders and administration site conditions				
(Continued)				
Discomfort NOS	0	1 (0.2%)	1 (0.1%)	NS
Feeling cold	0	1 (0.2%)	1 (0.1%)	NS
Feeling hot	0	1 (0.2%)	1 (0.1%)	NS
Inflammation NOS	0	1 (0.2%)	1 (0.1%)	NS
Lethargy	1 (0.2%)	0	1 (0.1%)	NS
Malaise	0	1 (0.2%)	1 (0.1%)	NS
Oedema peripheral	0	1 (0.2%)	1 (0.1%)	NS
Thirst	1 (0.2%)	0	1 (0.1%)	NS
Hepatobiliary disorders				
Cholelithiasis	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Immune system disorders				
Seasonal allergy	0	3 (0.7%)	3 (0.4%)	NS
Drug hypersensitivity	0	2 (0.5%)	2 (0.2%)	NS
Allergy to arthropod sting	1 (0.2%)	0	1 (0.1%)	NS
Hypersensitivity NOS	1 (0.2%)	0	1 (0.1%)	NS
Infections and infestations				
Urinary tract infection NOS	43 (10.3%)	48 (11.1%)	91 (10.7%)	NS
Fungal infection NOS	14 (3.3%)	10 (2.3%)	24 (2.8%)	NS
Upper respiratory tract infection NOS	8 (1.9%)	15 (3.5%)	23 (2.7%)	NS
Vaginosis fungal NOS	5 (1.2%)	9 (2.1%)	14 (1.6%)	NS
Sinusitis NOS	3 (0.7%)	4 (0.9%)	7 (0.8%)	NS
Gastroenteritis viral NOS	2 (0.5%)	2 (0.5%)	4 (0.5%)	NS
Herpes simplex	1 (0.2%)	3 (0.7%)	4 (0.5%)	NS
Tooth abscess	1 (0.2%)	3 (0.7%)	4 (0.5%)	NS
Vaginal candidiasis	1 (0.2%)	3 (0.7%)	4 (0.5%)	NS
Vaginitis bacterial NOS	2 (0.5%)	2 (0.5%)	4 (0.5%)	NS
Beta haemolytic streptococcal infection	2 (0.5%)	1 (0.2%)	3 (0.4%)	NS
Vaginal infection NOS	2 (0.5%)	1 (0.2%)	3 (0.4%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 33 in the applicant's submission dated May 4, 2005

Clinical Review
 Joette M. Meyer, Pharm.D.
 NDA 21-744
 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 10 (continued)
Adverse Events:
Caucasian Patients in Clinical Studies 81-0005 and 81-0015

	Treatment Group			p-value
	Ciprofloxacin	Ciprofloxacin	Total	
	GR	IR		
Number (%) of Patients Received Treatment	418 (100%)	434 (100%)	852 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Infections and infestations (Continued)				
Vaginitis	1 (0.2%)	2 (0.5%)	3 (0.4%)	NS
Candidal infection NOS	0	2 (0.5%)	2 (0.2%)	NS
Pyelonephritis NOS	0	2 (0.5%)	2 (0.2%)	NS
Influenza	1 (0.2%)	0	1 (0.1%)	NS
Klebsiella infection NOS	1 (0.2%)	0	1 (0.1%)	NS
Lyme disease	0	1 (0.2%)	1 (0.1%)	NS
Oral candidiasis	1 (0.2%)	0	1 (0.1%)	NS
Otitis externa NOS	0	1 (0.2%)	1 (0.1%)	NS
Otitis media NOS	1 (0.2%)	0	1 (0.1%)	NS
Otitis media serous acute NOS	0	1 (0.2%)	1 (0.1%)	NS
Pharyngitis streptococcal	1 (0.2%)	0	1 (0.1%)	NS
Pharyngitis viral NOS	0	1 (0.2%)	1 (0.1%)	NS
Pharyngotonsillitis	1 (0.2%)	0	1 (0.1%)	NS
Pneumonia NOS	1 (0.2%)	0	1 (0.1%)	NS
Streptococcal infection NOS	1 (0.2%)	0	1 (0.1%)	NS
Upper respiratory tract infection viral NOS	1 (0.2%)	0	1 (0.1%)	NS
Viral infection NOS	1 (0.2%)	0	1 (0.1%)	NS
Injury, poisoning and procedural complications				
Muscle strain	1 (0.2%)	2 (0.5%)	3 (0.4%)	NS
Thermal burn	0	2 (0.5%)	2 (0.2%)	NS
Abrasion NOS	1 (0.2%)	0	1 (0.1%)	NS
Arthropod bite	0	1 (0.2%)	1 (0.1%)	NS
Heat exhaustion	1 (0.2%)	0	1 (0.1%)	NS
Joint sprain	0	1 (0.2%)	1 (0.1%)	NS
Skin laceration	1 (0.2%)	0	1 (0.1%)	NS
Investigations				
Blood bilirubin increased	3 (0.7%)	0	3 (0.4%)	NS
Gamma-glutamyltransferase increased	0	3 (0.7%)	3 (0.4%)	NS
Blood potassium increased	0	2 (0.5%)	2 (0.2%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.
 A patient may be reported in more than one category.
 The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.
 NS = Not statistically significant at 0.10 level.

Source: Table 33 in the applicant's submission dated May 4, 2005

Clinical Review
 Joette M. Meyer, Pharm.D.
 NDA 21-744
 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 10 (continued)
Adverse Events:
Caucasian Patients in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number (%) of Patients Received Treatment	418 (100%)	434 (100%)	852 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
<u>Investigations (Continued)</u>				
Abdominal aortic bruit	1 (0.2%)	0	1 (0.1%)	NS
Alanine aminotransferase increased	1 (0.2%)	0	1 (0.1%)	NS
Body temperature increased	1 (0.2%)	0	1 (0.1%)	NS
Culture urine positive	1 (0.2%)	0	1 (0.1%)	NS
Haematocrit decreased	0	1 (0.2%)	1 (0.1%)	NS
Haemoglobin decreased	0	1 (0.2%)	1 (0.1%)	NS
Platelet count decreased	1 (0.2%)	0	1 (0.1%)	NS
Red blood cell count decreased	0	1 (0.2%)	1 (0.1%)	NS
Metabolism and nutrition disorders	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Anorexia	1 (0.2%)	0	1 (0.1%)	NS
Appetite increased NOS	0	1 (0.2%)	1 (0.1%)	NS
Musculoskeletal and connective tissue disorders	14 (3.3%)	17 (3.9%)	31 (3.6%)	NS
Back pain	6 (1.4%)	7 (1.6%)	13 (1.5%)	NS
Joint swelling	1 (0.2%)	2 (0.5%)	3 (0.4%)	NS
Arthralgia	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Chest wall pain	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Myalgia	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Back pain aggravated	1 (0.2%)	0	1 (0.1%)	NS
Bursitis	0	1 (0.2%)	1 (0.1%)	NS
Costochondritis	0	1 (0.2%)	1 (0.1%)	NS
Facial pain	1 (0.2%)	0	1 (0.1%)	NS
Flank pain	0	1 (0.2%)	1 (0.1%)	NS
Groin pain	0	1 (0.2%)	1 (0.1%)	NS
Muscle cramp	0	1 (0.2%)	1 (0.1%)	NS
Night cramps	1 (0.2%)	0	1 (0.1%)	NS
Pain in limb	1 (0.2%)	0	1 (0.1%)	NS
Scoliosis	1 (0.2%)	0	1 (0.1%)	NS
Spinal osteoarthritis	0	1 (0.2%)	1 (0.1%)	NS
Tendonitis	0	1 (0.2%)	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.
 A patient may be reported in more than one category.
 The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.
 NS = Not statistically significant at 0.10 level.

Source: Table 33 in the applicant's submission dated May 4, 2005

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 Joette M. Meyer, Pharm.D.
 NDA 21-744
 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 10 (continued)
Adverse Events:
Caucasian Patients in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number (%) of Patients Received Treatment	418 (100%)	434 (100%)	852 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.5%)	0	2 (0.2%)	NS
Non-Hodgkin's lymphoma NOS	1 (0.2%)	0	1 (0.1%)	NS
Papillary thyroid cancer	1 (0.2%)	0	1 (0.1%)	NS
Nervous system disorders	20 (4.8%)	25 (5.8%)	45 (5.3%)	NS
Headache	10 (2.4%)	16 (3.7%)	26 (3.1%)	NS
Dizziness	6 (1.4%)	3 (0.7%)	9 (1.1%)	NS
Dysgeusia	0	2 (0.5%)	2 (0.2%)	NS
Migraine NOS	2 (0.5%)	0	2 (0.2%)	NS
Syncope	0	2 (0.5%)	2 (0.2%)	NS
Disturbance in attention	1 (0.2%)	0	1 (0.1%)	NS
Hypoaesthesia	0	1 (0.2%)	1 (0.1%)	NS
Paraesthesia	1 (0.2%)	0	1 (0.1%)	NS
Radiculopathy NOS	1 (0.2%)	0	1 (0.1%)	NS
Sciatica	1 (0.2%)	0	1 (0.1%)	NS
Sinus headache	1 (0.2%)	0	1 (0.1%)	NS
Tension headaches	0	1 (0.2%)	1 (0.1%)	NS
Pregnancy, puerperium and perinatal conditions	1 (0.2%)	0	1 (0.1%)	NS
Pregnancy NOS	1 (0.2%)	0	1 (0.1%)	NS
Psychiatric disorders	1 (0.2%)	6 (1.4%)	7 (0.8%)	NS
Depression	0	2 (0.5%)	2 (0.2%)	NS
Insomnia	0	2 (0.5%)	2 (0.2%)	NS
Depression aggravated	0	1 (0.2%)	1 (0.1%)	NS
Disorientation	0	1 (0.2%)	1 (0.1%)	NS
Mood swings	1 (0.2%)	0	1 (0.1%)	NS
Renal and urinary disorders	26 (6.2%)	12 (2.8%)	38 (4.5%)	0.019
Micturition urgency	8 (1.9%)	4 (0.9%)	12 (1.4%)	NS
Urinary frequency	6 (1.4%)	5 (1.2%)	11 (1.3%)	NS
Dysuria	9 (2.2%)	1 (0.2%)	10 (1.2%)	0.010

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 33 in the applicant's submission dated May 4, 2005

Clinical Review
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 NDA 21-744
 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 10 (continued)
Adverse Events:
Caucasian Patients in Clinical Studies 81-0005 and 81-0015

	Treatment Group			p-value
	Ciprofloxacin	Ciprofloxacin	Total	
	GR	IR		
Number (%) of Patients Received Treatment	418 (100%)	434 (100%)	852 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Renal and urinary disorders (Continued)				
Haematuria	4 (1.0%)	1 (0.2%)	5 (0.6%)	NS
Cystitis NOS	2 (0.5%)	1 (0.2%)	3 (0.4%)	NS
Nephrolithiasis	2 (0.5%)	1 (0.2%)	3 (0.4%)	NS
Urine odour abnormal	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Bladder pain	1 (0.2%)	0	1 (0.1%)	NS
Bladder spasm	0	1 (0.2%)	1 (0.1%)	NS
Chromaturia	1 (0.2%)	0	1 (0.1%)	NS
Costovertebral angle tenderness	1 (0.2%)	0	1 (0.1%)	NS
Cystocele	1 (0.2%)	0	1 (0.1%)	NS
Incontinence NOS	1 (0.2%)	0	1 (0.1%)	NS
Urethral cyst	1 (0.2%)	0	1 (0.1%)	NS
Urethral pain	1 (0.2%)	0	1 (0.1%)	NS
Urethral syndrome	0	1 (0.2%)	1 (0.1%)	NS
Reproductive system and breast disorders				
Genital pruritus female	13 (3.1%)	9 (2.1%)	22 (2.6%)	NS
Ovarian cyst	2 (0.5%)	4 (0.9%)	6 (0.7%)	NS
Adnexa uteri pain	1 (0.2%)	3 (0.7%)	4 (0.5%)	NS
Dysmenorrhoea	0	2 (0.5%)	2 (0.2%)	NS
Vaginal burning sensation	2 (0.5%)	0	2 (0.2%)	NS
Vaginal haemorrhage	0	2 (0.5%)	2 (0.2%)	NS
Dyspareunia NOS	2 (0.5%)	0	2 (0.2%)	NS
Endometrial hypertrophy	1 (0.2%)	0	1 (0.1%)	NS
Metrorrhagia	1 (0.2%)	0	1 (0.1%)	NS
Pelvic pain NOS	1 (0.2%)	0	1 (0.1%)	NS
Uterine pain	0	1 (0.2%)	1 (0.1%)	NS
Vaginal discharge	1 (0.2%)	0	1 (0.1%)	NS
Vaginal disorder NOS	1 (0.2%)	0	1 (0.1%)	NS
Vaginal irritation	1 (0.2%)	0	1 (0.1%)	NS
Vulvovaginal dryness	1 (0.2%)	0	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.
 A patient may be reported in more than one category.
 The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.
 NS = Not statistically significant at 0.10 level.

Source: Table 33 in the applicant's submission dated May 4, 2005

Clinical Review
 Joette M. Meyer, Pharm.D.
 NDA 21-744
 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 10 (continued)
Adverse Events:
Caucasian Patients in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number (%) of Patients Received Treatment	418 (100%)	434 (100%)	852 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Respiratory, thoracic and mediastinal disorders	29 (6.9%)	19 (4.4%)	48 (5.6%)	NS
Nasopharyngitis	10 (2.4%)	5 (1.2%)	15 (1.8%)	NS
Pharyngitis	5 (1.2%)	4 (0.9%)	9 (1.1%)	NS
Nasal congestion	4 (1.0%)	1 (0.2%)	5 (0.6%)	NS
Bronchitis NOS	1 (0.2%)	2 (0.5%)	3 (0.4%)	NS
Cough	0	3 (0.7%)	3 (0.4%)	NS
Dyspnoea NOS	1 (0.2%)	2 (0.5%)	3 (0.4%)	NS
Sinus congestion	2 (0.5%)	1 (0.2%)	3 (0.4%)	NS
Postnasal drip	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Rhinitis seasonal	2 (0.5%)	0	2 (0.2%)	NS
Rhinorrhoea	2 (0.5%)	0	2 (0.2%)	NS
Emphysema	0	1 (0.2%)	1 (0.1%)	NS
Epistaxis	1 (0.2%)	0	1 (0.1%)	NS
Haemoptysis	0	1 (0.2%)	1 (0.1%)	NS
Laryngitis NOS	1 (0.2%)	0	1 (0.1%)	NS
Pleurisy	0	1 (0.2%)	1 (0.1%)	NS
Pleuritic pain	0	1 (0.2%)	1 (0.1%)	NS
Rhinitis allergic NOS	1 (0.2%)	0	1 (0.1%)	NS
Rhonchi	1 (0.2%)	0	1 (0.1%)	NS
Sinus pain	1 (0.2%)	0	1 (0.1%)	NS
Wheezing	1 (0.2%)	0	1 (0.1%)	NS
Skin and subcutaneous tissue disorders	7 (1.7%)	10 (2.3%)	17 (2.0%)	NS
Rash NOS	2 (0.5%)	2 (0.5%)	4 (0.5%)	NS
Contusion	2 (0.5%)	1 (0.2%)	3 (0.4%)	NS
Acne NOS	1 (0.2%)	1 (0.2%)	2 (0.2%)	NS
Erythema	0	2 (0.5%)	2 (0.2%)	NS
Dermatitis contact	0	1 (0.2%)	1 (0.1%)	NS
Eczema	1 (0.2%)	0	1 (0.1%)	NS
Parapsoriasis	0	1 (0.2%)	1 (0.1%)	NS
Pruritus	1 (0.2%)	0	1 (0.1%)	NS
Rash maculo-papular	0	1 (0.2%)	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 33 in the applicant's submission dated May 4, 2005

Clinical Review
 Joette M. Meyer, Pharm.D.
 NDA 21-744
 Proquin XR™ (ciprofloxacin extended-release) tablets

TABLE 10 (continued)
Adverse Events:
Caucasian Patients in Clinical Studies 81-0005 and 81-0015

	Treatment Group		Total	p-value
	Ciprofloxacin	Ciprofloxacin		
	GR	IR		
Number (%) of Patients Received Treatment	418 (100%)	434 (100%)	852 (100%)	
<u>Number (%) of Patients Who Reported Adverse Events by System Organ Class</u>				
Skin and subcutaneous tissue disorders (Continued)				
Sweating increased	0	1 (0.2%)	1 (0.1%)	NS
Surgical and medical procedures				
Nasal cyst removal	1 (0.2%)	0	1 (0.1%)	NS
Vascular disorders				
Aortic aneurysm	0	1 (0.2%)	1 (0.1%)	NS
Hot flushes NOS	0	1 (0.2%)	1 (0.1%)	NS
Hypertension NOS	0	1 (0.2%)	1 (0.1%)	NS
Hypertension aggravated	0	1 (0.2%)	1 (0.1%)	NS

Note: Adverse event mapping was based on the MedDRA Version 5.1 thesaurus.

A patient may be reported in more than one category.

The p-values were obtained from the Fisher's Exact test and were presented if they are less than 0.10.

NS = Not statistically significant at 0.10 level.

Source: Table 33 in the applicant's submission dated May 4, 2005

**APPEARS THIS WAY
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