

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-744

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA Number: 21-744
Serial Number: 000
Date Received by Center: 7/19/04
Product: Proquin™ (Ciprofloxacin HCl extended-release)
500 mg Tablets
Clinical Population: Adult Women
Sponsor: Depomed, Inc.
1360 O'Brien Drive
Menlo Park, CA 94025-1436

Review Division: Special Pathogen and Immunologic Drug
Products (HFD-590)
Reviewer: Stephen G. Hundley, Ph.D., DABT
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Review Submission Date (DFS): 5/6/05

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EXECUTIVE SUMMARY

Recommendations

Approvability:

The sponsor seeks approval of an extended release tablet of ciprofloxacin HCl for the treatment of uncomplicated urinary tract infection. The ciprofloxacin dose formulation presents no pharmacology/toxicology issues and can be approved.

Additional Nonclinical Studies:

Nonclinical studies, in addition to those studies submitted in the NDA, were not requested of the sponsor.

Labelling:

The sponsor's proposed product label included language summarizing results from the genetic toxicology and reproductive toxicology studies conducted by the sponsor. The sponsor also included

Summary of Nonclinical Findings

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™ gastro-retentive tablets to Cipro® tablets (500 mg). None of the dosing regimens resulted in compound-related toxicity. The NOAEL for the study was 1000 mg ciprofloxacin (two 500 mg Proquin™ 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 labelling 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™ (ciprofloxacin HCl).

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 DRUG INFORMATION

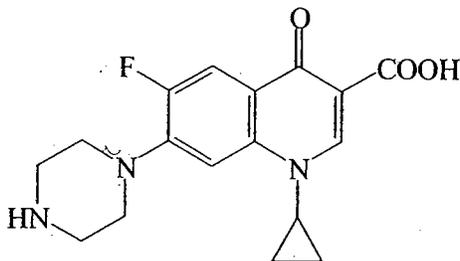
NDA: 21-744
Type of Submission: Original (new formulation)
Review Number: 1
Date of Submission: 7/19/04
Information to Sponsor: Yes (x) No ()

Sponsor: Depomed, Inc.
1360 O'Brien Drive
Menlo Park, CA 94025-1436
650-462-5900

Reviewer: Stephen G. Hundley, Ph.D., DABT
Pharmacology/Toxicology Reviewer
Review Division: Special Pathogen and Immunologic Drug Products
HFD-590
Review Completion Date: 4/19/05

Drug Information

Trade Name: Proquin™ (Ciprofloxacin HCl extended release)
Generic Name: Ciprofloxacin HCl
Code Name: Not Applicable
Chemical Name: 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[1-piperazinyl]-3-quinoline-carboxylic acid
CAS#: 85721-33-1
Molecular Formula: C₁₇H₁₈FN₃O₃
Molecular Weight: 331.4 (385.8 for the monochloride monohydrate salt)
Molecular Structure:



Relevant Submission: IND 62,386

Drug Class: Antimicrobial Fluoroquinolone

Indication: Uncomplicated Urinary Tract Infection

Clinical Formulation: Gastro-retentive Tablet

Route of Administration: Oral

Proposed Use: 500 mg Tablet Once Daily for Three Days

Studies reviewed for this submission:

A 28-Day Oral (Tablet) Toxicity Study of Ciprofloxacin GR in Beagle Dogs, Study No. 80-0002.

Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay with Ciprofloxacin Hydrochloride Monohydrate. (Study no. 7439-106; 80-0004).

Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells for Ciprofloxacin Hydrochloride Monohydrate. (Study no. 7439-107; 80-0005).

In Vivo Rat Micronucleus Assay with Ciprofloxacin Hydrochloride Monohydrate. (Study no. 7439-108; 80-006).

Rat Developmental Toxicity Study with Ciprofloxacin HCl. (Study No. 7439-102; 80-0009)

Rabbit Developmental Toxicity Study with Ciprofloxacin HCL. (Study No. 7439-103; 80-0010).

Oral Gavage Study of Fertility and Early Embryonic Development to Implantation in Rats with Ciprofloxacin HCl. (Study no. 7439-105; 80-0011).

Study for the Effects on Pre- and Postnatal Development, Including Maternal Function, in the Rat with Ciprofloxacin HCl. (Study no. 7439-104; 80-0012).

2.6.2 PHARMACOLOGY

2.6.2.1 Summary

A pharmacology summary is not needed for the Pharmacology/Toxicology Review of this NDA.

2.6.2.2 Pharmacodynamics (primary)

A pharmacodynamics review is not needed for this Pharmacology/Toxicology Review of the NDA.

2.6.2.3 Pharmacodynamics (secondary)

A secondary pharmacodynamics review is not applicable.

2.6.2.4 Safety Pharmacology

A nonclinical safety pharmacology review is not needed for the Pharmacology/Toxicology Review of this NDA.

2.6.2.5 Pharmacodynamic drug interactions

A pharmacodynamic drug interactions review is not applicable.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

A tabulated pharmacology summary is not needed for this review.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

None of the following Pharmacokinetics/Toxicokinetics sections are applicable for this review.

2.6.4.1 Brief Summary**2.6.4.2 Methods of Analysis****2.6.4.3 Absorption****2.6.4.4 Distribution****2.6.4.5 Metabolism****2.6.4.6 Excretion****2.6.4.7 Pharmacokinetic drug interactions****2.6.4.8 Other pharmacokinetic studies****2.6.4.9 Discussion and conclusion****2.6.4.10 Tables and Figures****2.6.5 PHARMACOKINETICS TABULATED SUMMARY**

A tabulated pharmacokinetics summary is not needed for this review.

2.6.6 TOXICOLOGY

2.6.6.1 Toxicology Summary

The sponsor conducted a 28-day repeat-dose toxicity study with the Proquin™ drug product (Ciprofloxacin GR tablets) in adult male and female beagle dogs. Three groups received 1/2, 1, or 2 Ciprofloxacin GR tablets daily (250, 500, or 1000 mg of ciprofloxacin, respectively), while a fourth group received a single Cipro® tablet daily (500 mg of ciprofloxacin). No compound-related clinical, hematological, or serum chemistry effects were observed in male and female dogs from any of the ciprofloxacin dosing regimens. Compound-related effects were not observed in ECG's taken at T_{max} following the initial and final ciprofloxacin doses (QTc prolongation was not observed). Gross necropsy revealed "black pinpoint particulates" in the gallbladder from animals at all dose levels (including the zero-level vehicle control). Crystals were also observed in urine samples from one animal at each of the ciprofloxacin dose levels. The gallbladder particulates and urinary crystals were consistent with bilirubin. No histopathological effects were noted at any dose level from the organs and tissues taken at the terminal sacrifice. The ciprofloxacin NOAEL for this study was 1000 mg (approximately 92 and 144 mg/kg for males and females, respectively). No differences in toxicity were noted between Ciprofloxacin GR (Proquin™) tablets and Cipro® tablets.

Genotoxicity studies conducted by the sponsor demonstrated that ciprofloxacin was not mutagenic in the bacterial reverse mutation assay in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and in *E. coli* strain WP2uvrA. Ciprofloxacin was prohibitively bactericidal at incubation plate levels of 300 ng and above. Chinese hamster ovary (CHO) cell cultures were used to evaluate the genotoxicity of ciprofloxacin in mammalian cells. Excessive cytotoxicity (>80 % reduction in mitotic index) resulted from ciprofloxacin cell culture concentrations \geq 1370 μ g/ml (without S-9 metabolic activation). Statistically significant increases in chromosomal aberrations resulted from ciprofloxacin concentrations of 471, 672, and 960 μ g/ml. In assays with the S-9 metabolic activation system statistically significant increases in chromosomal aberrations were observed at a ciprofloxacin concentration of 471 μ g/ml (higher concentrations resulted in 90 percent reduction in the mitotic index). Polyploidy and endoreplication were not induced by any cell culture concentration of ciprofloxacin.

The *in vivo* mammalian genotoxic activity of ciprofloxacin was evaluated in the rat micronucleus assay (males) at ciprofloxacin dose levels of 500, 1000, and 2000 mg/kg. Polychromatic and Normochromatic erythrocyte ratios determined from bone marrow smears 24 and 48 hours after a single oral ciprofloxacin dose did not indicate evidence of bone marrow toxicity at any ciprofloxacin dose level. Ciprofloxacin did not induce elevated numbers of micronucleated PCE's compared to the zero-level vehicle control. Ciprofloxacin was negative for genotoxicity in the rat micronucleus assay.

Embryo/fetal developmental toxicity was evaluated in pregnant rats at ciprofloxacin dose levels of 50, 300, and 600 mg/kg/day. Maternal toxicity was observed at the 600 mg/kg

dose level and consisted of statistically significant reductions in body weight and body weight gain at the 600 mg/kg dose level. No additional compound-related maternal effects were observed. Embryo toxicity was not observed and reproductive parameters were not affected at any ciprofloxacin dose level. The only statistically significant fetal developmental effect was elevated incidence of a 14th rudimentary rib in fetuses from pregnant dams from the 600 mg/kg dose level. The NOAELs for both maternal toxicity and embryo-fetal developmental toxicity were 300 mg/kg. Ciprofloxacin plasma AUC values generated from pregnant dams at the 600 mg/kg dose level ranged from approximately 12 to 14 $\mu\text{g} \cdot \text{hr}/\text{ml}$.

An embryo/fetal toxicity study in pregnant female rabbits was conducted at ciprofloxacin dose levels of 3, 10, and 30 mg/kg/day. The 10 and 30 mg/kg dose levels resulted in aborted fetuses in 2 of 22 and 8 of 22 pregnant does, respectively. Reduced fecal excretion was observed for most of the pregnant does from the 30 mg/kg dose level and half of the pregnant does from the 10 mg/kg dose level. Statistically significant body weight and weight gain reductions and reduced food consumption resulted from the 30 mg/kg dose level. Embryo-fetal lethality was elevated in pregnant does dosed at the 30 mg/kg dose level and fetal developmental effects included lower average fetal weight, elevated incidence of unossified hyoid bodies, talus, and 5th & 6th sternebra, and reduced number of ossified cauda vertebra. No compound-related effects were observed for soft tissue variations and malformations and skeletal malformations. The NOAEL for embryo-fetal effects was 10 mg/kg and the NOAEL for maternal toxicity was 3 mg/kg.

Fertility reproductive toxicity was evaluated in male and female rats at ciprofloxacin dose levels of 50, 300, and 600 mg/kg/day. The only observed compound-related clinical effect was a modest reduction in body weight gain in males at the 300 and 600 mg/kg dose levels. No compound-related effects were observed in any of the measures of fertility and reproduction (pregnancy rates, implantation sites, percent preimplantation loss, post implantation loss, and number of live fetuses). No pregnant dams aborted at any of the ciprofloxacin dose levels. In males (following approximately 70 days of dosing), no compound-related gross pathological effects were observed in any of the sex organs (epididymis, testes, seminal vesicles, and prostate). Sperm count and motility were not affected by any dose level of ciprofloxacin. The ciprofloxacin no-observed effect level for male and female rat fertility was 600 mg/kg.

Peri/postnatal reproductive toxicity was evaluated in pregnant female rats and their F₁ offspring at dose levels of 50, 300, and 600 mg/kg/day to pregnant female rats from Day 6 of Gestation to Day 20 of Lactation. Body weight gain was reduced for the Gestation 6 through Gestation Day 20 period at the 300 and 600 mg/kg dose levels. No compound-related effects were observed for any of the reproduction parameters (number of dams delivering, viable pups per litter, implantation sites, pup male/female ratios, and average pup weight at birth). No compound-related effects to the F₁ pups were noted during the lactation period (body weight gain, survival, and developmental parameters). Learning capabilities of the F₁ pups following weaning were not affected as a result of ciprofloxacin dosing to the F₀ dams during pregnancy and lactation. The no-observed

effect level for reproductive and developmental effects was 600 mg/kg and the NOAEL for the pregnant F₀ dams was 50 mg/kg.

2.6.6.2 Single-dose toxicity

No single-dose toxicity studies were requested or submitted for this NDA.

2.6.6.3 Repeat-dose toxicity

A 28-Day Oral (Tablet) Toxicity Study of Ciprofloxacin GR in Beagle Dogs, Study No. 80-0002.

The 28-day oral toxicity study in beagle dogs was contracted by the sponsor (DepoMed, Inc.), to _____ The study was conducted in accordance with GLP requirements and was audited by a Quality Assurance group. Male and female beagle dogs (approximately 19 months of age) were randomly assigned to five dosing groups each consisting of three males and three females. The dosing groups were defined as; 1) zero-level control (placebo tablet); 2) Ciprofloxacin GR, 1/2 tablet (approx. 250 mg of ciprofloxacin); 3) Ciprofloxacin GR, 1 tablet (approx. 500 mg of ciprofloxacin); 4) Ciprofloxacin GR, 2 tablets (approx. 1,000 mg of ciprofloxacin); and 5) Cipro®, 1 tablet (500 mg of ciprofloxacin). Each animal was orally administered a single daily dose for 28 consecutive days.

General clinical monitoring was conducted twice daily and detailed clinical observations were conducted once weekly. Observations for overt toxic effects were conducted approximately 30 minutes and 2 hours following each daily dose. Complete physical examinations by a veterinarian were conducted prior to the initiation of the dosing routines and on Day 27 of the study. Individual body weights were determined prior to dosing and weekly thereafter. Daily food intake was also recorded for individual animals.

Blood samples were drawn from each animal for hematological and serum chemistry analyses prior to the initiation of the dosing routines and on Day 28. Hematology included erythrocyte count, hematocrit, hemoglobin concentration, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, reticulocyte count, total and differential leukocyte counts, prothrombin time, and activated partial thromboplastin time. Serum chemistry included the following:

| | | |
|----------------------------|------------------------|------------|
| Alanine aminotransferase | Total bilirubin | Calcium |
| Aspartate aminotransferase | Triglycerides | Phosphorus |
| Alkaline phosphatase | Albumin | Sodium |
| Creatine phosphokinase | Total serum protein | Potassium |
| Creatinine | Globulin | Chloride |
| Blood urea nitrogen | Albumin/Globulin Ratio | |
| Cholesterol | Glucose | |

Overnight urine samples were collected prior to initiation of the dosing routine and on Day 27 to Day 28. Urinalysis consisted of urine volume, bilirubin, glucose, ketones, protein, specific gravity, pH, blood, gross appearance, and sediment (microscopic evaluation). Ophthalmological examinations were conducted on each dog prior to initiation of the dosing routine and on Day 22. Cardiac electrocardiograms (leads I, II, III, aV_R, aV_L, and aV_F) were generated for all dogs on study prior to the initiation of the dosing routines and approximately 2 hours post-dosing on Day 1 and Day 26. Only tracings from lead II were examined. Toxicokinetic information (limited pharmacokinetics) was generated by taking sequential blood samples from all ciprofloxacin-dosed animals following the initial dose and dosing on Day 24. Blood was drawn prior to dose administration and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dosing.

Gross necropsy and pathology were conducted on each animal at the terminal sacrifice, 24 hours following the final dose. Weights were determined for the adrenal glands, brain, heart, kidneys, liver with gallbladder, ovaries, pituitary gland, spleen, testes, and thyroid with parathyroid. Bone marrow smears were also prepared at the time of necropsy. The following table lists all of the organs and tissues that were removed, preserved and prepared for histopathology.

| | | |
|-------------------------|-----------------------------|----------------------------|
| Adrenals | Knee & Elbow joints | Sternum |
| Gross lesions | Liver | Stomach |
| Aorta | Lungs (with Bronchi) | Submandibular Lymph Node |
| Brain | Mammary glands | Testes |
| Cecum | Salivary Gland (Mandibular) | Ovaries |
| Colon | Mediastinal Lymph Node | Thymus |
| Duodenum | Mesenteric Lymph Node | Thyroid (with Parathyroid) |
| Esophagus | Pancreas | Tongue |
| Eyes (with Optic Nerve) | Sciatic Nerve | Trachea |
| Femur | Pituitary Gland | Urinary Bladder |
| Gallbladder | Rectum | Prostate |
| Heart | Skeletal Muscle | Epididymides |
| Ileum | Skin | Uterus |
| Jejunum | Spinal cord | Vagina |
| Kidneys | Spleen | |

Results

No compound-related clinical effects were noted during the study. Body weight gain and food consumption were also not affected by any ciprofloxacin dosing routine. No biologically meaningful effects attributed to ciprofloxacin were observed in the hematological, serum chemistry, and ophthalmoscopic measurements. No compound-related effects were noted in the ECG's and in the blood pressure measurements taken following the initial dose and dosing on Day 26. ECG's were generated 2 hours post-dosing (plasma concentration data indicated that the T_{max} ranged from 2 to 4 hours post-dosing). QT and QTc intervals were not affected at any ciprofloxacin dose level.

Crystals were observed in urine samples collected for urinalysis. The crystals were consistent with bilirubin according to the observations made by the study director and were observed in one animal from each of the following groups; the mid and high ciprofloxacin GR groups (500 mg and 1000 mg) and the Cipro® (500 mg tablet) group. Gross necropsy revealed abnormal contents in the gallbladder from all groups (including the zero-level control). The particulate matter described as "black pinpoint particulates" was presumed to be bilirubin. Necropsy, gross pathology, and organ weight determinations did not reveal any compound-related effects. Histopathological examination of all listed organs and tissues did not reveal compound-related histopathological effects.

This study demonstrated that the ciprofloxacin GR formulation at the highest dosing rate of 2 tablets (approximately 1,000 mg ciprofloxacin; 92 to 144 mg/kg dose level for males and females, respectively) induced no observable adverse effects in male and female beagle dogs. The currently marketed Cipro® 500 mg tablet also did not generate any observable adverse effects. The toxicokinetic data indicated that the plasma ciprofloxacin AUC values (15 to 24 $\mu\text{g} \cdot \text{hr/ml}$) for 1 Ciprofloxacin GR tablet (approximately 500 mg of ciprofloxacin) were similar to the AUC values (17 to 18 $\mu\text{g} \cdot \text{hr/ml}$) generated following dosing with Cipro® (500 mg tablet). AUC values for the 2 Ciprofloxacin GR tablet regimen (approximately 1000 mg of ciprofloxacin) ranged from 20 to 38 $\mu\text{g} \cdot \text{hr/ml}$.

2.6.6.4 Genetic toxicity

Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay with Ciprofloxacin Hydrochloride Monohydrate. (Study no. 7439-106; 80-0004).

The bacterial reverse mutation assay was contracted by the sponsor to _____ The study was conducted in accordance with GLP requirements and was audited by a Quality Assurance group. The mutagenicity potential of ciprofloxacin was evaluated in the following *Salmonella typhimurium* strains; TA98, TA100, TA1535, and TA1537, and in *Escherichia coli* strain WP2uvrA. The mutagenicity assays were conducted according to standard accepted procedures that included; initial determination of cytotoxicity (bactericidal activity) to define the proper incubation concentrations for ciprofloxacin, concurrent assays in the absence and presence of a rat hepatic S-9 metabolic activation system from rats induced with Aroclor 1254, and accepted standard positive control chemical for each test system.

Due to the potent bactericidal activity of ciprofloxacin the incubation concentrations for ciprofloxacin in the initial mutagenicity assays ranged from 3.33 ng/plate to 333 ng/plate. A confirmatory series of assays were also conducted at ciprofloxacin concentrations that ranged from 10 ng/plate to 500 ng/plate. In the initial assay series, ciprofloxacin was cytotoxic at concentrations of 200 and 333 ng/plate. The number of revertants for each strain tested, both in the presence and absence of the hepatic S-9 metabolic activation

system, did not exceed the number of revertants in the corresponding vehicle control incubations. The same results were obtained in the confirmatory assays. The positive control chemicals induced elevated numbers of revertant colonies consistent with positive results historically observed in this laboratory. Ciprofloxacin was negative for mutagenicity activity in the bacterial reverse mutation assay.

Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells for Ciprofloxacin Hydrochloride Monohydrate. (Study no. 7439-107; 80-0005).

The mammalian cell culture chromosomal aberration assay was contracted by the sponsor to _____ The study was conducted in accordance with GLP requirements and was audited by a Quality Assurance group. Chinese hamster ovary (CHO) cell cultures were incubated with different cell culture concentrations of ciprofloxacin in the presence and absence of a rat hepatic S-9 metabolic activation system. The ciprofloxacin cell culture concentrations ranged from 27 to 2800 µg/ml. The treatment period was approximately 3 hours and cell cultures were harvested approximately 20 hours following the initiation of the incubations.

The assay conditions were in accordance with generally accepted procedures and included the appropriate positive controls for incubations in the presence and absence of an S-9 metabolic activation system. Approximately 100 cells from each replicate incubation were evaluated for chromosomal aberrations. The mitotic index was determined for each replicate incubation (# of mitotic cells in incubations containing ciprofloxacin relative to the # of mitotic cells in the vehicle control incubations).

Cell culture incubations in the absence of the S-9 metabolic activation system exceeded 80 percent reduction of the mitotic index at ciprofloxacin cell concentrations ≥ 1370 µg/ml. Ciprofloxacin concentrations of 471, 672, and 960 µg/ml induced significant increases in chromosomal aberrations. In assays with S-9 metabolic activation a statistically significant increase in chromosomal aberration was observed in replicate incubations containing 471 µg/ml (higher ciprofloxacin concentrations resulted in ≥ 90 percent reductions of the mitotic index). Ciprofloxacin did not induce polyploidy or endoreplication at any cell culture concentration in the presence or absence of the S-9 metabolic activation system.

In Vivo Rat Micronucleus Assay with Ciprofloxacin Hydrochloride Monohydrate. (Study no. 7439-108; 80-006).

The rat micronucleus assay was contracted by the sponsor to _____ The study was conducted in accordance with GLP requirements and was audited by a Quality Assurance group. Adult male CD rats were dosed orally by gavage at 500, 1000, or 2000 mg ciprofloxacin/kg body weight. Also included were zero-level vehicle control and positive chemical control (cyclophosphamide, 60 mg/kg) groups. Each dosing routine consisted of six male rats that were sacrificed 24 hours after the respective dose administrations. The 2000 mg/kg ciprofloxacin and zero-level vehicle control groups also included six male rats that were sacrificed 48 hours after oral-

gavage dose administration. All animals were monitored for clinical evidence of compound-related toxicity.

Bone marrow was taken from the tibias of each animal at the designated sacrifice timepoints. Glass slides were prepared for light microscopy from the bone marrow samples of five animals from each dosing routine. Each slide was scored for polychromatic erythrocytes (PCEs), normochromatic erythrocytes (NCEs), and micronucleated PCEs. At least 2000 PCEs were scored for each animal while the PCE/NCE ratio was determined by scoring at least 500 erythrocytes from each animal.

Results of this study indicated no clinically observed toxicity at any ciprofloxacin dose level. The bone marrow analysis of the PCE/NCE ratios did not indicate evidence of compound-related bone marrow toxicity due to ciprofloxacin compared to the zero-level vehicle control ratio. Ciprofloxacin did not induce elevated numbers of micronucleated PCEs compared to the zero-level vehicle control for both the 24- and 48-hour sacrifices. All samples analyzed from these groups were within the historical background control frequency of 0.0 to 0.4 percent. The positive reference compound, cyclophosphamide, generated a micronucleated PCE frequency of approximately 2.6 percent which was consistent with historical data. Under the conditions of this assay, ciprofloxacin was negative in the rat bone marrow micronucleus assay.

2.6.6.5 Carcinogenicity

No carcinogenicity studies were requested or submitted for this NDA.

2.6.6.6 Reproductive and developmental toxicity

Rat Developmental Toxicity Study with Ciprofloxacin HCl. (Study No. 7439-102; 80-0009)

The rat developmental toxicity study was contracted by the sponsor to _____

_____ The study was conducted in accordance with GLP requirements and was audited by a Quality Assurance group. The ciprofloxacin dose levels (Lot no. 311717) were 50, 300, and 600 mg/kg/day and were administered orally by gavage on Gestation Days 6 through 17. Each dose level, including the zero-level vehicle control, consisted of 25 pregnant Sprague-Dawley derived female CD rats.

Clinical signs were monitored twice daily beginning with the initial dose on Gestation Day 6. Body weights were determined on Gestation Days 0, 4, 6, 8, 10, 12, 14, 16, 18, and 20. Food consumption was determined on successive three day intervals beginning on Gestation Day 0 and ending on Gestation Day 20. All female rats were sacrificed and C-sectioned on Gestation Day 20. Gross necropsy was performed on each female rat and uterine weights determined. Fetal sex was determined and fetal weights recorded. All individual fetuses were examined for external, visceral, and skeletal abnormalities.

Minimal evidence of compound-related maternal toxicity was observed and included alopecia and white urogenital discharge in 4 of 25 pregnant female rats at the 600 mg/kg dose level (Gestation Days 13 through 18). Pregnant dams from the 600 mg/kg dose level exhibited statistically significant depressed average body weights and body weight gain relative to the zero-level vehicle control dams (approximately 4 percent and 16 percent, respectively). Mean maternal food intake was also reduced as a result of the 600 mg/kg dose level of ciprofloxacin.

The only maternal observation at necropsy was the presence of green/black amniotic fluid in one female from the 600 mg/kg dose level. There were no compound-related effects upon gravid uterine weights whereas the corrected maternal body weights were reduced by 6 percent (statistically significant) at the 600 mg/kg dose level compared to the zero-level vehicle control. No pregnancies were aborted and there were no early deliveries. There were no dead fetuses at any dose level. No compound-related effects were observed for the following: mean corpora lutea, mean implantation loss, percent preimplantation loss, total resorptions, post-implantation loss, male to female ratio, and fetal weights.

No external fetal variations were observed at any dose level. The only external malformation observed was cleft palate in one fetus at the 300 mg/kg dose level. No compound-related fetal soft tissue variations were observed. Tissue malformations included anophthalmia in one fetus at the 600 mg/kg dose level and microphthalmia in two fetuses from the 50 mg/kg dose level, one fetus from the 300 mg/kg dose level and one fetus from the 600 mg/kg dose level. Fetal skeletal variations included elevated incidence rate (approximately 4 percent) of a 14th rudimentary rib at the 600 mg/kg dose level and may be compound-related. Fetal skeletal malformation was limited to one incidence of major fusion of sternbrae at the 600 mg/kg dose level and was apparently random and not compound-related. The only fetal observation that was statistically significant was the 4 percent incidence rate of a 14th rudimentary rib.

Maternal toxicity, though mild, was evident as body weight gain reduction at the 600 mg/kg dose level. Effects observed at the 300 mg/kg dose level were equivocal. The NOAEL for fetal development was 300 mg/kg. No compound-related embryotoxicity was observed.

Plasma ciprofloxacin concentrations were characterized at the 50 and 600 mg/kg dose levels following the initial ciprofloxacin dose and the dose administered on Gestation Day 17. Average values for C_{max} and AUC_{0-6hr} were generated from six pregnant females from the two dose levels and are included in the following table.

| Dose Levels (mg/kg) | Gestation Day 6 | | Gestation Day 17 | |
|------------------------|--------------------------|------------------|--------------------------|------------------|
| | C _{max} (µg/ml) | AUC (µg · hr/ml) | C _{max} (µg/ml) | AUC (µg · hr/ml) |
| 50 | 1.0 | 1.4 | 0.5 | 0.7 |
| 600 | 3.8 | 13.9 | 3.2 | 12.0 |

The AUC_{0-6hr} values increased in proportion to the increased dose levels and did not appreciably change between Gestation Days 6 and 17 at the respective dose levels.

Rabbit Developmental Toxicity Study with Ciprofloxacin HCL. (Study No. 7439-103: 80-0010).

The rabbit embryo/fetal developmental toxicity study was contracted by the sponsor to _____ The study was conducted in accordance with GLP requirements and was audited by a Quality Assurance group. The ciprofloxacin dose levels (Lot no. 311717) were 3, 10, and 30 mg/kg/day and were administered orally by gavage on Gestation Days 7 through 20. Each dose level, including the zero-level vehicle control, consisted of 22 pregnant New Zealand White female rabbits.

Clinical signs were monitored twice daily for indications of pain and stress or mortality beginning with the initial dose on Gestation Day 0. Body weights were determined on Gestation Days 0, 4, 7, 9, 11, 13, 15, 21, 24, 27, and 29; detailed clinical observations were made at each body weight determination. Food consumption was determined on successive three day intervals beginning on Gestation Day 0 and ending on Gestation Day 29. All female rabbits were scheduled for sacrifice and C-sectioning on Gestation Day 29. Gross necropsy was performed on each female rabbit and uterine weights determined. Fetal sex was determined and fetal weights recorded. All individual fetuses were examined for external, visceral, and skeletal abnormalities. For unscheduled deaths or sacrifices, does were examined for gross abnormalities in the cervical, thoracic, or abdominal viscera while the uteri and ovaries were examined for implantations and corpora lutea.

At the scheduled sacrifice the uterine contents were examined and any gross abnormalities noted. The uterus was excised, weighed, and examined for the uterine implantation sites, live and dead fetuses, early or late resorptions, and any abnormalities. The right and left ovaries were examined for the number of corpora lutea. Live and dead fetuses were weighed and examined for external abnormalities. A mid-coronal slice was made to the head of each fetus to evaluate the cranium contents. The internal organs of the thoracic and abdominal cavities of all fetuses were examined. The remaining carcasses were processed for skeletal evaluations (skull, vertebral column, rib cage, pectoral and pelvic girdles, long bones, and extremities), bone alignment, and degree of ossification. All fetal abnormalities were classified as variations or malformations.

Results

The 10 and 30 mg/kg dose levels resulted in aborted pregnancies at respective rates of 2 of 22 and 8 of 22 pregnant does. In addition, 2 pregnant does from the 30 mg/kg dose level delivered litters two days early. There were no remarkable compound-related clinical observations at any ciprofloxacin dose level. Fecal excretion was reduced for almost all of the pregnant does at the 30 mg/kg dose level and half of the pregnant does at the 10 mg/kg dose level. The mean body weight was reduced by approximately 10 percent at the 30 mg/kg dose level compared to the zero-level vehicle control. The mean

body weight gain was substantially reduced (over 2-fold) for pregnant does from the 30 mg/kg dose level compared to the zero-level vehicle control group from Day 7 to 21 of gestation (the period of ciprofloxacin dosing). Mean food consumption was reduced by approximately 78 percent for the 30 mg/kg dose level.

Two of the pregnant does from the 30 mg/kg dose level had no viable fetuses. The remaining 10 does at the high dose level delivered viable fetuses. The mean gravid uterus weight taken from does at the 30 mg/kg dose level was approximately 25 percent lower than the mean gravid uterus weight from does at the zero-level vehicle control dose level. No compound-related differences were observed for the following: number of corpora lutea; number of implantation sites; percent preimplantation loss; and dead fetuses. Increased embryo-fetal lethality was observed at the 30 mg/kg dose level as indicated by an elevated percent of total resorptions (late resorptions), elevated percent of post-implantation loss, and lower average number of live fetuses per litter. Fetal development was also affected by the 30 mg/kg dose level as indicated by lower average fetal weight, elevated incidence of unossified hyoid bodies, talus, and 5th & 6th sternbra and reduced number of ossified caudal vertebra. There were no compound-related effects on the incidence of soft tissue variations and malformations and skeletal malformations.

Maternal toxicity was pronounced at the 30 mg/kg dose level and was sufficiently severe to induce abortions in 8 of the 22 pregnant female rabbits. All of the observed effects on embryo/fetal viability and fetal development at the 30 mg/kg dose level can be attributed to the observed maternal toxicity. There was no evidence of embryo/fetal effects at the two lower ciprofloxacin dose levels (3 and 10 mg/kg). There was no evidence of ciprofloxacin-incuded teratological effects at any dose level. The maternal and embryo/fetal No-Observed-Adverse-Effect Levels were 3 and 10 mg/kg, respectively.

Oral Gavage Study of Fertility and Early Embryonic Development to Implantation in Rats with Ciprofloxacin HCl. (Study no. 7439-105; 80-0011).

The rat fertility and early embryonic development study was contracted by the sponsor to _____ the study was conducted in accordance with GLP requirements and was audited by a Quality Assurance group. The ciprofloxacin dose levels (Lot no. 311717) were 50, 300, and 600 mg/kg/day and were administered orally by gavage. Each dose level, including the zero-level vehicle control, consisted of 20 male and 20 female Sprague-Dawley CD rats. Daily dosing was initiated in male rats 28 days prior to mating and continued through mating. Daily dosing was initiated in female rats 14 days prior to mating, continued through the mating period to Day 7 of gestation. The mating period (both sexes dosed during this timeperiod) lasted approximately three weeks. The total dosing duration to males was approximately 10 weeks.

General clinical signs were monitored twice daily during the course of the study for both male and female rats. Males and females were weighed twice weekly. Once female rats were determined to be pregnant, body weights were determined on Days 0, 3, 7, 10, and

13 of gestation. All pregnant female rats were sacrificed and necropsied on Day 13 of gestation and evaluated for gross abnormalities in the cervical, thoracic, or abdominal viscera. Cesarean section was performed and the uterine contents evaluated for implantation sites, live fetuses, and early or late resorptions. The number of corpora lutea in the right and left ovaries was also determined.

All male rats were sacrificed and necropsied after the final dose (10 week dosing period). The following tissues were excised and weighed: epididymis, testis, seminal vesicles and prostate. Any gross lesions on these organs were noted. Sperm motility and total sperm count were assessed for each male rat.

Results

No overt clinical signs of toxicity were observed in male and female rats during the study. Modest depressions in mean body weight were observed in males from the 300 mg/kg dose level but not from the 600 mg/kg dose level. The only body weight parameter that was significantly reduced at both the 300 and 600 mg/kg dose levels was total body weight gain between Day 0 and Day 70. No compound-related body weight effects were observed in female rats.

Pregnancy rates were 100 percent for each of the three ciprofloxacin dose levels. No compound-related gross pathological effects were noted in pregnant females at the scheduled sacrifice on Day 13 of gestation. There were no compound-related effects on implantation sites, live fetuses, and the number of corpora lutea. There were no compound-related effects upon the mean percent preimplantation loss and mean postimplantation loss. No pregnant dams aborted or delivered early.

Gross pathological examination of male rats revealed no compound-related effects. None of the sex organs (epididymis, testis, seminal vesicles and prostate) exhibited evidence of gross pathology and there were no compound-related effects on mean organ weight. No compound-related effects were observed on sperm count and sperm motility. In summary ciprofloxacin, at the dose levels examined, had no meaningful effect upon male and female fertility and early embryonic viability.

Study for the Effects on Pre- and Postnatal Development, Including Maternal Function, in the Rat with Ciprofloxacin HCl. (Study no. 7439-104; 80-0012).

The rat peri- and postnatal development study was contracted by the sponsor to _____
_____ The study was conducted in accordance with GLP requirements and was audited by a Quality Assurance group. The ciprofloxacin dose levels (Lot no. 311717) were 50, 300, and 600 mg/kg/day and were administered orally by gavage. Each dose level, including the zero-level vehicle control, consisted of 25 pregnant female Sprague-Dawley CD rats. Daily dosing was initiated on Gestation Day 6 and continued through Lactation Day 20.

Clinical observations were made twice daily during the dosing phase of the study. The pregnant dams were weighed on Gestation Days 0, 4, 6, 8, 10, 14, 17, and 20. After delivery, the lactating dams were weighed on Lactation Day 0, 4, 7, 10, 14, 17, and 21. Food consumption was determined on successive three day intervals during gestation. All females were sacrificed following weaning (Lactation Day 21). Gross pathological examinations were conducted for any gross abnormalities.

The offspring (F₁ pups) were weighed at birth and each litter of more than 8 pups was culled on Lactation Day 4. All remaining pups were then weighed on Lactation Days 4, 7, 14, and 21. The culled pups were necropsied and examined for viscera abnormalities (thoracic, cervical, and abdominal). Growth, development, and functionality of all remaining pups were evaluated during lactation and included: pinna unfolding (Day 1), surface righting reflex (Day 4), hair growth (Day 7), incisor eruption (Day 7), eye opening (Day 11), and auditory startle (Day 21). The F₁ pups were weaned on Day 21 and followed for the maturation phase (7 weeks). Body weights were determined weekly during the maturation phase. Maturation and developmental parameters that were measured included: vaginal opening (Day 30 postpartum), cleavage of the balanopreputial gland (Day 35 postpartum), locomotor activity and pupillary reflex (Day 22 postpartum and Week 5 postweaning), water maze and memory assessment (Week 3 postweaning). Males and females of the F₁ generation were paired for mating upon sexual maturity (Week 7 postweaning). Mating of siblings was avoided. Clinical observations were made twice daily and body weights of the pregnant dams were determined on Gestation Day 0, 7, 14, 20 and Lactation Day 0. The litter size, sex, weights, and individual offspring observations were made on the F₂ pups at birth. The F₂ pups were then sacrificed on Lactation Day 1 and necropsied.

Results

No overt clinical signs of compound-related effects were observed in the pregnant/lactating dams during the ciprofloxacin dosing period (Day 6 of Gestation through Day 20 of Lactation). Red nose crust was observed in pregnant dams dosed with ciprofloxacin and the mean body weight gain was reduced during the Gestation Day 6 through 20 period at the 300 and 600 mg/kg/day dose levels compared to the zero-level vehicle control group. No compound-related body weight effects were noted during the lactation phase. No compound-related gross pathology was observed at the terminal sacrifice of the dams after the F₁ pups were weaned on Day 21 postpartum.

No compound-related effects were determined for any of the fertility and reproduction parameters (number of dams delivering, viable pups per litter, number of stillborn pups, number of implantation sites per dam, male/female ratio, average pup weight at birth). Each litter was culled on Day 4 of lactation. The culled pups were sacrificed and necropsied; no compound-related gross pathology was observed in the culled pups. No compound-related effects were noted for body weight gain and survival of the F₁ pups during lactation (Day 4 through Day 20).

Several developmental parameters of the F₁ pups were assessed and included: pinna unfolding; incisor eruption; hair growth; surface righting reflex; auditory reflex; pupil reflex; vaginal opening; and preputial separation. No compound-related effects were observed for any of these parameters. No compound-related effects were observed for open-field testing (activity) conducted on Day 22 postpartum and Week 4 postweaning. The Water M-Maze Test was used as a measure of learning capabilities for the F₁ pups; no compound-related effects were noted in results from this test.

F₁ generation males and females were mated and no compound-related effects were observed for any of the fertility and reproduction parameters previously listed for the F₀ pregnant dams.

The only notable adverse effect for the entire study was the reduction in body weight gain during gestation for the F₀ pregnant dams dosed at the 300 and 600 mg/kg ciprofloxacin dose level. The No Observed Adverse Effect Level for the pregnant F₀ dams was 50 mg/kg. The No Observed Adverse Effect Level for reproductive and developmental (F₁ generation) effects was 600 mg/kg.

2.6.6.7 Local tolerance

No local tolerance studies were requested or submitted for this NDA.

2.6.6.8 Special toxicology study

No special toxicology studies were requested or submitted for this NDA.

2.6.6.9 Discussion and Conclusions

The genetic toxicology studies were conducted in accordance with GLP requirements and under accepted methodologies. Ciprofloxacin was negative for mutagenicity in the bacterial reverse mutation assays in the presence and absence of an hepatic S-9 enzymatic activation system. The limitation of this assay with ciprofloxacin and other fluoroquinolones is due to their bactericidal activity at concentrations as low as 200 ng per assay plate. Most bacterial reverse mutation assays are conducted at test material levels in the 10 to 1000 µg per plate range. Ciprofloxacin induced chromosomal aberrations in the CHO cell culture assay. It is plausible that ciprofloxacin and other fluoroquinolones cause this effect because of their interference with DNA duplication due to their inhibition of topoisomerase enzymes from both bacterial and mammalian sources. Ciprofloxacin was negative for *in vivo* mammalian genotoxic activity based upon results from the rat micronucleus assay. Although no bone marrow toxicity was observed at the highest dose; the 2000 mg/kg dose level was as high as reasonably could be expected. The overall genotoxicity profile for ciprofloxacin is consistent with other fluoroquinolone products and no additional genotoxicity studies with ciprofloxacin are recommended.

The 28-day repeat-dose toxicity study with beagle dogs was conducted with the drug product which at the time of the study was referred to as Ciprofloxacin GR. The product name was subsequently changed by the sponsor to Proquin™. The study was conducted to directly compare the toxicity of the sponsor's product to the approved product, Cipro® (500 mg tablet). None of the ciprofloxacin dosing regimens resulted in biologically relevant or compound-related toxicity. The highest dose was two Proquin™ tablets (equivalent to 1000 mg of ciprofloxacin) administered daily for 28 days and was the NOAEL. The plasma ciprofloxacin AUC for males and females at this dose level was approximately 20 and 38 $\mu\text{g} \cdot \text{hr/ml}$, respectively. The human AUC for the single Proquin™ tablet was approximately 7.7 $\mu\text{g} \cdot \text{hr/ml}$ which represented the proposed therapeutic dose of 500 mg ciprofloxacin. Therefore, the NOAEL in dogs was 2.6- to 4.9-fold (males and females, respectively) higher than the delivered therapeutic dose to humans based upon systemic exposure as measured by the AUC values.

The recommended battery of reproductive toxicity studies was conducted by the sponsor. The embryo/fetal developmental toxicity study in rats resulted in maternal toxicity at the highest ciprofloxacin dose level of 600 mg/kg. The only statistically significant fetal developmental effect was an elevated incidence of a 14th rudimentary rib in fetuses from pregnant dams from the 600 mg/kg dose level. No other compound-related embryo or fetal effects were observed. Fetal effects were only observed at the maternally toxic dose level of 600 mg/kg. The ciprofloxacin plasma AUC in the pregnant rats at the 600 mg/kg dose level ranged from 12 to 14 $\mu\text{g} \cdot \text{hr/ml}$ from Day 7 to Day 20 of Gestation, or 1.6- to 1.8-fold the AUC value at the proposed therapeutic dose to humans.

Pregnant rabbits were more sensitive to ciprofloxacin than pregnant rats in the embryo/fetal developmental toxicity study. Body weight gain was depressed approximately 2-fold at the highest dose level of 30 mg/kg and both the 10 and 30 mg/kg dose levels induced aborted pregnancies in a dose-dependent incidence rate. Compound-related fetal lethality and developmental effects (skeletal variations) resulted from the 30 mg/kg dose level. The NOAEL for embryo/fetal effects was 10 mg/kg (approximately 0.4-fold the human therapeutic dose based upon body surface area conversions). The NOAEL for maternal effects was 3 mg/kg and is consistent with the sensitivity of rabbits to fluoroquinolones. This sensitivity is not due to a primary toxicity of ciprofloxacin or other fluoroquinolones but is secondary to the alteration of intestinal microflora as a result of the selective bactericidal activity of fluoroquinolones. Rabbits appear to be much more sensitive to the changes in intestinal microflora compared to other laboratory species.

The rat fertility reproductive toxicity study resulted in only a minor reduction in total body weight gain for male rats over the 70-day dosing regimen at the 300 and 600 mg/kg dose levels. No effects were observed in any measure of male and female fertility and early embryonic evaluations. The NOAEL for fertility reproductive effects in both sexes was 600 mg/kg. Similarly, no peri/postnatal reproductive toxicological effects were observed in the pregnant F0 dams and the F1 pups at the highest dose level of 600 mg/kg. The only maternal effect was a slight reduction in body weight gain at the 300 and 600 mg/kg dose levels during the Day 6 through 20 gestation period. The NOAEL for

reproductive effects in both studies for pregnant female rats was 600 mg/kg or approximately 1.8- fold the proposed human therapeutic dose based upon systemic exposure as measured by plasma ciprofloxacin AUC comparisons. F1 pups from pregnant dams dosed through gestation and to Day 20 of lactation exhibited no developmental effects as a result of the ciprofloxacin dosing routines to pregnant and lactating dams. The entire battery of reproductive toxicity studies indicated little potential for reproductive toxicity due to ciprofloxacin. These results were consistent with other fluoroquinolones.

2.6.6.10 Tables and figures

No additional tables and figures were needed for this review.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Tabulated summary is not needed for this review.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

The sponsor seeks approval for Proquin™, a gastric retentive tablet containing the drug substance ciprofloxacin HCl, for uncomplicated urinary tract infection. The proposed dosing regimen of a single daily oral administration of 500 mg of the drug substance for three consecutive days is consistent with currently approved ciprofloxacin indications. The nonclinical studies submitted by the sponsor are sufficient to support approval of this indication and meet the nonclinical information needs of the product label.

Unresolved Toxicology Issues:

There are no unresolved nonclinical toxicology issues.

Recommendations:

There are no additional pharmacology/toxicology related recommendations to convey to the sponsor.

Suggested Labelling:

The labelling language proposed by the Pharmacology/Toxicology Reviewer is listed in the following paragraphs. The suggested language is in italics and the accepted language from the sponsor is in regular type.

2 Page(s) Withheld

 Trade Secret / Confidential

 / Draft Labeling

 Deliberative Process

Concurrence:

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/s/

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