

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-678**

**PHARMACOLOGY REVIEW(S)**

**PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION**

NDA Number: 21-678  
Serial Number: 000  
Date Received by Center: 10/27/03 & 5/27/04  
Product: Tequin® (Gatifloxacin) Powder for Oral  
Suspension  
Clinical Population: Adults (Men and Women)  
Sponsor: Bristol-Myers Squibb Pharmaceutical  
Research Institute  
  
Review Division: Special Pathogen and Immunologic Drug  
Products (HFD-590)  
Reviewer: Stephen G. Hundley, Ph.D., DABT  
Pharmacology/Toxicology Reviewer  
  
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Review Submission Date (DFS): 8/13/04

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## EXECUTIVE SUMMARY

### Recommendations

#### Approvability:

The current NDA seeks a powder for oral suspension as an additional dosage formulation. The sponsor does not seek additional indications and does not change the approved dose amounts for currently approved indications. The powder for oral suspension dose formulation presents no pharmacology/toxicology issues and can be approved.

#### Additional Nonclinical Studies:

Additional nonclinical studies were not needed for approval of the new dosage form of Tequin® (gatifloxacin).

#### Labelling:

The sponsor submitted to the NDA a nonclinical arthrototoxicity study in juvenile beagle dogs

The Animal Pharmacology section of the product label should contain information from this juvenile dog arthrototoxicity study and include an appropriate animal to human dose comparison based upon previous safety and pharmacokinetic studies conducted with pediatric patients. The Warning section of the product label also needs to include appropriate information from the juvenile dog arthrototoxicity study.

### Summary of Nonclinical Findings

#### Pharmacologic Activity:

The pharmacologic activity of gatifloxacin was previously described in the initial approved NDA for Tequin® (NDA 21-061; 12/17/99). Additional discussion of the pharmacological activity and antibacterial mechanism of action of gatifloxacin is not needed for this review.

#### Nonclinical Findings Overview:

The nonclinical toxicological activity of gatifloxacin was extensively documented in the original Tequin® NDA approvals (NDA 21-061 & 21-062; 12/17/99) for indications that include: acute bacterial exacerbation of chronic bronchitis, acute sinusitis, community-acquired pneumonia, uncomplicated skin and skin structure infections, complicated urinary tract infections, pyelonephritis, and uncomplicated urethral and cervical gonorrhea. Restatement of the nonclinical toxicological profile for gatifloxacin is not needed for the current Pharmacology/Toxicology Review and Evaluation.

#### Nonclinical Safety Issues:

As a class, fluoroquinolones produce arthrototoxicity in juvenile beagle dogs following 7 to 14 days of oral dosing. A juvenile dog study with gatifloxacin was included in the original NDA 21-061 submission and provided gross and histopathological evidence of arthrototoxicity at an oral dose level of 20 mg/kg/day. Histopathological evidence of arthrototoxicity was observed at an oral dose level of 10 mg/kg/day. The Clinical and Pharmacology Reviewers concluded that juvenile dog arthrototoxicity needed additional evaluation to specifically address the issues of post-dose recovery and the potential for latent arthrototoxicity during musculoskeletal maturation.

The study conducted by the sponsor examined multiple weight bearing joints during two weeks of dosing with gatifloxacin at oral dose levels of 5, 10, and 20 mg/kg/day.

No evidence (clinical and histopathological) of arthrototoxicity was observed in male and female juvenile dogs dosed for 14 days at the 5 mg/kg/day dose level at the 24-hour post-dosing terminal sacrifice. Clinical effects due to gatifloxacin dosing at 10, and 20 mg/kg dose levels were not observed during the two weeks of dosing. Beginning at Week 3, the post-dosing recovery animals exhibited clinical signs of arthrototoxicity. Two of six juvenile dogs at the 10 mg/kg dose level and six of six at the 20 mg/kg dose level exhibited minimal effects (hyperextension of the hindlimbs and forelimbs). Importantly, there were no observations of pain, lameness, or altered gait. The observed effects for all but one animal were completely resolved by Week 19.

Gross pathology at the terminal dose sacrifice detected articular cartilage blisters or vesicles in two males and one female from the 20 mg/kg dose level. Articular cartilage effects were observed by histopathology in five of six dogs at the 20 mg/kg dose level. Multiple joints in each animal were affected and included the proximal femur, distal femur, talus, and proximal humerus and were consistent with fluoroquinolone-induced articular cartilage damage. Minimal histopathology to articular cartilage was observed in one female dog and in only one joint (no effects in males) at the 10 mg/kg dose level. Electron microscopy of articular cartilage detected ultrastructural effects to chondrocytes

and the extracellular matrix in samples from animals at the 20 mg/kg dose level. Evidence of compound-related chondrocyte damage by electron microscopy was not conclusive at the 10 mg/kg dose level.

Unlike other fluoroquinolones, histopathological effects to growth plate cartilage were also observed. These effects were seen in all animals from the 10 and 20 mg/kg dose levels at the terminal dose sacrifice. The severity of these lesions was dose dependent and the lesions were observed in the proximal and distal femur, proximal humerus, and proximal tibia. Multiple joints were affected in each animal.

Gross pathology to articular cartilage was not observed at the six-month post-dose recovery sacrifice in males and females from the 5 mg/kg dosing routine and in females from the 10 mg/kg dosing routine. Articular cartilage gross pathology was observed in one male from the 10 mg/kg dosing routine and erosions in articular cartilage were observed in all but one dog (female) from the 20 mg/kg dosing routine. These erosions were observed in multiple joints from each animal and included the distal femur, proximal humerus, and distal femur. Minimal articular cartilage histopathology was observed in one male and one female from the 10 mg/kg dosing routine at the six-month post-dose recovery sacrifice. Articular cartilage histopathology was observed in multiple joints from all males and females from the 20 mg/kg dosing routine. These effects were indicative of a persistent effect although the observations were consistent with recuperative responses to an initial insult to chondrocytes. Ultrastructural analysis (electron microscopy) indicated subtle effects in animals from the 10 mg/kg dosing routine and definite effects to chondrocytes and the extracellular matrix in samples from dogs that received the 20 mg/kg dosing routine. These observations confirmed the persistence of toxicological effects to chondrocytes through the six-month post-dosing recovery period.

Histopathological examination did not detect any growth plate cartilage effects from any animals at the six-month post-dose recovery sacrifice indicating complete resolution of the effects noted at the terminal dose sacrifice.

The arthrototoxic effects to articular cartilage and chondrocytes resulted from gatifloxacin dose levels that were similar, based upon plasma AUC values, to therapeutic dose levels to pediatric patients. The representative average plasma AUC value in juvenile dogs receiving the 20 mg/kg gatifloxacin dose level was approximately 40  $\mu\text{g} \cdot \text{hr/ml}$ . AUC values in pediatric patients ranged from 28 to 43  $\mu\text{g} \cdot \text{hr/ml}$ . The no effect level for arthrototoxicity in this study is 5 mg/kg with an average AUC value of 8.6  $\mu\text{g} \cdot \text{hr/ml}$  (approximately 0.3 times the lowest therapeutic AUC in pediatric patients). One recovery male from the 5 mg/kg dose level exhibited an articular cartilage lesion, however this may not be compound related due to the absence of any precursor lesions in any of the other animals at this dose level and an absence of dose response (severity of histopathological classification) when compared to the 10 mg/kg six-month post-dose recovery group.

## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 DRUG INFORMATION

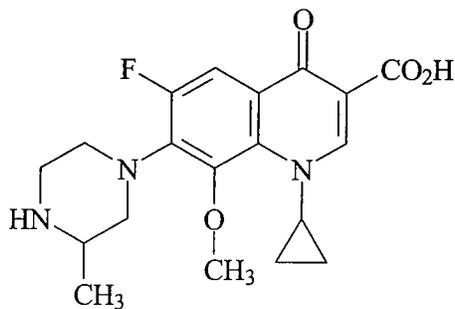
**NDA:** 21-678  
**Type of Submission:** Original (new formulation)  
**Review Number:** 1  
**Date of Submission:** 10/27/03 & 5/27/04  
**Information to Sponsor:** Yes ( ) No (x)

**Sponsor:** Bristol-Myers Squibb Company  
5 Research Parkway  
Wallingford, CT 06492-7660  
203-677-6163

**Reviewer:** Stephen G. Hundley, Ph.D., DABT  
Pharmacology/Toxicology Reviewer  
**Review Division:** Special Pathogen and Immunologic Drug Products  
HFD-590  
**Review Completion Date:** 8/2/04

#### Drug Information:

**Drug Product:** Tequin® (Gatifloxacin) powder for oral suspension  
**Generic Name:** Tequin® (Gatifloxacin)  
**Drug Substance:** Gatifloxacin sesquihydrate  
**Chemical Name:** (±)-1-Cyclopropyl-6-fluoro-1,4,-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate  
**CAS#:** 180200-66-2  
**Molecular Formula:** C<sub>19</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>4</sub> • 1 1/2 H<sub>2</sub>O  
**Molecular Weight:** 402.4  
**Molecular Structure:**



**Related Submissions:** IND's 52,081 & 53,521; NDA's 21-061 & 21-062

**Drug Class:** Antimicrobial (Fluoroquinolone)

**Intended Population:** Adults (men and women)

**Indications:** Currently approved for: acute exacerbation of chronic bronchitis; community-acquired pneumonia; complicated urinary tract infections; uncomplicated urinary tract infections; pyelonephritis; uncomplicated urethral and cervical gonorrhea

**Clinical Formulation:** Tequin® (Gatifloxacin) powder for oral suspension; 40 mg/ml

**Route of Administration:** Orally

**Proposed Use:** 400 mg orally in 10 ml daily for 7 to 14 days

**Disclaimer:**

Tabular and graphical information were constructed by the reviewer unless cited otherwise.

**Studies Reviewed within this submission:**

BMS-206584: Two-Week Oral Articular Toxicity Study in Juvenile Dogs with Six-Month Recovery Period, (Study No. DN02053).

## **2.6.2 PHARMACOLOGY**

### **2.6.2.1 Summary**

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

### **2.6.2.2 Pharmacodynamics (primary)**

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

**2.6.2.3 Pharmacodynamics (secondary)**

Secondary pharmacodynamics is not applicable.

**2.6.2.4 Safety Pharmacology**

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

**2.6.2.5 Pharmacodynamic drug interactions**

Pharmacodynamic drug interactions is not applicable.

**2.6.3 PHARMACOLOGY TABULATED SUMMARY**

Tabulated summary 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**

Tabulated summary is not needed for this review.

**2.6.6 TOXICOLOGY****2.6.6.1 Toxicology Summary**

Toxicology summary is not needed for this review.

The following nonclinical toxicology sections are not needed for this review (2.6.6.2 through 2.6.6.7).

**2.6.6.2 Single-dose toxicity**

**2.6.6.3 Repeat-dose toxicity**

**2.6.6.4 Genetic toxicity**

**2.6.6.5 Carcinogenicity**

**2.6.6.6 Reproductive and developmental toxicity**

**2.6.6.7 Local tolerance**

**2.6.6.8 Special toxicology study**

*BMS-206584: Two-Week Oral Articular Toxicity Study in Juvenile Dogs with Six-Month Recovery Period, (Study No. DN02053).*

The sponsor (Bristol-Myers Squibb Pharmaceutical Research Institute) contracted the juvenile dog arthrotoxicity study to

The study was conducted in accordance with GLP requirements and was audited by a Quality Assurance Group. Juvenile male and female beagle dogs approximately 3 months of age were divided into the following dose groups; 0, 5, 10, and 20 mg/kg (gelatin capsules; gatifloxacin batch number O0X5690; analytical purity). Each dose group consisted of six males and six females; all juvenile dogs received a single daily oral dose for fourteen consecutive days. Half of the juvenile dogs at each dose level were sacrificed approximately 24 hours after the terminal dose. The remaining juvenile dogs were held for a six-month post-dose recovery period and then sacrificed.

During the course of the study, twice daily clinical evaluations were made of each animal while more extensive physical examinations were conducted once weekly on each animal by a veterinarian until termination of the six-month post-dose recovery period. The physical examinations included observations of the general conditions of the skin, eyes, nose, oral cavity, abdomen, genitalia, respiration, and extensive evaluations of the joints and locomotion. Body weights were determined twice weekly during the dosing phase and once weekly during the post-dosing period. Food consumption was visually estimated on a daily basis.

Serial blood samples were drawn from each juvenile dog in the gatifloxacin dose groups after oral dose administration on Day 9 (1, 2, 4, 6, 8, and 24 hours post-dosing). Plasma gatifloxacin concentrations were determined for the purpose of generating pharmacokinetic values.

Gross pathological examinations were conducted on each animal at the scheduled sacrifices. Necropsies consisted of external and detailed internal examinations with gross examinations of the following weight-bearing joints:

Scapulo-humeral joint (scapula/proximal humerus)

Humero-radial joint (distal humerus/proximal radius/proximal ulna)  
Carpal joint (distal radius/distal ulna)  
Proximal ulna/radius  
Coxo-femoral (acetabulum/proximal femur)  
Femoro-tibial joint (distal femur/proximal tibia)  
Tarsal or stifle joint (distal tibia/tibial-tarsal bone)

Gross lesions were described, measured, and graded following disarticulation of each of the previously listed joints.

Bone and articular cartilage were obtained from the weight-bearing joints listed below and preserved for both light- and electron-microscopic analysis.

Proximal femur (left & right)  
Distal femur (left & right)  
Proximal humerus (left & right)  
Proximal tibia (left & right)  
Talus (left & right)  
Ulna/radius (only lesions were analyzed)

Samples from these joints were prepared for light microscopy from each animal at each dose group at the terminal and post-dose recovery sacrifices. The preserved samples were decalcified, processed, and sectioned then stained with hematoxylin and eosin for morphological evaluation and with Safranin-O (fast green counterstain) for proteoglycan evaluation. Six slides from each joint were generated with alternating hematoxylin/eosin and Safranin-O staining.

Biopsy samples from the articular surface of the proximal humerus and proximal femur from each animal from the zero-level control and the 10 and 20 mg/kg dose levels (terminal and post-dose recovery sacrifices) were processed for electron microscopy (ultrastructural analysis). Five micrographs were prepared for each sample.

Results from the study indicated no body weight or food intake effects at any dose level of gatifloxacin during the two-week dosing phase. Additionally, there were no observations of adverse clinical effects during the dosing phase. The post-dose recovery dogs exhibited no compound-related effects on body weight gain. The juvenile dogs approximately doubled their body weight during the course of the post-dose recovery period.

No clinical evidence of arthrotoxicity was observed during the two-week dosing period at any gatifloxacin dose level and no effects were observed during the post-dose recovery period for male and female dogs that received the 5 mg/kg dose level. Clinical evidence of arthrotoxicity was observed beginning with Week 3 of the study in animals from the 10 and 20 mg/kg dose levels. Hyperextension of the hind- and forelimbs was observed and was defined as laxity of limb joints absent clinical lameness, hyperextension of the carpal and metacarpal joints, hyperflexion of tarsal joints, and hyperextension of

metatarsal joints. Hyperextension of forelimbs was observed in 1 of 3 males and 1 of 3 females from the 10 mg/kg dose level beginning at Week 3, and persisting as long as Week 19. The effects were graded as minimal. Hyperextension of forelimbs was observed in 2 of 3 males and 2 of 3 females from the 20 mg/kg dose level while hyperextension was noted in forelimbs and hindlimbs from the remaining male and female beagle dogs. The clinical effects were resolved by Week 19 for all but one dog. Minimal effects persisted for one female dog until Week 26. No lameness or altered gait was reported at any gatifloxacin dose level.

Gross pathology at the terminal dose sacrifice focused on weight-bearing joints. No compound-related gross pathology was noted in joints from male and female dogs at the 5 and 10 mg/kg dose levels. At the 20 mg/kg dose level, vesicles or blisters were observed on the surface of the articular cartilage in 2 of 3 males and 1 of 3 females. These vesicles were observed on the proximal humerus and proximal femur. Compound-related histopathology was not observed in male and female dogs from the 5 mg/kg dose level. Histopathological effects were observed in the articular and growth plate cartilage in dogs from the 10 and 20 mg/kg dose levels and are detailed in the following table.

#### Histopathology at the Terminal Dose Sacrifice

10 mg/kg Dose Level	
Articular Cartilage	Growth Plate Cartilage
1 of 3 Females: Chondrocyte Clusters and Moderate Reduction in Proteoglycan Staining (possibly compound-related)	3 of 3 Males and 3 of 3 Females: Minimal to Mild Disorganization of Chondrocyte Columns and Reduction in Proteoglycan Staining (Multiple Joints in each animal)
No Effects Observed in Males	
20 mg/kg Dose Level	
3 of 3 Males and 2 of 3 Females: Vesicles, Chondrocyte Clusters, Hypocellularity, Perpendicular & Parallel Collagen Fibers, Marked Reduction in Proteoglycan Staining  [Multiple Joints in Each Animal]	3 of 3 Males and 3 of 3 Females; Moderate to Marked Disorganization of Chondrocyte Columns and Moderate to Severe Reduction in Proteoglycan Staining.  [Multiple Joints in Each Animal]

Histopathology of articular cartilage cited in the previous table was observed in the proximal femur, distal femur, talus, and proximal humerus. The histopathological effects observed in the growth plate cartilage were observed in the proximal and distal femur, proximal humerus, and proximal tibia.

No gross pathological effects were noted in male and female dogs from the 5 mg/kg dose routine and in female dogs from the 10 mg/kg dose routine at the six-month post-dose recovery sacrifice. Only one of three males from the 10 mg/kg dosing routine exhibited an erosion in articular cartilage (distal femur). Articular cartilage erosions were observed

in 3 of 3 males and 2 of 3 females from the 20 mg/kg dosing routine. These erosions were observed in multiple joints from each animal that included the distal femur, proximal humerus, and distal femur.

No histopathological effects were noted in the growth plate cartilage at the six-month post-dose recovery sacrifice in animals from any of the gatifloxacin dosing routines. No compound-related histopathology was observed in the articular cartilage from female dogs at the 5 mg/kg dose level. One male dog from the 5 mg/kg dose level exhibited articular cartilage histopathology (erosion, chondrocyte hypercellularity and proteoglycan reduction) in one joint but was not thought to be compound related. Minimal effects to articular cartilage were noted in 1 of 3 males and 1 of 3 females from the 10 mg/kg dose level and were described as articular cartilage surface irregularity, chondrocyte cloning, and slight to moderate reduction in proteoglycan staining. Only one joint was involved in each animal.

Compound-related histopathological effects were noted in all male and female dogs in the post-dose recovery group that had received the 20 mg/kg dose of gatifloxacin for 14 days. Observations included clefts or erosions that ranged in severity (transitional to radial to calcified zones and disorganized cartilage), chondrocyte hypocellularity, chondrocyte cloning, reduced proteoglycan (mild to total absence), and cartilage crossed with blood vessels. These effects were noted in multiple joints in 2 of 3 males and 1 of 3 females. Single joints were involved in the remaining animals. The joints most commonly involved included the distal femur, proximal humerus, and distal humerus although histopathological effects were also noted less frequently in the proximal femur, proximal tibia, and talus.

Ultrastructural changes were evaluated by electron microscopy in all male and female beagle dogs from the zero-level vehicle control, 10 mg/kg, and 20 mg/kg dose levels (terminal dose and post-dose recovery groups). Compound-related effects were not unequivocally established in electron micrographs from male and female dogs in the 10 mg/kg terminal sacrifice group. Effects were observed primarily in electron micrographs from the proximal humerus and proximal femur from all male and female beagles at the 20 mg/kg dose level. The chondrocyte effects included swelling of the rough endoplasmic reticulum, cytoplasmic vacuolation, and larger than normal chondrocytes. Cartilage matrix effects included increased vacuolation of the territorial matrix, electron dense particle accumulation in the territorial and extracellular matrices, clumped collagen fibrils, and less organized extracellular matrix (compared to non-dosed controls). These effects are associated with chondrocyte damage.

Electron micrographs from the post-dose recovery groups indicated a subtle but observational difference between the zero-level control and 10 mg/kg groups. A slight increase in degenerate or degenerating chondrocytes was observed in electron micrographs from the 10 mg/kg dose group. Higher incidences of variable-sized disorganized collagen fibrils and variable-sized electron dense particles were observed in the territorial and extracellular matrices. Ultrastructural effects were more pronounced in electron micrographs from all animals in the 20 mg/kg post-dose recovery group. The

incidence of degenerate chondrocytes and clumped vimentin filaments was higher as was the occurrence of multiple chondrocytes in one nest. The matrix effects included disorganized extracellular matrix, lipid debris, proteoglycan deposits, and vacuolation of territorial and extracellular matrices. These observations were indicative of toxicological insult to chondrocytes as a result of dosing with gatifloxacin for 14 days that resulted in degeneration during the six-month recovery period with indications that chondrocytes had not recovered.

The toxicokinetic data from all animals at the 5, 10, and 20 mg/kg dose levels provided a basis for comparing systemic exposure to gatifloxacin between juvenile dogs and pediatric patients. The following table lists the average toxicokinetic values.

Average Values  
(Six per sex per dose)

	5 mg/kg		10 mg/kg		20 mg/kg	
	Male	Female	Male	Female	Male	Female
C <sub>max</sub> ( $\mu\text{g}/\text{ml}$ )	1.15	1.12	3.6	2.8	5.3	5.2
T <sub>max</sub> (hr)	1.5	2	3	3	2	2
AUC ( $\mu\text{g} \cdot \text{hr}/\text{ml}$ )	8.6	8.6	22	21	40.3	42.1

The C<sub>max</sub> and AUC values increased in proportion to the increased dose level. Gatifloxacin AUC in juvenile dogs (males and females) averaged approximately 40  $\mu\text{g} \cdot \text{hr}/\text{ml}$  at the 20 mg/kg dose level. Clinical studies with pediatric patients of different age groups generated AUC values that ranged in average from 28 to 43  $\mu\text{g} \cdot \text{hr}/\text{ml}$  and C<sub>max</sub> values ranging from 3.5 to 4.2  $\mu\text{g}/\text{ml}$  following a proposed oral therapeutic dose level of 10 mg/kg (Phase I PK & Safety Clinical Trial). Therefore, the systemic exposure to gatifloxacin was similar between juvenile dogs and pediatric patients at the 20 mg/kg dose level administered to juvenile dogs in the arthrotoxicity study.

#### 2.6.6.9 Discussion and Conclusions

Clinical effects due to gatifloxacin dosing were not observed during the two weeks of dosing at any dose level. Beginning at Week 3, two of six juvenile dogs at the 10 mg/kg dose level and six of six at the 20 mg/kg dose level (post-dosing recovery groups) exhibited hyperextension of the hindlimbs and forelimbs that were categorized as minimal effects. Importantly, there were no observations of pain, lameness, or altered gait. The observed effects did not become more severe and for all but one animal were completely resolved by Week 19.

Gross pathology at the terminal dose sacrifice detected articular cartilage blisters or vesicles in two males and one female from the 20 mg/kg dose level on the proximal

humerus and proximal femur and was consistent with fluoroquinolone-induced articular cartilage damage. Articular cartilage histopathology, classified as minimal in one joint, was observed in only one female dog at the 10 mg/kg dose level (no effects in males). This observation was not unequivocally compound-related. Articular cartilage effects were observed in five of six dogs at the 20 mg/kg dose level. Multiple joints in each animal were affected and included the proximal femur, distal femur, talus, and proximal humerus. Electron microscopy of articular cartilage detected ultrastructural effects to chondrocytes and the extracellular matrix in samples from animals at the 20 mg/kg dose level. Equivocal evidence of compound-related chondrocyte damage by electron microscopy was observed at the 10 mg/kg dose level.

Unlike other fluoroquinolones, histopathological effects to growth plate cartilage were also observed. These effects were seen in all animals from the 10 and 20 mg/kg dose levels at the terminal dose sacrifice. The severity of these lesions was dose dependent with lesions observed in multiple joints (proximal and distal femur, proximal humerus, and proximal tibia).

Gross pathology to articular cartilage persisted to the six-month post-dose recovery sacrifice in one male from the 10 mg/kg dosing routine and all but one female dog from the 20 mg/kg dosing routine. Articular cartilage erosions were observed in multiple joints from each animal and included the distal femur, proximal humerus, and distal femur.

Articular cartilage histopathology also persisted in one male and one female from the 10 mg/kg dosing routine and in all males and females from the 20 mg/kg dosing routine. These effects were indicative of a persistent effect although the observations were consistent with recuperative responses to an initial cellular insult to articular cartilage chondrocytes. Histopathological examination did not detect any growth plate cartilage effects from any animals at the six-month post-dose recovery sacrifice indicating complete resolution of the effects noted at the terminal dose sacrifice. Ultrastructural analysis (electron microscopy) also indicated subtle effects in animals from the 10 mg/kg dosing routine and definite effects to chondrocytes and the extracellular matrix in samples from dogs that received the 20 mg/kg dosing routine.

The clinical, pathological, histopathological, and ultrastructural effects to articular cartilage and chondrocytes resulted from gatifloxacin dose levels that were similar, based upon plasma AUC values, to proposed therapeutic dose levels in pediatric patients. The representative plasma AUC values in juvenile dogs receiving the 10 and 20 mg/kg gatifloxacin dose levels were approximately 21 and 40  $\mu\text{g} \cdot \text{hr}/\text{ml}$ , respectively, compared to AUC values in pediatric patients that ranged from 28 to 43  $\mu\text{g} \cdot \text{hr}/\text{ml}$ . Growth plate cartilage histopathology also resulted from the 10 and 20 mg/kg dose levels at the time of the terminal dose sacrifice and were resolved during the six-month post-dosing recovery period. Histopathological effects to the articular cartilage persisted during the six-month post-dosing recovery period at the 10 and 20 mg/kg dose levels. The apparent no effect level for arthrototoxicity in this study is 5 mg/kg with an average AUC value of 8.6  $\mu\text{g} \cdot \text{hr}/\text{ml}$  (approximately 0.3-times the lowest therapeutic AUC in pediatric patients). One

recovery male from the 5 mg/kg dose level exhibited an articular cartilage lesion, however, this lesion may not be compound related due to the absence of any lesions in any of the other animals at this dose level and an absence of dose response (severity of histopathological classification) relative to the 10 mg/kg six-month post-dose recovery group.

#### **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 a powder for oral suspension of Tequin® using an approved dosing regimen for currently approved indications. The nonclinical toxicology and pharmacology studies submitted to support these approved indications are sufficient to support approval of the powder for oral suspension formulation.

#### Unresolved Toxicology Issues:

There are no unresolved nonclinical toxicology issues relative to the powder for oral suspension formulation and the currently approved indications.

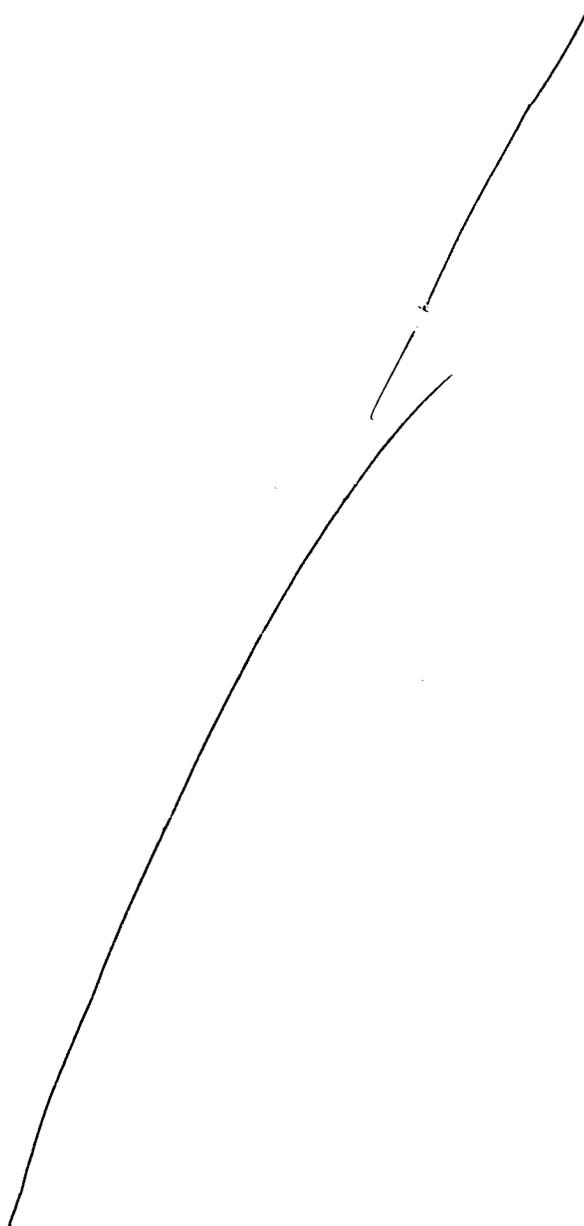
#### Recommendations:

The sponsor needs to include language in the labelling describing the new information from the juvenile dog arthrototoxicity study; specifically regarding the persistence of articular cartilage histopathology during the six-month post-dosing period of musculoskeletal maturation.

#### Suggested Labelling:

The sponsor provided product labelling language that did not include information from the juvenile dog arthrototoxicity study reviewed in the current NDA submission. The Pharmacology/Toxicology Reviewer added appropriate language to the WARNING, PRECAUTIONS (Pediatric Use), and ANIMAL PHARMACOLOGY sections. The

italicized wording was taken from the sponsors proposed label and will remain unchanged.



The remaining language in the Carcinogenesis, Mutagenesis, Impairment of Fertility; Pregnancy Category; and Animal Pharmacology sections of the proposed label are

identical to the currently approved label for Tequin®. The Pharmacology/Toxicology Reviewer does not recommend any changes to these segments of the product label.

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Stephen G. Hundley, Ph.D., DABT  
Acting Team Leader & Pharmacology/Toxicology Reviewer  
Division of Special Pathogen and Immunologic Drug Products

Concurrence:

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Steve Gitterman, M.D.  
Deputy Division Director  
Division of Special Pathogen and Immunologic Drug Products  
HFD-590

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/s/

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Steve Hundley  
8/13/04 08:53:56 AM  
PHARMACOLOGIST

Renata Albrecht  
8/17/04 02:52:05 PM  
MEDICAL OFFICER