

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-678

CHEMISTRY REVIEW(S)



NDA 21-678

Tequin® (gatifloxacin) Powder for Oral Suspension

Bristol-Myers Squibb

**Balajee Shanmugam
Division of Special Pathogen and
Immunologic Drug Products
HFD-590**



Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
The Executive Summary	8
I. Recommendations.....	8
• A. Recommendation and Conclusion on Approvability.....	8
• B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	8
II. Summary of Chemistry Assessments	8
• A. Description of the Drug Product(s) and Drug Substance(s)	8
• B. Description of How the Drug Product is Intended to be Used	9
• C. Basis for Approvability or Not-Approval Recommendation	9
III. Administrative.....	10
• A. Reviewer’s Signature	10
• B. Endorsement Block	10
• C. CC Block.....	10
Chemistry Assessment.....	11
I. DRUG SUBSTANCE.....	11
• 1. Regulatory Specification	11
II. DRUG PRODUCT	11
• 1. Components/Composition	11
• 2. Specification & Methods For Drug Product Ingredients.....	13
a. Active Ingredient(s).....	13
b. Inactive Ingredients	14



- **3. Manufacturer15**
- **4. Methods Of Manufacturing And Packaging16**
 - a. Production Operations..... 16
 - b. In-Process Controls & Tests..... 21
 - c. Reprocessing Operations 22
- **5. Regulatory Specification And Methods For Drug Product23**
 - a. Sampling Procedures 23
 - b. Regulatory Specification And Methods..... 23
 - c. Batch Analyses on Drug Product 33
- **6. Container/Closure System.....34**
- **7. Microbiology.....35**
- **8. Drug Product Stability35**
- III. INVESTIGATIONAL FORMULATIONS41**
- IV. ENVIRONMENTAL ASSESSMENT43**
- V. METHODS VALIDATION43**
- VI. LABELING44**
- VII. ESTABLISHMENT INSPECTION45**
- VIII. DRAFT DEFICIENCY LETTER45**



Chemistry Review Data Sheet

1. NDA 21-678

2. REVIEW #: 1 (Drug Product)

See Chemistry Review for NDA 21-061 (TEQUIN[®] tablets, 200 mg and 400 mg), prepared by Dr. John Smith for drug substance CMC.

3. REVIEW DATE: 24-Aug-04

4. REVIEWER: Balajee Shanmugam, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original NDA

27-OCT-2003

BC (Confirmation of facilities)

03-FEB-2004

BC (Response and stability update)

20-JUL-2004

BC (Response)

04-AUG-2004

BL

24-AUG-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Bristol-Myers Squibb

Address: 5 Research Parkway, P.O. Box 5100
Wallingford, CT 06492

Representative: Joan Fung-Tomc, Ph.D.
Director, Regulatory Science

Telephone: (203) 677-6370

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Tequin®
b) Non-Proprietary Name (USAN): gatifloxacin
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Powder for oral suspension

12. STRENGTH/POTENCY: 40 mg/ml

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

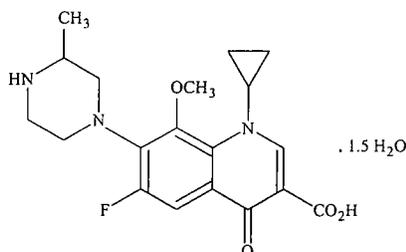
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate.

Molecular Formula: $C_{19}H_{22}FN_3O_4 \cdot 1.5 H_2O$

Molecular Weight: 402.42





CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
				4	Adequate		
	II			3	Adequate		
	II			1	Adequate	JAN-2004	
	II			1	Adequate	APR-2004	
	II			3	Adequate		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-061	TEQUIN [®] Tablets

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a		
EES	Acceptable	23-AUG-2004	Janine M. D Ambrogio
Pharm/Tox	n/a		
Biopharm	n/a		
LNC	n/a		
Methods Validation	To be determined		
DMETS	Revisions recommended	16-AUG-2004	Felicia Duffy
EA	Categorical exclusion acceptable	12-JUL-2004	B. Shanmugam
Microbiology	n/a		



The Chemistry Review for NDA 21-678

The Executive Summary

I. Recommendations

• A. Recommendation and Conclusion on Approvability

The application is recommended for approval from the chemistry, manufacturing and controls perspective.

• B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

• A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is a powder for oral suspension (POS) which will be commercially supplied in plastic bottles providing 1 g, 2 g, 3 g, or 4 g of gatifloxacin. Upon constitution of the dry powder with water, the oral suspension will provide 40 mg/ml gatifloxacin.

The powder contains the following common compendial -grade excipients: xylitol, aspartame, microcrystalline cellulose and sodium carboxymethylcellulose, methylparaben, polyparaben, titanium dioxide and sucrose and two non-compendial excipients spray dried artificial guarana flavor and cream de vanilla powder (natural and artificial) with 5% silicon dioxide. The two non-compendial excipients have been adequately described in the application and also referenced to their respective DMFs. Long-term stability studies indicate that the drug product is stable at 25°C/60% RH and constitution stability studies indicate it to be stable for up to 14 days at 5°C.

Gatifloxacin is a synthetic broad-spectrum 8-methoxyquinolone antibacterial compound. It kills bacteria by targeting DNA gyrase (topoisomerase II) and topoisomerase IV the two most important enzymes for bacterial DNA replication, transcription, repair and recombination. The drug substance has been approved by the Agency and is marketed as tablets and injection.



Executive Summary Section

B. Description of How the Drug Product is Intended to be Used

Gatifloxacin powder for oral suspension (POS) is indicated for adults. Gatifloxacin tablets and intravenous injection have been approved by the Agency to treat the following indications: acute bacterial exacerbation of chronic bronchitis; community-acquire pneumonia; complicated and uncomplicated urinary tract infections; pyelonephritis; uncomplicated urethral and cervical gonorrhea and uncomplicated skin and skin structures. Tequin® for oral suspension will be supplied in various sizes: 25 ml, 50 ml, 75 ml, and 100 ml (commercial). The sponsor have submitted data to indicate that Tequin® POS is bioequivalent to the currently marketed Tequin® tablets and therefore seek approval for indications in the product insert for Tequin® tablets. Note that in correspondence dated July 26, 2004, the applicant has indicated that they will not be providing the [redacted] that was originally proposed. The applicant has requested a 24 month shelf-life for drug product stored at 25°C and a 14-day use period for the constituted drug product refrigerated (2°C-8°C)

C. Basis for Approvability or Not-Approval Recommendation

The drug substance gatifloxacin used in the manufacture of Tequin® tablets and intravenous dosage forms has been previously approved by the Agency and reference to the corresponding CMC reviews is provided above. Manufacturing of the [redacted]

[redacted] gatifloxacin POS has been adequately described. Stability studies indicate that the drug product is stable and shows no apparent trend. The studies also support the proposed storage condition and shelf-life. The sponsor has also committed to conduct stability post-approval on the first three production lots to include each fill size and at least one lot each year thereafter to include the largest and smallest fill size.

There were some minor CMC issues and these were communicated to the applicant. At this time point, all CMC issues have been adequately negotiated with the applicant. The drug substance and drug product manufacturing and testing facilities were inspected for cGMP compliance and the Office of Compliance has issued an overall recommendation of Acceptable for this NDA. The labeling information provided was found to be adequate. The firm was provided with the recommendations made by DMETS and the applicant has accepted most of the CMC-related recommendations and has committed to incorporate the same in the label. BMS did not accept two minor DMETS recommendations. The revisions to the carton and container labeling and package insert presented on August 24, 2004 are acceptable from a CMC perspective.



Executive Summary Section

III. Administrative

• **A. Reviewer's Signature**

{see Electronic Signature Page}

• **B. Endorsement Block**

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

• **C. CC Block**

35 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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

/s/

Balajee Shanmugam
8/24/04 04:05:32 PM
CHEMIST
N21-678 ChemRev1

Mark Seggel
8/24/04 04:11:53 PM
CHEMIST