CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-821

CHEMISTRY REVIEW(S)

NDA 21-821

Tygacil
(tigecycline) for injection

Wyeth Pharmaceuticals

Shrikant N. Pagay
Anti-Infective Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-821

2. REVIEW #: 1

3. REVIEW DATE: 2/11/05

4. REVIEWER: Shrikant N. Pagay

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	9/27/04
Amendment (stability update)	3/10/2005
Amendment (Response to deficiency comments)	3/18/05
Amendment (Response to deficiency comments)	5/4/05
Correspondence (Response to deficiency comments)	5/27/05
Amendment (Response to label comments)	6/2/05
Amendment (update)	6/13/05

7. NAME & ADDRESS OF APPLICANT:

Name:	Wyeth Pharmaceuticals
Address:	P. O. Box 8299, Philadelphia, PA 19101-8299
Representative:	Mr. Norris Pyle
Telephone:	(484)- 865- 3218

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Tygacil
b) Non-Proprietary Name (USAN): Tigecycline
c) Code Name/# (ONDC only): GAR-936; WAY 156936
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P
-

9. LEGAL BASIS FOR SUBMISSION: 505 (b)

10. PHARMACOL. CATEGORY: Anti-infective

11. DOSAGE FORM: Injectable (lyophilized powder)

12. STRENGTH/POTENCY: 50 mg/vial

13. ROUTE OF ADMINISTRATION: Injectable

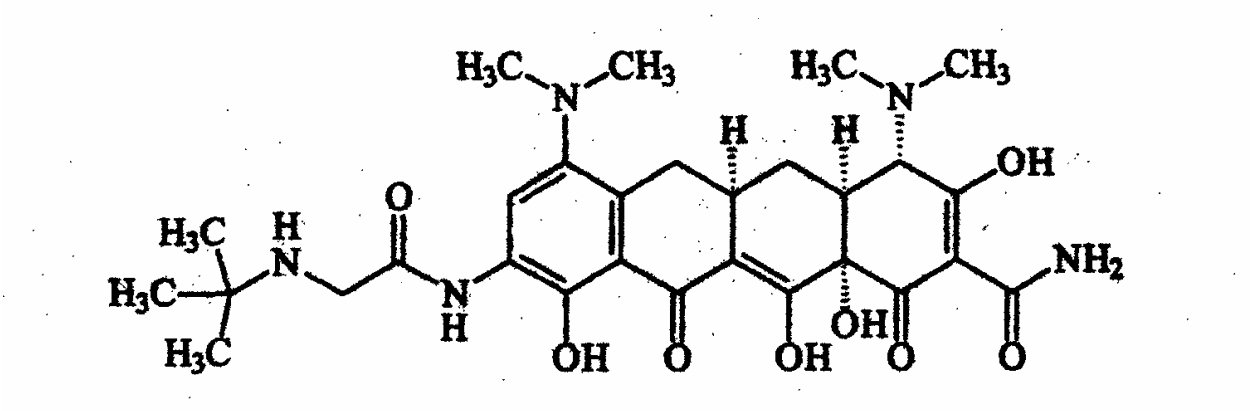
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Empirical Formula: $C_{29}H_{39}N_5O_8$
Molecular Weight: 585.66
Chemical Name: [4S-(4α,4aα,5aα,12aα)]-4,7-Bis(dimethylamino)-9-[2-(1,1-dimethylethyl)acetylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.
Laboratory Codes: Tigecycline; GAR-936; WAY-156936; RS 738-6; 898595C.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	5/12/2004	
	III	(b) (4)	(b) (4)	3	Adequate	5/24/2004	

[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)

B. Other Documents: NA

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	56,518	Original & Amendments

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	3/8/05	Office Of Compliance
Pharm/Tox	NA		
Biopharm	NA		
LNC	Acceptable	5/16/05	Consult
Methods Validation	Satisfactory	5/2/2005	Consult - OPS Laboratory
OPDRA	Acceptable	3/18/05	Consult
EA	Acceptable	6/14/05	CMC Review
Microbiology	Satisfactory	3/23/05	Bryan Riley- consult

19. COMMENTS:

Please note that all italicized portion of Chemistry Assessment Section are reviewer's comments. The remaining information (data, figures and some responses to deficiencies) is directly incorporated from the submission. This does not apply to the Chemistry Review Data Sheet and the Executive Summary Sections.

Regulatory specifications, i.e., specifications agreed upon CMC review, EER, expiration date of the drug substance and shelf life of the drug product, stability study commitments are listed in the Appendix section for quick reference.

The Chemistry Review for NDA 021-821

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommendation to approve NDA 21-821 from CMC consideration.

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

NA

II. Summary of Chemistry Assessments

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

Drug Substance

Tigecycline is a tertiary-butyl glycyl substituted analogue of minocycline. Both tigecycline and minocycline are semi-synthetic tetracycline class of drugs. The chemical structure qualifies it as an new molecular entity. It is a broad spectrum antibiotic. The drug substance is an orange colored odorless powder and melts at (b) (4) Tigecycline is (b) (4) However, the proposed drug substance (b) (4) The synthesis for tigecycline is a (b) (4)

The drug is (b) (4) Tigecycline has (b) (4). The drug substance is freely soluble (b) (4) as well as at pH (b) (4) and (b) (4) The drug is unstable in aqueous solution, and susceptible to oxidation. However, it is stable as solid when placed in the proposed packaging of (b) (4) glass bottles and stored between (b) (4) for at least 18 months. It is poorly absorbed through the gastro-intestinal tract. The manufacturer of the drug substance is (b) (4)

Drug Product

The drug product is a sterile lyophilized powder (50 mg/vial) constituted with normal (0.9%) saline or 5% dextrose as an injectable solution. Tigecycline could not be developed as a tablet or capsule or oral suspension due to poor oral biovailability. Also, (b) (4) were necessary to manufacture a sterile drug product (b) (4). Formulation and process development studies were performed to determine the effects of (b) (4) Based on the results of these studies, a stable formulation was developed that contains simply the drug substance, (b) (4) The product is manufactured by (b) (4) lyophilization, filling and packaging into vials. Each of these unit operations involves several steps and in-process controls. The process controls include (b) (4) operations. A (b) (4) overage i.e. fill weight of (b) (4) for the 50 mg per vial was necessary to account for the losses during withdrawal of the 50 mg from each vial. The lyophilized drug powder in a dry state is stable for up to 18 months when stored at 25ºC/.60% RH. The drug is further diluted into IV bags immediately upon constitution of the vial. The drug product is manufactured at Wyeth's Carolina, Puerto Rico facility by (b) (4)

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

The drug product is intended to be used intravenously following infections in complicated skin and skin structure and complicated abdominal infections. Each vial contains 53 mg tigecycline lyophilized powder constituted with 5.3 mL of normal saline or 5% dextrose solution to achieve a final concentration of 10 mg/mL. Thereafter, 5 mL of the reconstituted solution should be immediately withdrawn from the vial and added to a 100 mL IV bag for infusion. For 100 mg dose, transfer 2 reconstituted vials into the IV bag. The maximum concentration of reconstituted solution in the IV bag should not exceed 1 mg/mL. The reconstituted solution should be orange or yellow in color; if it is discolored, e.g., green or black, then, discard the solution. Examine the solution for particulate matter. The reconstituted solution in the IV bag is stable at room temperature for up to 6 hours and in refrigerator for up to 24 hours. The recommended dosage regimen is an initial dose of 100 mg followed by 50 mg every 12 hours. The infusion time is between 30 to 60 minutes.

C. Basis for Approvability or Not-Approval Recommendation

Critical CMC Considerations for the Approval of NDA 21-821

Both the drug substance and drug product are well characterized. The manufacturing processes are well established. The shelf life for both the drug substance and the drug product are based on sufficient stability data for batches stored under long term storage conditions. The in-process and final drug substance and drug product specifications are set with full justification.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Shrikant N. Pagay
ChemistryTeamLeader Name/Date: James Vidra
Project Manager Name/Date: Judit Milstein

C. CC Block

75 Pages Have Been Withheld In Full as b4 (CCI/TS) Immediately Following This Page

---

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

/s/

Shrikant Pagay
6/15/05 10:52:53 AM
CHEMIST

Jim Vidra
6/15/05 11:14:31 AM
CHEMIST

Norman Schmuff
6/15/05 11:25:25 AM
CHEMIST