

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209481Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA 209481- Multi-disciplinary Review and Evaluation

Application Type	NDA 505(b)(2)
Application Number	209481
Priority or Standard	Standard
Resubmit Date	October 09, 2017
Received Date	October 09, 2017
PDUFA Goal Date	April 10, 2018
Extended Goal Date	July 10, 2018
Division/Office	DAIP/OAP
Review Completion Date	See DARRTS electronic signature page
Established Name	Vancomycin hydrochloride
(Proposed) Trade Name	Vancomycin Hydrochloride for Injection, USP
Pharmacologic Class	Glycopeptide antibacterial
Applicant	MYLAN Pharmaceuticals, Inc
Formulation(s)	250 mg/vial, 750 mg/vial, 1.25 g/vial, and 1.5 g/vial
Proposed Indication(s)/Population(s)	<ul style="list-style-type: none"> •Septicemia •Infective Endocarditis •Skin and skin structure infections •Bone infections •Lower respiratory tract infections <p>Adult and Pediatric Patients</p>
Recommendation on Regulatory Action	Approval

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Reviewers of Multi-Disciplinary Review and Evaluation

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Product Quality Team Lead	Dorota M. Matecka, PhD	CDER/OPQ	Section: 3	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Acknowledged <input checked="" type="checkbox"/> Approved
	Signature: Dorota M. Matecka -S <small>Digitally signed by Dorota M. Matecka -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300123291, cn=Dorota M. Matecka -S Date: 2018.07.05 12:20:18 -04'00'</small>			
Nonclinical Reviewer	Terry J. Miller, Ph.D.	CDER/DAIP	Section: 4	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Acknowledged <input type="checkbox"/> Approved
	Signature: Terry J. Miller -S <small>Digitally signed by Terry J. Miller -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300233444, cn=Terry J. Miller -S Date: 2018.07.05 11:17:52 -04'00'</small>			
Nonclinical Supervisor	Terry J. Miller, Ph.D.	CDER/DAIP	Section: 4	Select one: <input type="checkbox"/> Authored <input type="checkbox"/> Acknowledged <input checked="" type="checkbox"/> Approved
	Signature: Terry J. Miller -S <small>Digitally signed by Terry J. Miller -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300233444, cn=Terry J. Miller -S Date: 2018.07.05 11:18:20 -04'00'</small>			
Clinical Pharmacology Reviewer	Seong H. Jang, PhD	CDER/DCP4	Section: 5	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Acknowledged <input type="checkbox"/> Approved
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NDA Multi-disciplinary Review and Evaluation – NDA 209481
 Vancomycin Hydrochloride for Injection, USP

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Clinical Pharmacology Team Leader	Seong H. Jang, PhD	CDER/DCP4	Sections: 5	Select one: <input type="checkbox"/> Authored <input type="checkbox"/> Acknowledged <input checked="" type="checkbox"/> Approved
				Signature: Seong H. Jang -S <small>Digitally signed by Seong H. Jang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Seong H. Jang -S, 0.9.2342.19200300.100.1.1=1300193054 Date: 2018.07.05 10:55:02 -04'00'</small>
Clinical Reviewer	Alma Davidson, MD	CDER/DAIP	Section:7	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Acknowledged <input type="checkbox"/> Approved
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				Signature: S
Clinical Team Leader (Acting)	Peter Kim, MD,MS	CDER/DAIP	Section: 7	Select one: <input type="checkbox"/> Authored <input type="checkbox"/> Acknowledged <input checked="" type="checkbox"/> Approved
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NDA Multi-disciplinary Review and Evaluation – NDA 209481
 Vancomycin Hydrochloride for Injection, USP

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Clinical Microbiology Reviewer	Simone Shurland, PhD	CDER/DAIP	Section; 6	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Acknowledged <input type="checkbox"/> Approved
	Signature: Simone Shurland -S <small>Digitally signed by Simone Shurland -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000273852, cn=Simone Shurland -S Date: 2018.07.05 10:51:49 -0400</small>			
Clinical Microbiology Team Leader	Avery Goodwin, PhD	CDER/DAIP	Section 6	Select one: <input type="checkbox"/> Authored <input type="checkbox"/> Acknowledged <input checked="" type="checkbox"/> Approved
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NDA Multi-disciplinary Review and Evaluation – NDA 209481
 Vancomycin Hydrochloride for Injection, USP

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Regulatory Project Manager (DAIP)	Deepak Aggarwal, MS(Engg), MSPH		Section: 2	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Acknowledged <input checked="" type="checkbox"/> Approved
	Signature: Deepak Aggarwal -S <small>Digitally signed by Deepak Aggarwal -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001762237, cn=Deepak Aggarwal -S Date: 2018.07.05 11:20:57 -04'00'</small>			
Division Director (DAIP)	Sumati Nambiar, MD, MPH		Section: 1	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Acknowledged <input checked="" type="checkbox"/> Approved
	Signature: Sumathi Nambiar -S <small>Digitally signed by Sumathi Nambiar -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300145731, cn=Sumathi Nambiar -S Date: 2018.07.05 14:51:06 -04'00'</small>			

1. Executive Summary

1.1. Product Introduction

Vancomycin Hydrochloride for Injection USP, Lyophilized Powder, 250 mg/vial, 750 mg/vial, 1.25 g/vial and 1.5 g/vial. This 505(b)(2) application references ANDA 060180 Vancomycin hydrochloride.

1.2. Conclusions on the Substantial Evidence of Effectiveness

No new clinical studies were conducted with this formulation of vancomycin. The Applicant is relying on the Agency's prior findings of safety and effectiveness of vancomycin. The listed drug is ANDA 060180.

All reviewers recommend approval of this application. There are no outstanding issues precluding approval of the NDA.

2. Regulatory Background

The New Drug Application (NDA) 209481 dated July 20, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vancomycin Hydrochloride for Injection USP, Lyophilized Powder, 250 mg/vial, 750 mg/vial, 1.25 g/vial and 1.5 g/vial was received at FDA on July 20, 2016.

The application provides for the use of Vancomycin Hydrochloride for Injection USP, Lyophilized Powder, 250 mg/vial, 750 mg/vial, 1.25 g/vial and 1.5 g/vial for Septicemia, Infective Endocarditis, Skin and Skin Structure Infections, Bone Infections and Lower Respiratory Tract Infections. This 505(b)(2) application references ANDA 060180 Vancomycin hydrochloride.

On May 19, 2017, this application received a Complete Response (CR) action because of product quality issues including manufacturing facilities deficiencies.

The submission received on October 10, 2017, constituted a complete response to the Agency's May 19, 2017, action letter.

On March 29, 2018, the Applicant submitted new information regarding product quality microbiology. This was considered a major amendment and the goal date was extended by three months.

3. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

3.1 Product Quality

The product quality assessment encompasses chemistry, manufacturing, and controls (CMC), sterility, biopharmaceutical and facility reviews.

Novel excipients: No

Any impurity of concern: No

Sufficient controls to insure safety and efficacy of the commercial product: Yes

Although the majority of the Product Quality information submitted in the original NDA was found adequate, the NDA was recommended for Complete Response in the first cycle by the Office of Pharmaceutical Quality (OPQ) Review Team due to the unacceptable status of the drug substance and drug product manufacturing facilities. Therefore, the OPQ review of this resubmission focused primarily on the responses to the product quality deficiencies identified in the first review cycle. Based on a review of the application and inspectional documents, the manufacturing facilities are acceptable to support this NDA. In addition, the Applicant provided acceptable information to address the elemental impurities issue and the drug product stability update to further support the originally proposed expiration dating of 24 months. During the labeling review, additional chemical and microbiological in-use stability information was provided and found acceptable to support the proposed storage time and condition statements for the reconstituted and further diluted solutions of vancomycin for intravenous administration (using the reconstitution and dilution agents listed in the proposed package insert). (b) (4)

Based on the above assessments and the overall manufacturing inspection recommendation of “Approve” entered by the Office of Process and Facilities (OPF) into Panorama on February 16, 2018, this NDA is now recommended for approval by the OPQ review team.

4. Nonclinical Pharmacology/Toxicology

4.1 Executive Summary

The Applicant did not submit any new relevant pharmacology / toxicology information for review in this NDA. No pharmacology/toxicology information was reviewed to support this NDA.

The Applicant provided a Letter of Authorization from (b) (4) allowing the Applicant to reference Drug Master File # (b) (4) for the drug substance, Vancomycin hydrochloride, USP. The impurities and degradants detected in the final drug product do not exceed the NMT 4.0% specification limits described in the USP monograph for vancomycin for injection, except for monodechlorovancomycin (NMT 4.7%). While there are no pharmacology/toxicology assessments that can qualify such a minimal increase in the specified

limit of impurities, the Chemistry review team has determined that the impurity specifications are acceptable.

The labeling for the relevant pharmacology/toxicology sections submitted in the original NDA were modified by the Applicant to be compliant with Physician Labeling Rule (PLR), including Pregnancy Lactation Labeling Rule (PLLR). The remaining pharmacology/toxicology relevant sections of the Applicant's proposed labeling appear consistent with the latest drug product labeling for the listed drug (ANDA 060180). The reviewer provided recommended labeling changes to Section **8.1 Pregnancy** and concurs with the Division's changes to Section **8.2 Lactation** of the Applicant's proposed labeling in Appendix 3.

RECOMMENDATION:

Pharmacology/Toxicology has no objection to the approval of NDA 209481 for Vancomycin for Injection. The Applicant referenced the FDA approved product labeling for the listed drug, ANDA 060180 and modified the labeling to include PLLR compliant language in Section 8. The remaining pharmacology/toxicology relevant sections of the Applicant's proposed labeling appear consistent with the latest drug product labeling for the listed drug.

5. Clinical Pharmacology

5.1 Executive Summary

There were no new clinical pharmacology data/information provided by the Applicant in this NDA. The revisions to the labeling with respect to clinical pharmacology (see Section 7.3 of this review) were made for further clarification.

6. Clinical Microbiology Review

6.1 Executive Summary

There were no new clinical microbiology data provided by the Applicant for this NDA. There were revisions to the labeling with respect to clinical microbiology (see Section 7.3 of this review and Section 12.4 of the labeling).

7. Statistical and Clinical Safety Evaluation

7.1 Statistical

There are no new clinical trials conducted by the Applicant for this NDA.

7.2 Clinical Safety Update

The reader is referred to the original submission of the Clinical Review in DARRTS dated 05/04/2017 for clinical safety information.

Additionally, based on a review of the recent literature publication (Witkin AJ, Chang DF, Jumper JM, et al. Vancomycin-associated hemorrhagic occlusive retinal vasculitis, American Journal of Ophthalmology 2017; 124(5):583-595)¹, the following serious adverse reaction related to an unapproved use of vancomycin: “Hemorrhagic Occlusive Retinal Vasculitis (HORV)”, was added to the WARNINGS section of the Vancomycin Injection prescribing information:

WARNINGS

Hemorrhagic Occlusive Retinal Vasculitis (HORV)

Hemorrhagic occlusive retinal vasculitis, including permanent loss of vision, occurred in patients receiving intracameral or intravitreal administration of vancomycin during or after cataract surgery. The safety and efficacy of vancomycin administered by the intracameral or the intravitreal route have not been established by adequate and well-controlled trials. Vancomycin is not indicated for prophylaxis of endophthalmitis.”

(Please see Tracked Safety Issue #1830- Clinical Review Memo for Vancomycin-Associated Hemorrhagic Occlusive Retinal Vasculitis in DARRTS, dated 09/14/2017 for details.)

Recommendation: From a clinical perspective, this New Drug Application is recommended for approval.

7.3 Labeling Recommendations

The clinical reviewer has the following labeling comments for Vancomycin HCl for Injection, USP Prescribing Information (PI):

Reviewer’s Comment: We recommended the consistent use of the terminology “Vancomycin Hydrochloride [or HCl] for Injection” throughout the PI when referring to the drug product.

The Applicant agreed to this labeling change.

Labeling content has been revised in several sections of the Vancomycin HCl for Injection, USP prescribing information to comply with the Physician’s Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) regulations. Generally, revisions involved limited re-writing aimed at clarifying text, eliminating redundancies, and updating outdated terminology. Information was re-ordered and re-formatted to enhance labeling organization, presentation, readability and ease of use. For example, some of the following sections were revised:

I. INDICATIONS AND USAGE

- Under the INDICATIONS OF USAGE section, the pharmacologic class was updated to “glycopeptide antibacterial” to reflect the approved EPC text phrase for vancomycin HCl.
- Under the INDICATIONS AND USAGE section, contents are edited to include headings for each listed indication, and updating outdated clinical terms and bacterial nomenclature as follows:

1. Septicemia

Vancomycin Hydrochloride for Injection is indicated in adults and pediatric patients (neonates and older) for the treatment of septicemia due to:

Reviewer's Comment: We recommended including age group(s) in the indication statement to provide clear and consistent communication to healthcare providers about the indicated populations.

The Applicant agreed to this labeling change.

- Susceptible isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase negative staphylococci.
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

Reviewer's Comment: The above edits were recommended to improve clarity that the drug is indicated for MRSA and coagulase-negative staphylococci, and methicillin-susceptible staphylococci in penicillin allergic patients, or those patients who cannot receive or have failed to respond to other drugs, including penicillins or cephalosporins by using bullets.

2. Infective Endocarditis

Vancomycin Hydrochloride for Injection is indicated in adults and pediatric patients (neonates and older) for the treatment of infective endocarditis due to:

- Susceptible isolates of MRSA.
- Viridans group streptococci *Streptococcus gallolyticus* (previously known as *Streptococcus bovis*), *Enterococcus* species and *Corynebacterium* species. For enterococcal endocarditis, use Vancomycin hydrochloride for Injection in combination with an aminoglycoside.
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

Reviewer's Comment: The outdated bacterial nomenclatures were updated (i.e., *Streptococcus bovis* to *Streptococcus gallolyticus* and diphtheroids to *Corynebacterium* species).

Vancomycin Hydrochloride for Injection is indicated in adults and pediatric patients (neonates and older) for the treatment of early-onset prosthetic valve endocarditis caused by *Staphylococcus epidermidis* in combination with rifampin and an aminoglycoside.

3. Skin and Skin Structure Infections

Vancomycin Hydrochloride for Injection is indicated in adults and pediatric patients (neonates and older) for the treatment of skin and skin structure infections due to:

- Susceptible isolates of MRSA and coagulase negative staphylococci.

- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

4. Bone Infections

Vancomycin Hydrochloride for Injection is indicated in adults and pediatric patients (neonates and older) for the treatment of bone infections due to:

- Susceptible isolates of MRSA and coagulase negative staphylococci.
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

5. Lower Respiratory Tract Infections

Vancomycin Hydrochloride for Injection is indicated in adults and pediatric patients (neonates and older) for the treatment of lower respiratory tract infections due to:

- Susceptible isolates of MRSA
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

II. DOSAGE AND ADMINISTRATION

2.4 Dosage in Patients With Renal Impairment

Dosage adjustment must be made in patients with renal impairment. The initial dose should be no less than 15 mg/kg, in patients with any degree of renal impairment.

In premature infants and the elderly, greater dosage reductions than expected may be necessary because of decreased renal function. Measure trough vancomycin serum concentrations to guide therapy, especially in seriously ill patients with changing renal function.

For functionally anephric patients, an initial dose of 15 mg/kg of body weight should be given to achieve prompt therapeutic serum concentrations. A dose of 1.9 mg/kg/24 hrs should be given after the initial dose of 15 mg/kg.”

Reviewer’s Comment: This subsection was revised to provide clearer information regarding dosing patients with renal impairment.

III. WARNINGS AND PRECAUTIONS

- Under the WARNINGS and PRECAUTIONS section: The numbering of Warnings has been edited to take into account frequency and severity of the adverse reactions related to vancomycin. In a recent Vancomycin Injection, USP labeling supplement (approved September 29, 2017), a serious adverse reaction associated with an off-label use of vancomycin known as “Hemorrhagic Occlusive Retinal Vasculitis (HORV) was added to the WARNINGS section of the prescribing information.

5.5 Hemorrhagic Occlusive Retinal Vasculitis (HORV)

Hemorrhagic occlusive retinal vasculitis, including permanent loss of vision, occurred in patients receiving intracameral or intravitreal administration of vancomycin during or after cataract surgery. The safety and efficacy of vancomycin administered by the intracameral or the intravitreal route have not been established by adequate and well-controlled trials. Vancomycin is not indicated for the prophylaxis of endophthalmitis.”

IV. ADVERSE REACTIONS

● Under the ADVERSE REACTIONS section: The adverse reactions associated with the use of Vancomycin HCl for Injection as identified in clinical studies or postmarketing reports are listed.

V. DRUG INTERACTIONS

● Under the DRUG INTERACTIONS section: This section has been updated to include the statement regarding concomitant use of piperacillin/tazobactam and vancomycin may be associated with an increased incidence of acute kidney injury.

7.2 Piperacillin-Tazobactam

Studies have detected an increased incidence of acute kidney injury in patients administered concomitant piperacillin/tazobactam and vancomycin as compared to vancomycin alone. Monitor kidney function in patients receiving concomitant piperacillin/tazobactam and vancomycin. No pharmacokinetic interactions have been noted between piperacillin/tazobactam and vancomycin.”

Reviewer’s Comment: The following references were cited as review materials for the drug-interaction language:

- *Luther MK, Timbrook TT et al. Vancomycin Plus Piperacillin-Tazobactam and Acute Kidney Injury in Adults: A Systematic Review and Meta-Analysis. Crit Care Med. 2018 Jan;46(1):12-20.*
- *Giuliano CA, Patel CR et al. Is the Combination of Piperacillin-Tazobactam and Vancomycin Associated with Development of Acute Kidney Injury? A Meta-analysis. Pharmacotherapy. 2016 Dec;36(12):1217-1228.*
- *Downes KJ, Cowden C et al. Association of Acute Kidney Injury With Concomitant Vancomycin and Piperacillin/Tazobactam Treatment Among Hospitalized Children. JAMA Pediatr. 2017 Dec 4;171(12).*

VI. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Animal data describing the absence of fetal malformations or fetal developmental toxicities in pregnant rats and rabbits administered vancomycin during organogenesis at a dose less than or equal to the clinically relevant dose was added to the Risk Summary and Animal Data. Similarly, a statement on maternal toxicity observed at the highest dose tested in rats and rabbit was added under Animal Data.

Reviewer's Comment: Please see the PLLR review by Dr. Leyla Sahin from the Division of Pediatric and Maternal Health in DARRTS dated 04/19/2017 for details.

VII. PATIENT COUNSELING INFORMATION

Under the PATIENT COUNSELING INFORMATION section: The counseling information is updated to reflect the WARNINGS section statement regarding frequency and severity of the adverse reactions related to vancomycin and reflect the major warnings of the drug for which a patient may need to do something actionable (e.g., contact the healthcare provider, immediately discontinue the drug, or seek emergency medical care) and how the patient may mitigate or manage the adverse reactions.

“Infusion Reactions During or After Intravenous Use

Advise patients that generalized skin redness, skin rash, itching, flushing, muscle pain, chest pain, shortness of breath, wheezing, or dizziness may occur during Vancomycin Hydrochloride for Injection infusion. These reactions can be lessened or prevented by infusing the drug over at least 60 minutes.

Acute Kidney Injury

Advise patients that Vancomycin Hydrochloride for Injection can result in kidney damage and that blood tests are required to monitor vancomycin blood levels and kidney function during therapy.

Hearing Loss or Balance Problems

Advise patients that Vancomycin Hydrochloride for Injection may result in decreased hearing and to report hearing loss or balance problems to their health care provider.

Antibacterial Resistance

Patients should be counseled that antibacterial drugs including Vancomycin Hydrochloride for Injection should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Vancomycin Hydrochloride for Injection is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Vancomycin Hydrochloride for Injection or other antibacterial drugs in the future.

Diarrhea

Diarrhea is a common problem caused by antibacterial drugs which usually ends when the antibacterial drug is discontinued. Sometimes after starting treatment with antibacterial drugs, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterial drug. If this occurs, patients should contact their physician as soon as possible.”

8. Appendices

8.1 *References*

Witkin AJ, Chang DF, Jumper JM, et al. Vancomycin-associated hemorrhagic occlusive retinal vasculitis, American Journal of Ophthalmology 2017; 124(5):583-595

Tracked Safety Issue #1830- Clinical Review Memo for Vancomycin-Associated Hemorrhagic Occlusive Retinal Vasculitis in DARRTS, dated 09/14/2017

Vancomycin Hydrochloride for Injection USP -For Intravenous Use (ANDA-060180) by ANI PHARMS INC-approved 12/18/2017.

Luther MK, Timbrook TT et al. Vancomycin Plus Piperacillin-Tazobactam and Acute Kidney Injury in Adults: A Systematic Review and Meta-Analysis. Crit Care Med. 2018 Jan;46(1):12-20.

Giuliano CA, Patel CR et al. Is the Combination of Piperacillin-Tazobactam and Vancomycin Associated with Development of Acute Kidney Injury? A Meta-analysis. Pharmacotherapy. 2016 Dec;36(12):1217-1228.

Downes KJ, Cowden C et al. Association of Acute Kidney Injury With Concomitant Vancomycin and Piperacillin/Tazobactam Treatment Among Hospitalized Children. JAMA Pediatr. 2017 Dec 4;171(12).

8.2 *Financial Disclosure*

There is no financial disclosure report provided in this application because there are no new clinical trials conducted by the Applicant.

Division Director (Clinical/DAIP)

Concur with review

Sumathi
Nambiar -S



Digitally signed by Sumathi Nambiar-S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300145731,
cn=Sumathi Nambiar-S
Date: 2018.07.05 12:27:24 -0400'

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEEPAK AGGARWAL
07/05/2018

SUMATHI NAMBIAR
07/05/2018

Cross-Discipline Team Leader Review (CDTL Review # 2)

NOTE: This is an amended version of CDTL Review previously placed in Panorama on May 18, 2017. This review (CDTL Review # 2) can be considered a final and a stand-alone CDTL review for this NDA.

Date	(electronic stamp)
From	Dorota Matecka, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	209481
Applicant	Mylan Laboratories Limited
Date of Submission	July 20, 2016
PDUFA Goal Date	May 19, 2017
Proprietary Name / Established (USAN) names	Vancomycin Hydrochloride for Injection* (vancomycin hydrochloride)
Dosage forms/Strength	Powder for injection 250 mg/vial; 750 mg/vial; 1.25 g/vial; 1.50 g/vial
Proposed Indication(s)	(b) (4)
	<ul style="list-style-type: none"> • Septicemia • Bone infections • Lower respiratory tract infections • Skin and skin structure infections
	(b) (4)
Recommended:	Complete Response

* No proprietary/trade name was proposed for the drug product

1. Introduction

This 505(b)(2) NDA provides for several new strengths (i.e., a total vial content) of injectable formulation of vancomycin hydrochloride (b) (4)

In the initial NDA submission, the Applicant referred to Fresenius Kabi's Vancomycin Hydrochloride for Injection, 500 mg/vial, 1 g/vial, 5 g/vial, and 10 g/vial (approved under ANDA 62663) as the listed drug for the current NDA. However, ANDA 62663 does not contain full reports of safety and effectiveness. Therefore, in response to the FDA comment, in a subsequent amendment dated September 14, 2016, the Applicant revised the basis for submission to include a reference to: 1) Vancomycin Hydrochloride for Injection, 500 mg/vial and 1 g/vial, approved via ANDA 60180 (a discontinued listed drug) for the FDA's determination of safety and effectiveness of Vancomycin Hydrochloride for

Injection; and 2) Vancomycin Hydrochloride for Injection approved via ANDA 62663 to provide a scientific bridge of the proposed drug product to the currently marketed product.

The drug product strengths proposed via this NDA include the following: 250 mg/vial, 750 mg/vial, 1.25 g/vial, and 1.50 g/vial. No other changes have been proposed in the formulation of the current drug product. In view of the similarities between the proposed and the listed drugs, the Applicant is relying on previous findings of efficacy and safety for Vancomycin for Injection. A biowaiver for conducting in-vivo bioequivalence studies was requested by the Applicant.

2. Background

Vancomycin hydrochloride for injection is indicated for the treatment of serious or severe infections caused by susceptible strains of methicillin-resistant (β -lactam-resistant) staphylococci. It is indicated for penicillin-allergic patients, for patients who cannot receive or who have failed to respond to other drugs, including the penicillins or cephalosporins, and for infections caused by vancomycin-susceptible organisms that are resistant to other antimicrobial drugs.

The bactericidal action of vancomycin results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis. There is no cross-resistance between vancomycin and other antibiotics. Vancomycin is not active in vitro against gram-negative bacilli, mycobacteria, or fungi.

3. Product Quality

The Product Quality review team included the following individuals:

DISCIPLINE	PRIMARY REVIEWER
Drug Substance	Haripada Sarker
Drug Product	George Lunn
Process	Nancy Waites
Microbiology	Wendy Tan
Facilities	Jonathan Swoboda
Biopharmaceutics	Yang Zhao
Regulatory Business Process Manager	Luz Rivera
Environmental Assessment	George Lunn
Application Technical Lead	Dorota Matecka

The chemistry manufacturing and controls (CMC) information for vancomycin hydrochloride drug substance has been provided via a reference to DMF Type II (b) (4) held by (b) (4) (b) (4) DMF (b) (4) has been previously found adequate in support of

several ANDAs and most recently in support of the current NDA by the Drug Substance Reviewer (via review dated April 3, 2017, in DARRTS).

The proposed drug product, vancomycin for injection, consists of vancomycin hydrochloride lyophilized in a glass vial with a rubber stopper and aluminum overseal supplied in the following strengths, 250 mg/vial; 750 mg/vial; 1.25 g/vial; 1.50 g/vial. The overall information provided for the drug product, including the proposed specification, was found acceptable. In addition, based on the overall stability information provided for three representative batches of each strength of the proposed drug product, the proposed 24-month expiration dating for the drug product to be stored at room temperature has been found acceptable by the Drug Product Reviewer.

The proposed manufacturing process consists of (b) (4) and based on the information provided in the initial NDA and in response to several comments from the Agency, it was found acceptable. In addition, the product quality microbiology aspects of the proposed drug product, such as sterilization process, container closure integrity, and microbiology controls proposed in the drug product specifications, were found adequate by the Product Quality Microbiology Reviewer.

The biopharmaceutics review focused on the review of the request submitted by the Applicant to waive the requirement to conduct bioavailability/bioequivalence studies for all proposed drug product strengths. Based on the information provided in the NDA, the biowaiver request has been granted by the Biopharmaceutics Reviewer for the proposed drug product (b) (4).

The vancomycin hydrochloride drug substance is manufactured by (b) (4) and the drug product is manufactured by Mylan Laboratories Limited, India. Due to the unacceptable status of the drug substance and drug product sites, the overall recommendation for this NDA entered into Panorama by the Office of Process and Facilities on May 17, 2017 is "Withhold". Therefore, the OPQ team recommended this NDA for Complete Response (review dated May 18, 2017 in Panorama).

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Reviewer was Terry Miller, Ph.D. who stated that no new relevant pharmacology/toxicology information was submitted. Dr. Miller recommended several changes in the pharmacology/toxicology sections of the package insert (refer to the review dated May 8, 2017 in DARRTS).

5. Clinical Pharmacology

Yongheng Zhang, Ph.D. was the Clinical Pharmacology Reviewer for this application. Dr. Zhang stated that no clinical pharmacology issues were submitted for review in this NDA and referred to the biopharmaceutics review for the assessment of the biowaiver request. In

addition, Dr. Zhang outlined several recommended revisions in the proposed package insert (refer to review dated May 10, 2017, in DARRTS).

6. Clinical Microbiology

Simone Shurland, Ph.D., was the Clinical Microbiology Reviewer for this application.

No new clinical microbiology information was submitted with this application. Dr. Shurland filed a memo (dated May 16, 2017 in DARRTS) stating that labeling will be reviewed in the next cycle when the CMC deficiencies are resolved.

7. Clinical/Efficacy and Safety

Alma C. Davidson, MD, was the Clinical Reviewer and Karen Higgins, ScD, was the Statistical Reviewer for this NDA.

No new clinical studies were conducted for the current 505(b)(2) NDA as the Applicant is relying on the previous findings of safety for the listed drug. The Applicant conducted the literature searches of the National Library of Medicine databases (NIH/NLM PubMed Central) and other internet sources for safety and efficacy of vancomycin hydrochloride and its pharmacokinetics, bioavailability, pharmacodynamics, dose adjustment, drug interaction, and tolerability. Based on the review of this information, Dr. Davidson concluded that due to a generally favorable safety and tolerability profile, vancomycin remains an important and effective therapeutic agent as long as resistance to vancomycin remains controlled. However, due to pending CMC and labeling issues, Dr. Davidson does not currently recommend this application for approval (review dated May 5, 2017 in DARRTS).

Dr. Higgins had no statistical comments as no new clinical studies were conducted for this NDA (review dated May 17, 2017 in DARRTS).

8. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application (the product is not an NME).

9. Pediatrics

The drug product proposed via this 505(b)(2) NDA does not contain a new active ingredient and is not a new dosage form. No new indication is proposed and no new dosing regimen is proposed. There is no new route of administration associated with the new product. For these reasons, the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), does not apply to this application. No pediatric studies will be required as a condition of approval.

10. Other Relevant Regulatory Issues

No clinical studies/trials were conducted in support of this NDA. Therefore, no inspection request was sent to the Office of Scientific Investigations (OSI).

Based on the information in the electronic Orange Book, there are no unexpired patents and exclusivities for the listed drug.

11. Labeling

The proposed labeling and labels for Vancomycin Hydrochloride for Injection were submitted in the NDA. No trade name was proposed for the drug product.

A number of labeling revisions and recommendations were provided by the reviewers. That includes recommendations from the Division of Pediatric and Maternal Health (DPMH) to the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections in the proposed package insert, to comply with the current PLLR requirements (review by Leyla Sahin, MD, dated April 19, 2017, in DARRTS). However, due to the anticipated Complete Response action for this NDA, several disciplines including DMEPA (refer to Memorandum dated May 16, 2017 in DARRTS) postponed completion of the labeling review to the next review cycle.

(b) (4)



12. Recommendations/Risk Benefit Assessment

I concur with the assessments made by the review team and recommend the issuance of a Complete Response (CR) for this NDA due to the unacceptable status of manufacturing facilities proposed for commercial use. The following CR comment should be included in the CR letter:

During a recent inspection of the [REDACTED] (b) (4) and Mylan Laboratories Ltd. (FEI 3008255419), manufacturing facilities for this application, our field investigator observed objectionable conditions at the facilities and conveyed that information to the representative of each of the facilities at the close of the inspections. Satisfactory resolution of these observations is required before this application may be approved.

In addition, the following additional (non-CR) comments will be included in the letter:

Product Quality

You have proposed to [REDACTED] (b) (4)

[REDACTED] (b) (4)

Regulatory

In your application, we note that you specified that you are relying on FDA's findings of safety and effectiveness for the listed drugs approved under ANDA 062663 and ANDA 060180. Based upon Agency records, it appears that ANDA 060180 is actually an NDA although it is listed as a discontinued ANDA in the Orange Book. We acknowledge that you have chosen to rely on FDA's finding of safety and effectiveness for a discontinued listed drug with the understanding that you are using the ANDA product listed in the Orange Book (i.e., ANDA 062663 that you have identified in your application) to establish a bridge between your proposed drug product and the specified listed drug.

Cross Discipline Team Leader Review

However, your application cannot rely upon ANDA 062663 which does not contain full reports of safety and effectiveness. When you resubmit your application, please identify ANDA 060180 as the application containing full reports of investigations of safety and effectiveness upon which your application relies. When completing the 356h form, please remove ANDA 062663 from the space designated for “Application Number or Relied Upon Products.”

Dorota M.
Matecka -S

Digitally signed by Dorota M. Matecka, S
DN: cn=US, ou=US Government, ou=HRIS,
ou=FDA, ou=People,
o=9 2342 19200300 100 11=1300123291
c=Dorota M. Matecka, S
Date: 2017.05.19 10:00:54 -0400

STATISTICAL REVIEW AND EVALUATION

NDA/BLA #: 209481
Drug Name: Vancomycin Hydrochloride for Injection, USP
Lyophilized powder for injection, 250mg/vial, 750 mg/vial,
1.25g/vial, and 1.5 g/vial
Applicant: Mylan Pharmaceuticals, c/o Mylan laboratories Limited
Date(s): Stamp date: July 20, 2017
Goal date: May 20, 2017
Biometrics Division: Division of Biometrics IV
Statistical Reviewer: Karen Higgins, ScD
Concurring Reviewers: Daphne Lin, PhD
Medical Division: Division of Anti-Infective Products
Project Manager: Deepak Aggarwal, MS, MSPH

Summary

The Applicant, Mylan Pharmaceuticals, seeks approval, via the 505(b)(2) pathway, for Vancomycin HCl for Injection USP lyophilized powder in the following strengths 250mg/vial, 750 mg/vial, 1.25 g/vial and 1.5 g/vial. The Applicant's vancomycin formulation is purportedly similar to Fresenius Kabi USA/LLC (ANDA 062663) reference listed drug (RLD) approved March 17, 1987. The applicant intends to rely on the Agency's findings of efficacy and safety for Fresenius Kabi's Vancomycin for Injection.

No new clinical studies were submitted by the Applicant in this NDA. Therefore, there are no statistical comments regarding the safety and efficacy for NDA 209481. The label is consistent with RLD prescribing information in that it does not contain a clinical studies section. There is no statistical review needed for this NDA submission.

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/s/

KAREN M HIGGINS
05/16/2017

TSAE YUN D LIN
05/17/2017

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 209481
Submission Date(s): July 20, 2016
Submission Type 505(b)(2)
PUDFA: May 19, 2017
Drug Vancomycin
Product/Formulation; Strength(s) Injection, lyophilized powder
Primary Reviewer Yongheng Zhang, Ph.D.
Team Leader Seong Jang, Ph D
OCP Division DCP4
OND Division DAIP
Applicant Mylan Laboratories LTD

Proposed indication

(b) (4)

Dose and Administration

1. SUMMARY

The Applicant submitted this 505(b)(2) application to introduce additional strengths for Vancomycin i.e., 250 mg/vial, 750 mg/vial, 1.25 g/vial and 1.50 g/vial. The Reference Listed Drug Vancomycin Hydrochloride for Injection, USP (ANDA 062663) held by Fresenius Kabi is available as 500 mg/vial, 1 g/vial, 5 g/vial and 10 g/vial.

A request for waiver of *in vivo* bioequivalence studies for these strengths pursuant to 21 CFR §320.22 (b)(1)(i) and (ii) was provided in this submission. We defer the decision of the bio-waiver request to the biopharmaceutical reviewers. There is no Clinical Pharmacology-related issue for approval of this NDA.

The Applicant also formatted the labeling in accordance with FDA’s Final Rule, “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling (June 2015)*”. The reviewer recommends labeling changes in Section 12.3, based on the recently issued Guidance for Industry: *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (December 2016)*”.

2. LABEL RECOMMENDATIONS

This 12.3 subsection is updated according to New Section 12 guidance.

Deletion by ~~strike through~~; Addition by underline.

12.3 Pharmacokinetics

(b) (4)

In subjects with normal kidney function, multiple intravenous dosing of 1 g of vancomycin (15 mg/kg) infused over 60 minutes produces mean plasma concentrations of approximately 63 mcg/mL immediately after the completion of infusion, mean plasma concentrations of approximately 23 mcg/mL 2 hours after infusion, and mean plasma concentrations of approximately 8 mcg/mL 11 hours after the end of the infusion. Multiple dosing of 500 mg infused over 30 minutes produces mean plasma concentrations of about 49 mcg/mL at the completion of infusion, mean plasma concentrations of about 19 mcg/mL 2 hours after infusion, and mean plasma concentrations of about 10 mcg/mL 6 hours after infusion. The plasma concentrations during multiple dosing are similar to those after a single dose.

(b) (4)

Distribution

The volume of distribution is from 0.3 to 0.43 L/kg. Vancomycin is approximately 55% serum protein bound as measured by ultrafiltration at vancomycin serum concentrations of 10 to 100 mcg/mL. After IV administration of vancomycin, inhibitory concentrations are present in pleural, pericardial, ascitic, and synovial fluids; in urine; in peritoneal dialysis fluid; and in atrial appendage tissue. Vancomycin does not readily diffuse across normal meninges into the spinal fluid, but when the meninges are inflamed, penetration into the spinal fluid occurs.

Elimination

Mean plasma clearance is about 0.058 L/kg/h, and mean renal clearance is about 0.048 L/kg/h. The mean elimination half-life of vancomycin from plasma is 4 to 6 hours in subjects with normal renal function.

(b) (4)

(b) (4)

In anephric patients, the (b) (4) elimination is 7.5 days. Total (b) (4) and renal (b) (4) clearance of vancomycin may be reduced in the elderly.

(b) (4)

Metabolism

There is no apparent metabolism of the (b) (4)

Excretion

In the first 24 hours, about 75% of an administered dose of vancomycin is excreted in urine by glomerular filtration. Renal dysfunction slows excretion of vancomycin.

(b) (4)

Comment [ZV1]: To the Applicant: Updated to make it consistent with the Labeling recommendations of the Clinical Pharmacology Labeling guidance.

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/s/

YONGHENG ZHANG
05/10/2017

SEONG H JANG
05/10/2017

Memo to the Division File

NDA 209481, Submitted 7/20/2016

Vancomycin for Injection USP, 250, 750, 1250, 1500 mg (Mylan Laboratories, Ltd)

From: Terry J. Miller, Ph.D., Pharmacology/Toxicology Reviewer, DAIP

Through: Deepak Aggarwal, MS. MPH

Date: May 5, 2017

Background:

The Applicant, Mylan Laboratories, Ltd. submitted a 505(b)(2) NDA requesting marketing approval to license Vancomycin for Injection, 250, 750, 1250, 1500 mg. The proposed drug product is intended to be a copy of the reference listed drug [RLD] Vancomycin Hydrochloride for Injection USP (Fresenius Kabi USA, LLC; ANDA#: 062663); [REDACTED] (b) (4)

[REDACTED] The Applicant provided a Letter of Authorization from [REDACTED] (b) (4) allowing the Applicant to reference Drug Master File # [REDACTED] (b) (4) for the drug substance, Vancomycin hydrochloride, USP. The impurities and degradants detected in the final drug product do not exceed the NMT 4.0% specification limits described in the USP monograph for vancomycin for injection, except for monodechlorovancomycin (NMT 4.7%). While there are no pharmacology/toxicology assessments that can qualify such a minimal increase in the specified limit, the decision on the overall acceptability of the impurity specifications are deferred to the Chemistry review team. Otherwise, only the total vial contents are different (250, 750, 1250, 1500 mg in the current product vs. 500, 750, or 1000 mg in the RLD).

The Applicant did not submit any new relevant pharmacology / toxicology information for review in their 505(b)(2) NDA. No pharmacology/toxicology information was reviewed to support this 505(b)(2) NDA. The labeling for the relevant pharmacology/toxicology sections submitted in the original NDA were modified to be compliant with Physician Labeling Rule (PLR), including Pregnancy Lactation Labeling Rule (PLLR). In addition, the applicant updated Section 13.1 **Carcinogenesis, Mutagenesis, Impairment of Fertility** with information from the published literature.

In the 74-day letter to the Applicant, Mylan Laboratories Inc. was recommended to further revise the package insert to ensure complete compliance with PLLR guidelines. The Applicant submitted the revised package insert to the NDA on 10/28/2016. The reviewer's recommended labeling changes in the pharmacology/toxicology relevant

sections of the labeling (Indications and Usage, Subsections 8.1, 8.2, and 13.1) can be found in red and strikethrough below.

Labeling:

-----INDICATIONS AND USAGE-----

Vancomycin hydrochloride for injection is a glycopeptide (b) (4) **antibacterial** indicated for: (1)

(Reviewer's comment: The FDA Established Pharmacologic Class (EPC) text phrase for vancomycin is "glycopeptide antibacterial".)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary



All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth

defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

(b) (4)



Data

Human Data

(b) (4)



(b) (4)

Animal Data

(b) (4)

*(Reviewer's comment: The clinical review team provided additional recommendations to the language in Section 8.1 **Pregnancy** that are not reflected in the labeling recommendations in this review).*

8.2 Lactation

Risk Summary

(b) (4)

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for vancomycin and any potential adverse effects on the breastfed infant from vancomycin or from the underlying maternal condition.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

13.2 Animal Toxicology and/or Pharmacology

In animal studies, hypotension and bradycardia occurred in dogs receiving an intravenous infusion of vancomycin hydrochloride 25 mg/kg, at a concentration of 25 mg/mL and an infusion rate of 13.3 mL/min.

Recommendation:

There are no pharmacology/toxicology issues with the approval of this NDA.

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/s/

TERRY J MILLER
05/08/2017

Clinical Review

NDA 209481	505(b)(2)
Date of Submission	July 20, 2016
PDUFA Goal Date	May 20, 2017
Action Date	May 19, 2017
Applicant	MYLAN Pharmaceuticals Inc.
Drug name	Vancomycin Hydrochloride for Injection, USP
Dosage Forms/Strengths	Lyophilized powder for injection /250mg/vial, 750 mg/vial, 1.25g/vial, and 1.5 g/vial
Proposed Indications	<div style="background-color: #cccccc; padding: 5px;">(b) (4)</div> <ul style="list-style-type: none"> • Treatment of Septicemia • Treatment of Bone infections • Treatment of Lower respiratory tract infections • Treatment of Skin and skin structure infections <div style="background-color: #cccccc; padding: 5px; text-align: right;">(b) (4)</div>
Clinical Reviewer	Alma C. Davidson, M.D.
Clinical Team Leader	Hala Shamsuddin, M.D.
Recommendation	Non-approval due to CMC deficiencies and labeling issues.

1. Introduction

The applicant has submitted this 505(b)(2) new drug application (NDA) for Vancomycin HCl for Injection, USP using Vancomycin hydrochloride for Injection, USP as the reference listed drug (RLD) held by Fresenius Kabi USA LLC (Application Number A062663) approved on March 17, 1987. Abbreviated new drug application (ANDA) 062663, the current RLD listed in FDA’s Orange Book provides a bridge to the currently marketed product. The dosage form of the RLD is Injection;

and strengths of the RLD are 500 mg/vial, 1 g/vial, 5 g/vial, and 10 g/vial. (b) (4)

There are no clinical trials conducted by the applicant to support this 505(b)(2) NDA for Vancomycin HCl for Injection, USP. The review for this NDA relies on the prior FDA determination of effectiveness and safety of Vancomycin HCl for Injection, USP based on studies which were not conducted by or for the applicant. In addition to this reference listed drug, the applicant's NDA also relies on Agency's finding of safety and/or effectiveness of VANCOCIN HYDROCHLORIDE of ANI Pharmaceuticals, Inc., (NDA Number 060180) approved on November 6, 1964, currently discontinued from the market.

New labeling issues of this 505(b)(2) new drug application encountered during the current review cycle

(b) (4)

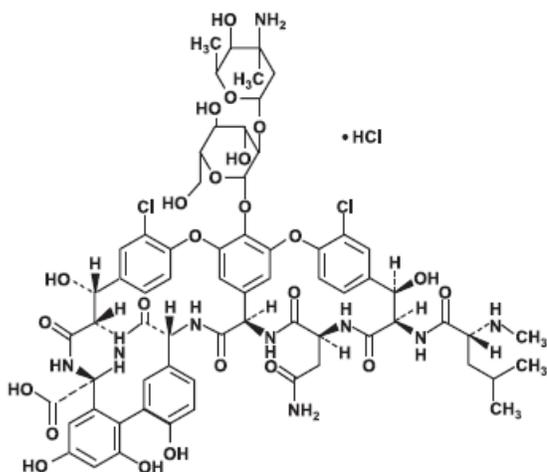
2. Background

Drug Information

Vancomycin is a tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*). The chemical name for vancomycin hydrochloride is (Sa)-(3S, 6R, 7R, 22R, 23S, 26S, 36R, 38aR)-44-[[2-O-(3-Amino- 2, 3, 6- trideoxy- 3-C-methyl- α -L- lyxo- hexopyranosyl)- β -D-glucopyranosyl]oxy]-3-(carbamoylmethyl)-10, 19-dichloro-2,3, 4 ,5 ,6, 7,23 ,24,25 ,26,36,37 ,38,38a-tetradecahydro-7,22,28,30 ,32-pentahydroxy-6-[(2R)-4- methyl-2-(methylamino) valeramido]-2, 5, 24, 38, 39-pentaoxo-22H-8,11 :18,21-dietheno-23, 36- (iminomethano)-13, 16: 31, 35-dimetheno- 1H, 16H- [1, 6, 9] oxadiazacyclohexadecino [4, 5- m] [10, 2, 16]- benzoxadiazacyclotetracosine-26- carboxylic acid, monohydrochloride.

The molecular formula is $C_{66}H_{75}Cl_2N_9O_{24} \cdot HCl$ and the molecular weight is 1485.71.

Vancomycin hydrochloride has the following structural formula:



Vancomycin hydrochloride for injection is a glycopeptide antibacterial indicated for:

(b) (4)

- treatment of (b) (4) septicemia, bone infections, lower respiratory tract infections, skin and skin structure infections

(b) (4)

3. Pediatric Assessment Waiver Request

The applicant submitted a pediatric waiver request for the following age groups: Age group (s) included in the waiver request: Neonates (0-1 month of age) and Pediatric patients of the formulation, Vancomycin Hydrochloride for Injection [250 mg/vial, 750 mg/vial, 1.250 g/vial and 1.50 g/vial] based on the following:

- Qualitative and quantitative sameness:

The active ingredient, Vancomycin Hydrochloride, contained in the proposed drug product, Vancomycin Hydrochloride for Injection [250 mg/vial, 750 mg/vial, 1.250 g/vial and 1.50 g/vial] is the same as that of the reference listed drug, Vancomycin Hydrochloride for Injection, USP, 500 mg/vial, 1 g/vial, 5 g/vial and 10g/vial held by Fresenius Kabi

(ANDA#062663]. The formulation contains only the active ingredient and water for injection.

- Administered in saline dosage form and same amount of active ingredients per dose:

Vancomycin hydrochloride for Injection [250 mg/vial, 750 mg/vial, 1.250 g/vial and 1.50 g/vial] is lyophilized product and it is reconstituted prior to administration and represents the same dosage form as RLD, a clear liquid for intravenous administration. The proposed product attains same concentration as that of the RLD, when reconstituted as per the approved RLD pack insert. Thus it shares the same toxicological profile as the of innovator product.

- Rely on Agency's findings for previously approved drug product:

The applicant states that they wish to completely rely on Agency's findings on safety and efficacy of the product for previously approved drug product Fresenius Kabi's Vancomycin for Injection (Application# A062663) and Ani Pharm's Vancocin Hydrochloride for injection (Application# N060I80). The information of recommended dosage for pediatric patients is provided below.

Pediatric Patients

The usual intravenous dosage of vancomycin is 10mg/kg per dose given every 6 hours. Each dose should be administered over a period of at least 60 minutes. Close monitoring of serum concentrations of vancomycin may be warranted in these patients.

Neonates

In pediatric patients up to the age of 1 month, the total daily intravenous dosage may be lower. In neonates, an initial dose of 15 mg/kg is suggested, followed by 10 mg/kg every 12 hours for neonates in the first week of life and every 8 hours thereafter up to the age of 1 month. Each dose should be administered over 60 minutes. In premature infants, vancomycin clearance decreases as postconceptional age decreases. Therefore, longer dosing intervals may be necessary in premature infants. Close monitoring of serum concentrations of vancomycin is recommended in these patients.

- Proposed package insert includes information on pediatric patients:

Proposed package insert for Vancomycin hydrochloride for Injection [250 mg/vial, 750 mg/vial, 1.250 g/vial and 1.50 g/vial] explains the indications along with the recommended dose for specific age groups and population including pediatrics. The proposed package insert for Vancomycin hydrochloride for Injection [250 mg/vial, 750 mg/vial, 1.250 g/vial

and 1.50 g/vial] is based upon the package insert of RLD Vancomycin hydrochloride for Injection held by Fresenius Kabi (ANDA# 062663) approved on March 17, 1987 as per current Orange Book.

4. Chemistry Manufacturing and Controls (CMC)

The CMC reviewer states that the Office of Process and Facilities found deficiencies in the drug substance facility inspection; and therefore, from the CMC perspective this NDA is recommended no approval during this submission cycle.

5. Clinical Safety Review

The applicant states that they performed literature searches of the National Library of Medicine databases (NIH/NLM PubMed Central) and other internet sources for safety and efficacy of vancomycin hydrochloride and its pharmacokinetics, bioavailability, pharmacodynamics, dose adjustment, drug interaction, tolerability, its CAS number (1404-90-6), as well as common synonyms for this agent were used for the searches.

Reviewer's Comment: The reviewer looked at the following recent literature publications related to safety profile of vancomycin for injection.

● **Continuous versus intermittent infusion of vancomycin in adult patients: A systematic review and meta-analysis. Jing-Jing Hao, Han Chen, Jian-Xin Zhou (2016). International Journal of Antimicrobial Agents 47, 28–35.**

Continuous infusion of vancomycin (CIV) and intermittent infusion of vancomycin (IIV) are two major administration strategies in clinical settings. However, previous articles comparing the efficacy and safety of CIV versus IIV showed inconsistent results. Therefore, a meta-analysis was conducted to compare the efficacy and safety of CIV and IIV. PubMed, the Cochrane Library and Web of Science up to June 2015 were searched using the keywords ‘vancomycin’, ‘intravenous’, ‘parenteral’, ‘continuous’, ‘intermittent’, ‘discontinuous’, ‘infusion’, ‘administration’ and ‘dosing’. Eleven studies were included in the meta-analysis. Neither heterogeneity nor publication bias were observed. Patients treated with CIV had a significantly lower incidence of nephrotoxicity compared with patients receiving IIV [risk ratio (RR) = 0.61, 95% confidence interval (CI) 0.47–0.80; $P < 0.001$]. No significant difference in treatment failure between the two groups was detected. Mortality between patients receiving CIV and patients receiving IIV was similar (RR = 1.15, 95% CI 0.85–1.54; $P = 0.365$). This meta-analysis showed that CIV had superior safety compared with IIV, while the clinical efficacy was not significantly different. The authors’ state that a further multicenter randomized controlled trial is required to confirm these results.

Adverse effects

Five studies analyzed adverse effects besides nephrotoxicity. Akers et al. reported a high number of onset of thrombocytopenia (16/90 in the CIV group and 11/81 in the IIV group; $P = 0.53$). In the study conducted by Vuagnat et al., adverse drug effect led to termination of treatment in two patients in the CIV group (with catheter phlebitis) and five patients in the IIV group (including two cases of allergic reaction and one case each of catheter phlebitis, severe neutropenia and severe depression). Red man syndrome was reported in two studies, which was observed only in the IIV group results.

Reviewer's Comment: Nephrotoxicity, thrombocytopenia, allergic reaction, phlebitis, neutropenia, and "red man" syndrome are mentioned in this article. These adverse reactions are all labeled reactions in the vancomycin for injection label.

**•Rocío Álvarez, Luis E. López Cortés, José Molina, José M. Cisneros, and Jerónimo Pachón
AAC Accepted Manuscript Posted Online 8 February 2016 Antimicrob. Agents Chemother.
VANCOMYCIN: OPTIMIZING ITS CLINICAL USEdoi:10.1128/AAC.03147-14**

This review article analyzes the new available information about vancomycin published in recent years, regarding pharmacokinetic and pharmacodynamics, serum concentration monitoring, and optimal vancomycin dosing in special situations (obese people, burn patients, renal replacement therapy, among others). Vancomycin efficacy is linked to a correct dosage which should aim to reach an area under the curve (AUC)/MIC ratio of ≥ 400 ; serum trough levels of 15 to 20 mg/liter are considered a surrogate marker of an AUC/MIC ratio of ≥ 400 for a MIC of ≤ 1 mg/liter. For *Staphylococcus aureus* strains presenting with a MIC > 1 mg/liter, an alternative agent should be considered. Vancomycin doses must be adjusted according to body weight and the plasma trough levels of the drug. Nephrotoxicity has been associated with target vancomycin trough levels above 15 mg/liter. Continuous infusion is an option, especially for patients at high risk of renal impairment or unstable vancomycin clearance. In such cases, vancomycin plasma steady-state levels and creatinine monitoring are strongly indicated.

Reviewer's Comment: This article describes nephrotoxicity associated with target vancomycin trough levels above 15 mg/liter. In a recent Tracked Safety Issue (TSI) of Acute Kidney Injury Associated with Vancomycin clinical memo review by Dr. Hala Shamsuddin (in DARRTS, dated 1/13/2017) also describes the relationship between troughs ≥ 15 mcg/mL and nephrotoxicity persisted after adjustment for covariates known to independently increase the risk of a nephrotoxicity event.¹

● **Vancomycin toxicity in neonates: a review of the evidence.** Lestner JM, Hill, LF, Heath PT, and Sharland M **Curr Opin Infect Dis.** 2016 Jun;29(3):237-47

This is a review article of vancomycin, a first-line agent in the treatment of serious Gram-positive infections in the neonatal population. The published evidence on vancomycin toxicity in neonates is limited. This review summarizes preclinical studies and clinical trials describing vancomycin toxicity. The authors discuss proposed pathophysiology and summarize evidence supporting dose–response relationships, genetic and environmental determinants, and consider future research required to further define vancomycin toxicity.

Current dosing regimens for vancomycin result in subtherapeutic levels in a large proportion of patients. Higher daily doses have been proposed, which have led to concerns regarding increased toxicity. Nephrotoxicity occurs in 1–9% of neonates receiving currently recommended doses. The incidence is highest in those receiving concomitant nephrotoxic drugs. Vancomycin-associated ototoxicity is rare in patients of all ages. Exposure–toxicity relationships in relation to nephrotoxicity and ototoxicity have not been clearly defined in neonates receiving vancomycin. The authors states that current evidence supports the favorable safety profile of vancomycin in neonates. Further studies that address safety concerns relating to high-dose intermittent dosing regimens are needed. Such studies must include robust and standardized definitions of renal and hearing impairment, and include follow-up of sufficient length to establish the long-term implications of experimental findings.

Reviewer’s Comment: The reviewer agrees with the authors that the current evidence supports a favorable safety profile of vancomycin in neonates. However, further robust studies in neonates are needed to address safety concerns such as nephrotoxicity and ototoxicity related to vancomycin.

● **Acute Kidney Injury in a Child Receiving Vancomycin and Piperacillin/Tazobactam.** Ibach BW, Henry ED, Johnson PN. **J Pediatr Pharmacol Ther.** 2016 Mar-Apr;21(2):169-75

Recent reports have described increased risk of acute kidney injury (AKI) in adults receiving concomitant vancomycin and piperacillin/tazobactam, but few reports exist in children. This case report describes an 8-year-old girl who was admitted to the pediatric intensive care unit with respiratory distress secondary to pneumonia. She began treatment with vancomycin and piperacillin/tazobactam. She developed AKI, and piperacillin/tazobactam and vancomycin were discontinued. Following a furosemide infusion, her AKI resolved and serum creatinine returned to baseline. She later resumed piperacillin/tazobactam monotherapy for multidrug-resistant tracheitis with no evidence of AKI and was eventually discharged to a long-term care facility. The Naranjo probability scale supports a probable drug-related adverse event. Clinicians must be aware of the possibility of AKI with this combination and should monitor renal function and

vancomycin concentrations vigilantly. The authors state that future prospective studies are needed to explore the incidence and clinical characteristics associated with AKI after this combination in children.

Reviewer’s Comment: Concomitant administration of vancomycin and piperacillin/tazobactam could lead to AKI if renal function and vancomycin concentrations are not monitored in patients. The currently approved ZOSYN® (piperacillin and tazobactam) for injection dated 06/10/2016 under Drug Interactions (Highlights of Prescribing Information section) states: “Co-administration of ZOSYN with vancomycin may increase the incidence of acute kidney injury. Monitor kidney function in patients receiving ZOSYN and vancomycin.”² This drug interaction statement should also be mentioned under the Drug Interactions section of the proposed Vancomycin HCl for Injection label.

● **Systematic Review and Meta-Analysis of Acute Kidney Injury Associated with Concomitant Vancomycin and Piperacillin/tazobactam. Hammond DA, Smith MN, Li C, Hayes SM, Lusardi K, Bookstaver PB. Clinical Infectious Diseases 2017;64(5):666–74**

Concomitant vancomycin and piperacillin/tazobactam (PT) may be associated with increased acute kidney injury (AKI) compared to vancomycin without PT. Medline, Cochrane, and Scopus were searched through October 2016 using “vancomycin,” “piperacillin,” “tazobactam,” and “AKI,” “acute renal failure,” or “nephrotoxicity.” A registered meta-analysis (PROSPERO: CRD42016041646) with relevant scenarios was performed. Fourteen observational studies totaling 3549 patients were analyzed. Concomitant vancomycin and PT was associated with AKI in unadjusted odds ratio (OR, 3.12; 95% confidence interval [CI], 2.04–4.78) and in adjusted OR (aOR, 3.11; 95% CI, 1.77–5.47) analyses. Similar findings were seen assessing studies in adults (aOR, 3.15; 95% CI, 1.72–5.76), children (OR, 4.55; 95% CI, 2.71–10.21), and when <50% of patients received care in an intensive care unit (aOR, 3.04; 95% CI, 1.49–6.22) but not ≥50% (aOR, 2.83; 95% CI, 0.74–10.85). Increased AKI with concomitant vancomycin and PT should be considered when determining beta-lactam therapy.

Reviewer’s Comment: Clinicians should be aware of this association with increased AKI when vancomycin and piperacillin/tazobactam are concomitantly administered.

● **Hypersensitivity Reaction Following Administration of Low-Dose Oral Vancomycin for the Treatment of *Clostridium difficile* in a Patient With Normal Renal Function. Baumgartner LJ, Brown L, Geier C. J Pharm Pract. 2016 Sep 14**

This case report describes a 51-year-old male was admitted to a large academic medical center for acute perineal cellulitis with abscess. He was treated with incision and drainage, followed by a course of IV vancomycin with subsequent trimethoprim–sulfamethoxazole. His medical history was significant for diverticulitis and a documented allergy to metronidazole. Thirteen

days following this admission, the patient presented to the emergency department (ED) with abdominal pain, abnormal stool (watery with mucus and dark red blood), and painful urination.

Laboratory test results at presentation included a serum creatinine of 0.88 mg/dL and WBC count of 23,300 cells/mL. A *C. difficile* toxin was sent to the laboratory, and the patient was started on vancomycin 125 mg by mouth every 6 hours as clinical suspicion for severe *C. difficile* infection (CDI) was high. The patient was eventually discharged to home to continue this regimen for 14 days. His diagnosis of CDI was later confirmed with a positive *C. difficile* toxin B gene.

Three days after starting the oral vancomycin, the patient presented back to the ED with a chief complaint of localized maculopapular rash to his left hip area with associated pruritus. He denied any shortness of breath and indicated that the diarrhea has “slowed down.” His vital signs, including temperature, were within normal limits. Given the systemic absorption from oral vancomycin administration is rare and not likely enough to cause an allergic reaction, it was decided to redose the patient with a single dose of oral liquid vancomycin (125 mg).

Approximately 3 hours after the dose was administered, the nurse noticed that the patient’s condition had worsened. The rash spread from the left hip down throughout the leg with visible urticarial. The patient was emergently treated with both histamine 1 and 2 receptor antagonists. The infectious disease service was consulted, and the patient was thought to be having an allergic reaction secondary to systemic absorption of oral vancomycin. It was eventually decided to discharge the patient with no CDI treatment and a prescription for histamine antagonists with education to return if diarrhea worsened. Applying the Naranjo adverse drug reaction probability scale to this case, a score of 5 was obtained, indicating a probable association between the administration of oral vancomycin and the hypersensitivity reaction.

Ten days after the last ED discharge, the patient presented back to the ED with worsening abdominal pain, right lower quadrant tenderness, and watery diarrhea and was subsequently diagnosed again with CDI. Due to allergies to both vancomycin and metronidazole, the patient was successfully treated with fidaxomicin 200 mg by mouth twice a day for 10 days.

Reviewer’s Comment: This case supports the possible occurrence of hypersensitivity reaction following low-dose oral vancomycin administration in a patient with severe C. difficile infection.

Safety Conclusion

In general vancomycin has a favorable safety and tolerability profile. The most frequent adverse reactions include infusion reactions, nephrotoxicity, ototoxicity, and hematologic toxicity. Patients may develop anaphylactoid reactions, including hypotension, wheezing, dyspnea, urticaria, or pruritus. Rapid infusion may also cause flushing of the upper body (“red man syndrome”) or pain and muscle spasm of the chest and back. It is thought to be mediated by histamine release from mast cells, and considered a pseudo-allergic drug reaction without underlying immunological processes.

Neutropenia is observed not infrequently in patients receiving vancomycin for longer periods of time. Thrombocytopenia, as well as leukocytosis, and eosinophilia have been associated with vancomycin.

Anaphylactic reaction is mediated by drug-specific IgE antibodies. Patients with anaphylactic reactions to vancomycin often have a history of multiple prior exposures. Oral administration of vancomycin, despite its poor systemic absorption can elicit a hypersensitivity reaction in a patient treated for *C. difficile* infection (CD) with a prior vancomycin exposure as reported by Baumgartner LJ et al.

Regarding information of vancomycin use in pregnancy, the Pregnancy and Lactation Labeling Rule (PLLR) Labeling review by Leyla Sahin, M.D., Division of Pediatric and Maternal Health, states in their risk summary: “There are no available data on vancomycin for injection use in pregnant women to inform a drug associated risk of major birth defects or miscarriage. Available published data on vancomycin use in pregnancy during the second and third trimesters have not shown an association with adverse pregnancy related outcomes.”

Likewise in their Lactation-risk summary, quote: “There are insufficient data to inform the levels of vancomycin in human milk. (b) (4)

. There are no data on the effects on the breastfed infant or milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for vancomycin and any potential adverse effects on the breastfed infant from vancomycin or from the underlying maternal condition.”

In conclusion, the clinical reviewer agrees with Rubinstein et. al., that vancomycin has been a very important therapeutic armamentarium and remains effective for many years as long as resistance to vancomycin remains controlled.⁵

6. Labeling Review

Labeling content has been revised in several sections of the Vancomycin HCl for Injection, USP prescribing information to comply with the Physician's Labeling Rule (PLR) regulations. Generally revisions involve limited re-writing aimed at clarifying text, eliminating redundancies, and updating outdated terminology. Information was re-ordered and re-formatted to enhance labeling organization, presentation, readability and ease of use. For example, some of the following clinical sections are revised:

- Under the INDICATIONS AND USAGE section, contents are edited to include headings for each listed indication, and updating outdated clinical terms and bacterial nomenclature.
- Under the WARNINGS and PRECAUTIONS section: The numbering of Warnings has been edited to take into account frequency and severity of the adverse reactions related to vancomycin.
- Under the ADVERSE REACTIONS section: The adverse reactions associated with the use of Vancomycin HCl for Injection as identified in clinical studies or postmarketing reports are listed.
- Under the DRUG INTERACTIONS section: This section has been updated to include the statement regarding concomitant use of piperacillin/tazobactam and vancomycin may be associated with an increased incidence of acute kidney injury.
- Under the PATIENT COUNSELING INFORMATION section: The counseling information is updated to reflect the warnings section statement regarding frequency and severity of the adverse reactions related to vancomycin.

Reviewer's Comment: The proposed Vancomycin HCl for Injection prescribing information will be reviewed in its entirety in the next review cycle of this application.

7. Conclusion and Recommendation

From the clinical standpoint, this NDA is recommended for non-approval due to CMC deficiencies and labeling issues.

References

1. TSI #/Subject 1507/Acute Kidney Injury Associated with Vancomycin- Clinical Memo by Hala Shamsuddin, M.D. (in DARRTS- NDA 050671, dated 01/13/2017)
2. ZOSYN® (piperacillin and tazobactam) for injection prescribing information- June 10, 2016
3. Pregnancy and Lactation Labeling Rule (PLLR) Labeling review by Leyla Sahin, M.D., Division of Pediatric and Maternal Health (in DARRTS- dated 04/21/2017).
4. Guidance for Industry: Labeling for Human Prescription Drug and Biological Products- Implementing the Physician Labeling Rule (PLR) Content and Format Requirements
5. Rubinstein E, Keynan Y. Vancomycin revisited - 60 years later. Front Public Health. 2014 Oct 31;2:217

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