CHEMISTRY REVIEW(S)
NDA 205-931

Doxycycline Hyclate Tablet

Aqua Pharmaceuticals

Shrikant Pagay, Ph.D.
ONDQA
Product Quality Review
for the
Division of Anti Infective Products
Chemistry Review Data Sheet

1. NDA 205-931

2. REVIEW #: Addendum 1 to Review 1

3. REVIEW DATE: July 21, 2014

4. REVIEWER: Shrikant Pagay

5. PREVIOUS DOCUMENTS:

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7. NAME & ADDRESS OF APPLICANT:

Name: Aqua Pharmaceuticals

Address: 158 West Gay Street, Suite 310
West Chester, PA, 193180

Representative: Kimberley Forbes-McKean

Telephone: 610-644-7000 x405
8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name:
   b) Non-Proprietary Name (USAN): Doxycycline Hyclate Tablet
   c) Code Name/# (ONDC only):
   d) Chem. Type/Submission Priority (ONDC only):
      • Chem. Type: 5 (new dosage form)
      • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

10. PHARMACOL. CATEGORY: Anti-infective

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 75 mg and 150 mg

13. ROUTE OF ADMINISTRATION: Oral

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:

   ![Chemical Structure Image]

   4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6
   methyl-1,11-dioxo-2-naphthacencarboxamide monohydrochloride, compound with ethyl
   alcohol (2:1), monohydrate

   \((C_{22}H_{24}N_{2}O_{8} \cdot HCl)_{2} \cdot C_{2}H_{6}O \cdot H_{2}O\)

   Molecular weight 1025.87
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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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:

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19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.  ____ Yes  ____ No  If no, explain reason(s) below:
The Chemistry Review for NDA 205-931

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:
The manufacturing and testing facilities were found overall acceptable by the Office of Compliance on 7/21/2014. Biopharmaceuticals has recommended for approval (Review date 6/10/2014). The product quality microbiology reviewer recommended approval (Review date 11/14/2013). The application is satisfactory and the product quality issues have been satisfactorily resolved. Therefore, the application is recommended for approval.

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:
Doxycycline hyclate information is provided through a reference to a DMF. The drug substance is manufactured in . The DMF was last reviewed on 9/30/2013 and found to be adequate.

The following information from the open portion of the DMF is provided for the drug substance. Doxycycline hyclate is a yellow, crystalline hygroscopic powder. The crystalline form is a solvate consists of ½ mol of ethanol and ½ mol of water. The melting point is 201°C. It is optically active chiral centers. Doxycycline hyclate is well characterized for the starting material, process related impurities, known degradants, and potential impurities. The are controlled under the GMP process. Doxycycline hyclate is stable and the re-test period established is when stored under controlled room temperature (25°C).
Drug Product:
The proposed drug products are 75 mg and 150 mg immediate release tablets. The 75 mg tablet is a round, light teal tablet debossed with “75” on one side and “AQ101” on the other side. The 150 mg tablet is an oblong capsule shaped, mossy-green tablet with two parallel score lines on both upper and lower side to provide flexible dosing of 50 and 100 mg. Each 50 mg split portion is debossed with “A” on one side while the other side is unmarked. The tablets contain microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium and magnesium stearate. The tablets are film coated with a commercially available formulation for 75 mg and green for 150 mg tablets. A is used to manufacture the two strengths.

The scored tablets upon splitting also meet the quality requirements for content uniformity, loss of mass, friability, dissolution, and assay for each split portion of the tablet. However, but within the proposed specification. Since pharmacies can provide up to 90 days supplies of medications, stability studies were performed for this in-use period. The split tablets are stable when stored at room temperature for up to 90 days. The tablets meet the USP Monograph. Although applicant’s plan for control strategy does not appear to be in the submission, the following components in the application are considered adequate for the drug product quality:

- Use of excipients with proven functionality in oral solid dosage products;
- Use of in-process parameter ranges for non-critical processes and critical process identification and parameter control;
- In-process testing and specification to control the manufacturing process;
- Release testing of final drug product for critical product attributes such as description, identity, assay, uniformity of dosage unit, dissolution, and microbial limits and tighter specifications for the degradation products and the shelf life;
- Inclusion of HDPE packaging with desiccant for protection from light and moisture;
- Blisters packs for the Physician’s sample from;
- Dissolution specifications for doxycycline hyclate tablet: Q=NLT % in 30 minutes.
B. Description of How the Drug Product is intended to be used
The usual adult dose is 200 mg on day 1 (100 mg every 12 hours) followed by 100 mg daily maintenance dose. Since these tablets are 75 mg and 150 mg, potential for 50 mg, 75 mg, 100 mg, and higher doses are possible. However, package insert should include dosage administration consistent with the available tablet strengths. The tablet should be administered with plenty of fluid to reduce the risk of irritation. The tablets are stored at 20 to 25°C.

C. Basis for Approvability or Not-Approval Recommendation
The DMF for doxycycline hyclate drug substance is adequate. The sponsor has provided sufficient information on the raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug product. The NDA also has provided sufficient stability information on the drug product to assure identity, strength, purity, and quality of the drug product through the approved shelf life. A separate Biopharmaceutics review covers the acceptability of the dissolution test method and the test results. The product quality microbiology has waived requirements for microbiological limit testing. The manufacturing and testing facilities were found overall acceptable by the Office of Compliance. The CMC reviewer made risk assessment with conclusion that the manufacturing and controls appear to be sufficient to maintain the product quality through the life cycle (with required regulatory changes) and documented in the table under Risk Assessment. The drug product shelf life for the commercial tablet in HDPE (60 tablets/bottle) is 18 months and for Physician sample container (blister) 12 months. Therefore, this NDA is now recommended for approval.
## Drug Product Risk Assessment

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III. Administrative

A. Reviewer’s Signature
B. Endorsement Block
   Chemist Name/Date: Same date as draft review
   Chemistry Team Leader Name/Date
   Project Manager Name/Date
C. CC Block

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

/s/

SHRIKANT N PAGAY
07/23/2014

RAPTI D MADUARWE
07/24/2014
NDA 205-931

Doxycycline Hyclate Tablet, 75 mg and 150 mg

Aqua Pharmaceuticals

Shrikant Pagay, Ph.D.

Product Quality Review
Office of New Drug Quality Assessment

for the
Division of Anti Infective Products
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    B. Endorsement Block ...................................................... 13
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NDA 205-931

Reference ID: 3528510
Chemistry Review Data Sheet

1. NDA 205-931

2. REVIEW #: 1

3. REVIEW DATE: May 1, 2014

4. REVIEWER: Shrikant Pagay

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7. NAME & ADDRESS OF APPLICANT:
Name: Aqua Pharmaceuticals

Address: 158 West Gay Street, Suite 310 West Chester, PA, 193180

Representative: Kimberley Forbes-McKeean
Telephone: 610-644-7000 x405

8. DRUG PRODUCT NAME/CODE/TYPE:
   
a) Proprietary Name:
b) Non-Proprietary Name (USAN): Doxycycline Hyclate Tablet
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
   • Chem. Type: 5 (new dosage form)
   • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

10. PHARMACOL. CATEGORY: Anti-infective

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 75 mg and 150 mg

13. ROUTE OF ADMINISTRATION: Oral

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:**

   ![](image.png)

   4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride, compound with ethyl alcohol (2:1), monohydrate

   
   \((C_{22}H_{24}N_2O_8\cdot HCl) \cdot C_2H_6O \cdot H_2O\)

   and a molecular weight of 1025.87

17. **RELATED/SUPPORTING DOCUMENTS:**

   **A. DMFs:**

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

B. Other Documents:

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19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.  _____ Yes  _____ No  If no, explain reason(s) below:
The Chemistry Review for A/NDA 205-931

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability: Pending
The biopharmaceutics reviewer has recommended approval of this NDA (Review date 6/10/2014). The product quality microbiology reviewer has accepted waiving microbial limits release testing (Review date 11/14/2013). From the product quality perspective, the application is satisfactory to assure the identity, strength, purity and quality of the drug product. All product quality issues have been satisfactorily resolved. Labeling comments are marked up in this review and will be finalized during labeling team review. The Office of Compliance has not yet made an overall recommendation for the manufacturing and testing facilities. Therefore, the application is not recommended for approval until an overall acceptable recommendation is received from the Office of Compliance.

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:**

Doxycycline hyclate CMC information is referenced to DMF A Letter of Authorization is provided. The drug substance is manufactured in

The following information from the open portion of the DMF is provided for the drug substance manufactured from . Doxycycline hyclate is a yellow, crystalline hygroscopic powder. The crystalline form is a solvate consisting of ½ mol of ethanol and ½ mol of water per mol of doxycycline. The melting point is 201°C. It is optically active chiral centers. Doxycycline hyclate is well characterized for the starting material, process related impurities, known degradants, and potential impurities. The are controlled under the GMP process. Doxycycline hyclate is stable and the re-test period established is when stored under USP controlled room temperature.
Drug Product:
The proposed drug products are 75 mg and 150 mg doxycycline immediate release tablets. The 75 mg tablet contains mg doxycycline hyclate and is a round, light teal tablet debossed with “75” on one side and “AQ101” on the other side. The 150 mg tablet contains mg doxycycline hyclate. It is an oblong capsule-shaped, mossy-green tablet with two parallel score lines on both upper and lower side to provide flexible dosing of 50 and 100 mg. Each 50 mg split portion is debossed with “A” on one side while the other side is unmarked. Since 300 mg dose is approved only for gonorrhea DAIP agreed to accept a dual-scored 150 mg tablet.

The tablets contain microcrystalline cellulose, sodium lauryl sulfate, and croscarmellose sodium and magnesium stearate. The tablets are film coated with a commercially available formulation for mg and mg tablets. All excipient are compendial and commonly used in tablet formulations.

The scored tablets upon splitting also meet the quality requirements for content uniformity, loss of mass, friability, dissolution, and assay for each split portion of the tablet. However, since pharmacies can provide up to 90 days supplies of medications, stability studies were performed for this in-use period. The split tablets are stable when stored at room temperature for up to 90 days. The tablets meet the USP Monograph.

Although the applicant’s control strategy is not discussed in the submission, the following components in the application are considered adequate for the drug product quality:

- Use of excipients with proven functionality in oral solid dosage products; most of the excipients used are controlled by adherence to compendial specifications.
- Use of in-process parameter ranges for non-critical processes and critical process identification and parameter control.
- In-process testing and specification to control the manufacturing process.
Executive Summary Section

- Release testing of final drug product for critical product attributes such as description, identity, assay, uniformity of dosage unit, dissolution, and microbial limits
- And tighter specifications for the degradation products than for the shelf life
- Inclusion of HDPE packaging with desiccant for protection from light and moisture
- Blister packs for the Physician’s sample
- Dissolution specifications for doxycycline hyclate tablet: Q=NLT 96% in 30 minutes.

The drug product shelf life granted for the commercial tablet in HDPE (60 tablets/bottle) is 18 months and for Physician sample in blister packs 12 months when stored at 20°C to 25°C.

B. Description of How the Drug Product is intended to be used
The usual adult dose is 200 mg on day 1 (100 mg every 12 hours) followed by 100 mg daily maintenance dose. Since these tablets are 75 mg and 150 mg, potential for 50mg, 75 mg, 100 mg, and higher doses are possible. Package insert includes dosage administration information on how these tablet strengths are to be used. The tablet should be administered with plenty of fluid to reduce the risk of irritation. The tablets are stored at 20 to 25°C (68° to 77°F) excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

C. Basis for Approvability or Not-Approval Recommendation
The DMFs for doxycycline hyclate drug substances is adequate. The sponsor has provided sufficient information on the raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug product. The NDA also has provided sufficient stability information on the drug product to assure identity, strength, purity, and quality of the drug product through the approved shelf life. A separate Biopharmaceutics review covers the acceptability of the dissolution test method and the test results, and recommends approval of the NDA. The product quality microbiology review has waived requirements for microbiological limit testing and also recommends approval of the NDA. The CMC reviewer’s risk assessment is given below. The overall conclusion from a CMC perspective is that the manufacturing and controls appear to be sufficient and risks are adequately mitigated to maintain adequate product quality through the life cycle (with required regulatory changes). The shelf life granted for the two configurations (for both strengths) reviewed under this NDA are: 18 months for the commercial HDPE bottle (60 tablets/bottle) and 12 months for the blister Physician sample.
### Drug Product risk assessment

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III. Administrative

A. Reviewer’s Signature
B. Endorsement Block
Chemist Name/Date: Same date as draft review
Chemistry Team Leader Name/Date
Project Manager Name/Date
C. CC Block
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHRIKANT N PAGAY
06/19/2014

RAPTI D MADURAWE
06/19/2014

Reference ID: 3528510