CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208253Orig1s000

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	March 22, 2016
Requesting Office or Division:	Division of Anti- Infective Products (DAIP)
Application Type and Number:	NDA 208253
Product Name and Strength:	Acticlate CAP (doxycycline hyclate) 75 mg per capsule
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Aqua Pharmaceuticals
Submission Date:	January 13, 2016
OSE RCM #:	2016-2554783
DMEPA Primary Reviewer:	Sevan Kolejian, Pharm. D.
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Acticlate CAP, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively. The Applicant did not submit an external name study for this proposed proprietary name.

2 REGULATORY HISTORY

Aqua Pharmaceuticals previously submitted the proposed proprietary name, (b) (4) ***, on June 29, 2015. However, the Division of Medication Error Prevention and Analysis (DMEPA) found the name, (b) (4) ***, unacceptable due to (b) (4) .

Subsequently, on November 20, 2015, Aqua Pharmaceuticals submitted the proposed name, (b) (4) as primary proprietary name and (b) (4) as alternative for review. At the team meeting, the review team discussed how to address the concerns related to dosing limitations with the capsule. Since the proposed strength for doxycycline hyclate capsules is 75 mg per capsule and the proposed adult dose for this product includes doses of 50 mg, 100 mg, and 200 mg. The division decided to ask the Sponsor if they would consider adding the 75 mg capsule to the currently approved Acticlate labeling (Prescribing Information) to mitigate strength and dosing related inconsistencies. Aqua has agreed to the Agency's proposal to include the 75 mg capsule information to the current Acticlate Tablet Prescribing Information.

Thus, Aqua Pharmaceuticals withdrew the name request for (b) (4) and submitted the name, Acticlate CAP***, for review on January 13, 2016. The Acticlate CAP*** will share full prescribing information with currently marketed Acticlate product.

2.1 PRODUCT INFORMATION

The following product information is provided in the January 13, 2016 proprietary name submission.

Table 1. Relevant Product Information for Acticlate CAP and Acticlate.

	Acticlate CAP	Acticlate (NDA 205931)
Initial Approval	N/A	July 25, 2014

[1] Kolejian, Sevan, Proprietary Name Review for (b) (4) NDA 208253). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 SEP 2. OSE RCM No.: 2015-826811.

Intended Pronunciation	aktə˛klāt kap	aktə˛klāt
Active ingredient	Doxycycline Hyclate	
Indication of use	Tetracycline-class antimicrobial indicated for: ▪ Rickettsial infections ▪ Sexually transmitted infections ▪ Respiratory tract infections ▪ Specific bacterial infections ▪ Ophthalmic infections ▪ Anthrax, including inhalational anthrax (post-exposure) ▪ Alternative treatment for selected infections when penicillin is contraindicated ▪ Adjunctive therapy in acute intestinal amebiasis and severe acne ▪ Prophylaxis of malaria	
Route of administration	Oral	
Dosage Form	Capsule[2]	Tablets
Strength	75 mg per capsule	• 75 mg per tablet • 150 mg per tablet (The tablet is marked with two scored lines for splitting into 3 equal portions).
Dose and Frequency	**Adults:** the usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg daily. In the management of more severe infections, 100 mg every 12 hours is recommended. Uncomplicated gonococcal infections in adults (except anorectal infections in men): 100 mg, by mouth, twice-a-day for 7 days. As an alternate single visit dose, administer 300 mg stat followed in one hour by a second 300 mg dose. For (b) (4) eight years of age: The recommended dosage schedule (b) (4) is 4.4 mg per kg of body weight divided into two doses on the first day of treatment, followed by 2.2 mg per kg of body weight given as a single daily dose or divided into two doses (b) (4) For (b) (4) 45 kg. (b) (4) adult dose (b) (4)	

[2] Each capsule contains doxycycline hyclate equivalent to 75 mg doxycycline, same as the Acticlate 75 mg per tablet formulation.

How Supplied:	○ Bottles of 60 capsules ○ 2 count blister – physician sample	○ 75 mg tablets: Bottles Of 60 Tablets ○ 150 mg tablets: Bottles Of 60 Tablets
Storage:	Store 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. Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.	
Reference Listed Drug	Vibramycin (doxycycline hyclate) capsules; NDA 050007	N/A

3 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

3.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. DMEPA and the Division of Anti-Infective Products (DAIP) concurred with the findings of OPDP's assessment of the proposed name.

3.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

3.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proprietary name[3].

3.2.2 Components of the Proposed Proprietary Name

This proprietary name is comprised of a root name and a modifier. The Applicant indicated in their submission that the proposed name, Acticlate CAP***, is derived from the Proprietary Name, Acticlate (doxycycline hyclate USP) Tablets, in approved NDA 205931 (Aqua Pharmaceuticals) and modifier "CAP"***. The Applicant indicated in their submission that the intended meaning for "CAP"*** is capsule and it is to differentiate between capsule and tablet formulation. We assess the modifier in *Section 3.2.4*.

[3]USAN stem search conducted on January 28, 2016.

3.2.3 Safety Assessment of the root name, Acticlate

This product contains the same active ingredient as Acticlate tablets, and shares the same, indications, route of administration, dose and frequency; however, the products differ in their dosage form, capsule vs. tablet. Additionally, on a milligram to milligram basis, the two products are substitutable. Our search of the FAERS database did not identify any name confusion with the existing Acticlate proprietary name. Thus, we find the use of the root name, Acticlate, for this product acceptable.

3.2.4 Safety Assessment of the Modifier "CAP"

We evaluated the safety of the modifier "CAP"*** to describe this product. We note that "CAP"*** is not a standard modifier. DMEPA recognizes there are limitations using a modifier with product line extensions. We note that modifiers may sometimes be omitted. Omission and oversight of the modifier was evident in FDA Prescription Simulation Studies. Omission of the modifier "CAP" could potentially lead to dispensing of Acticlate tablets. We note that Acticlate tablets share the same active ingredient, indications, route of administration, dose and frequency. The tablet formulation is currently marketed in two different strengths: 75 mg tablet and a 150 mg functionally scored tablet that has two parallel score lines for splitting into 3 equal portions, 50 mg per portion. The proposed capsule dosage form will be supplied in a single strength (75 mg per capsule) which cannot be divided and needs to be swallowed whole. The proposed capsule dosage form will share a package insert (PI) with the currently existing Acticlate tablet. Since the proposed product will be available as the same strength as of the Acticlate 75 mg tablets and is substitutable on a milligram per milligram basis; in the event that a patient receives the tablet formulation instead of the capsule or capsule instead of the tablet, we do not expect adverse clinical consequences to the patient.

We evaluated the safety of the term "CAP" to describe this product. We determine that the proposed modifier "CAP" conveys the differences between the marketed tablet and the proposed capsule dosage form. Therefore, we have not identified a safety concern at this time with the use of the "CAP" modifier and find it acceptable from a safety perspective.

3.2.5 FDA Name Simulation Studies

Seventy practitioners participated in DMEPA's prescription studies. Fourteen responses overlapped with a currently approved product, Acticlate. Twenty-two participants omitted the modifier, CAP, in the study. Of these twenty two participants, fourteen participants misinterpreted Acticlate CAP as Acticlate, thus they omitted the modifier. This misinterpretation involved both the inpatient, outpatient and voice study participants. Appendix B contains the results from the verbal and written prescription studies.

3.2.6 Comments from Other Review Disciplines at Initial Review

In response to the OSE, January 28, 2016 e-mail, the Division of the Division of Anti-Invective Products (DAIP), one reviewer commented on the need for the modifier "CAP" since the formulation "capsule" is part of the label and labeling and Acticlate CAP

(doxycycline hyclate) Capsules is like saying capsules twice. Another reviewer commented that the proposed proprietary name appears to give an impression that this is some special dosage formulation. We determined that the use of the modifier "CAP" in the proprietary name will not pose a safety concern, see section 3.2.4 above.

3.2.7 Medication Error Data Selection of Cases

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 2 (see Appendix A1 for a description of FAERS database) for name confusion errors involving **Acticlate** that would be relevant for this review. Our search did not retrieve any cases.

Table 2. FAERS Search Strategy	
Search Date	January 28, 2016
Drug Name	Acticlate [product name]
Event (MedDRA Terms)	**DMEPA Official Proprietary Name Review Search Terms Event List:** Product name confusion (PT) Medication error (PT) Intercepted medication error (PT) Drug dispensing error (PT) Intercepted drug dispensing error (PT) Circumstance or information capable of leading to a medication error (PT)
Date Limits	No limit

3.2.8 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Anti-Invective Products (DAIP) via e-mail on March 14, 2016. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Anti-Invective Products (DAIP) on March 15, 2016, they expressed that one potential concern with modifier "CAP" is that CAP is a common acronym used by clinicians for "Community Acquired Pneumonia" and the usual adult dosage for treatment of community acquired pneumonia is 100 mg doxycycline twice daily; however, the "Acticlate CAP" is a 75 mg capsule so there could be potential for confusion about the adult dose. We considered whether inclusion of the CAP modifier may be misinterpreted by healthcare professionals, leading them to believe CAP represents "community acquired pneumonia". We determined that the abbreviation "CAP" has varied meanings, one of which is also the dosage form, capsule[4]. We determine that the proposed modifier

[4] MediLexicon International Ltd, Medical Abbreviations Dictionary available online at: http://www medilexicon.org accessed on March 22, 2016.

"CAP" conveys the differences between the marketed tablet and the proposed capsule dosage form. Additionally, we note that proposed Acticlate CAP will share full prescribing information (FPI) with Acticlate (75 mg per tablet and 150 mg per tablet) and the FPI will have appropriate adult pneumonia dosing information. Thus, we have no safety concern and find the proposed "CAP" modifier acceptable from a medication error perspective (see section 3.2.4 above). We notified OPDP regarding possibility of associating Acticlate CAP with community acquired pneumonia. During an Acticlate CAP team meeting and per follow-up email communication dated March 17, 2016, OPDP stated they do not have any objections for the proprietary name Acticlate CAP from a promotional perspective.

4 CONCLUSIONS

The proposed proprietary name is acceptable.

If you have further questions or need clarifications, please contact Karen Townsend, OSE project manager, at 301-796-5413.

4.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Acticlate CAP, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your January 13, 2016 submission are altered prior to approval of the marketing application, the name must be resubmitted for review.

REFERENCES

1. ***USAN Stems (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page)***

   USAN Stems List contains all the recognized USAN stems.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment**: For prescription drug products, OPDP assesses the name for misbranding concerns. . For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [5]

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	**Is the proposed name obviously similar in spelling and pronunciation to other names?**
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.

[5] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

Y/N	**Are there medical and/or coined abbreviations in the proprietary name?**
	Proprietary names should not incorporate medical abbreviations (e.g., QD, BID, or others commonly used for prescription communication) or coined abbreviations that have no established meaning.
Y/N	**Are there inert or inactive ingredients referenced in the proprietary name?**
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	**Does the proprietary name include combinations of active ingredients?**
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	**Is there a United States Adopted Name (USAN) stem in the proprietary name?**
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	**Is this proprietary name used for another product that does not share at least one common active ingredient?**
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	**Is this a proprietary name of a discontinued product?**
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a

random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

c. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

   The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

   Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

   When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Appendix A1: Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Acticlate Study (Conducted on February 19, 2016)

<table>
<tr><th>Handwritten Requisition Medication Order</th><th>Verbal Prescription</th></tr>
<tr><td>Medication Order:
Acticlate CAP 1 capsule po twice daily</td><td rowspan="2">Acticlate Cap
Take One capsule by mouth twice daily
Dispense # 60</td></tr>
<tr><td>Outpatient Prescription:
Acticlate CAP
1 capsule po twice daily
#60</td></tr>
</table>

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies RepoCAP)

Study Name: Acticlate CAP
250 People Received
Study
70 People Responded

Total	**23**	**22**	**25**	
INTERPRETATION	**OUTPATIENT**	**VOICE**	**INPATIENT**	**TOTAL**
ACKTACLATE CAP	0	1	0	1
ACTACLATE	0	1	0	1
ACTACLATE CAPS	0	1	0	1
ACTICLATE	3	4	7	14
ACTICLATE CAP	15	8	8	31
ACTICLATE CAPSULES	0	0	1	1
ACTICLATI CAP	2	0	0	2
ACTICLOTI CAP	1	0	0	1
ACTIDATE	0	0	1	1
ACTIDATE CAP	0	0	3	3
ACTIKLAT CAP	0	1	0	1
ACTILATE	0	0	1	1
AFTACAVE	0	1	0	1
AICTIDATE CAP	0	0	1	1
APLITICLATE	0	1	0	1
ARTICLATE	0	0	1	1
ARTICLATE CAP	1	0	0	1
HACTICLATE CAP	0	1	0	1
HAPTICLATE	0	1	0	1
HECTICLATE CAP	0	1	0	1
OCTICLATE	0	0	1	1
OCTICLATE CAP	1	0	0	1
OCTICLATO CAP	0	0	1	1
PATACLAD CAP	0	1	0	1

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/s/

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PROPRIETARY NAME REVIEW

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Date of This Review:	September 2, 2015
Application Type and Number:	NDA 208253
Product Name and Strength:	(b) (4) (Doxycycline hyclate) capsule; 75 mg
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Aqua Pharmaceuticals
Panorama #:	2015- 826811
DMEPA Primary Reviewer:	Sevan Kolejian, Pharm. D.
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD
DMEPA Associate Director:	Irene Z. Chan, PharmD, BCPS
DMEPA Director:	Todd Bridges, RPh.

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IRENE Z CHAN
09/02/2015

TODD D BRIDGES
09/03/2015