CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214581Orig1s000

OTHER REVIEW(S)

LABELING CONSULT MEMORANDUM

DATE: December 20, 2021

FROM: Elizabeth O'Shaughnessy, MD, Clinical Reviewer, Division of Anti-Infectives (DAI)

Yuliya Yasinskaya, MD, Clinical Team Leader, DAI

THROUGH: Dmitri Iarikov, MD, PhD, Deputy Director, DAI

Peter Kim MD, MS, Division Director, DAI

TO: Keith Hull, MD, PhD, Clinical Reviewer,

Division of Rheumatology and Transplant Medicine (DRTM)

Anil Rajpal, MD, Clinical Team Lead, DRTM

Jane Filie, MD, DRTM

Re: NDA 214581

Subject: to review the instructions on the treatment and prophylaxis of malaria in the Dosage and Administration section of the draft labeling

MATERIALS REVIEWED:

- Original 505 (b)(2) NDA submission for hydroxychloroquine (HCQ) sulfate from Novitium Pharma LLC received 15-APRIL-2020
- Novitium Pharma LLC resubmission of NDA on 22-JULY-2021
- Draft labeling for hydroxychloroquine sulfate, NDA 214581

Background:

Novitium Pharm LLC submitted a 505 (b)(2) NDA 214581 for hydroxychloroquine (HCQ) sulfate tablets USP 200 mg, 300 mg, and 400 mg for the treatment of acute attacks of malaria due to *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale*, and susceptible strains of *Plasmodium falciparum*. HCQ is also indicated for the treatment of rheumatoid arthritis, systemic lupus erythematosus, and chronic discoid lupus erythematosus.

The Applicant selected PLAQUENIL (hydroxychloroquine sulfate) 200 mg tablets (NDA 009768; Concordia Pharmaceuticals Inc) as the listed drug (LD). The HCQ product (NDA 214581) contains the same active ingredient and is formulated in the same tablet dosage form as the referenced product. The oral route of administration, conditions of use, and therapeutic indications are the same as PLAQUENIL; however, the applicant is introducing a new scored 300 mg tablet.

Labeling Review

DRTM requested DAI to review draft labeling for the treatment and prophylaxis of malaria, specifically the Dosage and Administration section.

We note a change in the Dosage and Administration section as compared to the LD, PLAQUENIL. In the Dosage and Administration section of the draft labeling, (b) (4) (b) (4). As the proposed HCQ tablet cannot be crushed, and although the scored 300mg tablet can be split (150mg x 2), it cannot be split further to achieve doses less than 150mg. Therefore, we recommend that the prescribing information be revised to include a bodyweight cut-off ≥ 23kg for pediatric dosing (23 x 6.5mg=149.5mg).

Recommended revisions to the HIGHLIGHTS and DOSAGE AND ADMINISTRATION sections are outlined below, (new text: double underline; deleted text: ~~strikethrough~~).

(b) (4)

(b) (4)

Following discussions with DRTM, the following comment was sent to the Applicant on 12/01/2021:

"*We note that* (b) (4) (b) (4) *labeling states that the tablets should not be crushed and although the scored 300mg tablet can be split (150mg x 2), it cannot be split further to achieve doses less than 150mg. Labeling was revised to be consistent with the listed drug and reflect the supported dosing based on the submitted information.*"

The Applicant accepted the labeling changes and submitted a draft labeling with minor editorial changes on 12/07/2021. These are deemed acceptable.

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/s/

ELIZABETH M OSHAUGHNESSY
01/05/2022 07:44:18 AM

YULIYA I YASINSKAYA
01/05/2022 09:20:18 AM

DMITRI IARIKOV
01/05/2022 09:32:25 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 3, 2022
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	NDA 214581
Product Name and Strength:	(Hydroxychloroquine sulfate) Tablets, 200 mg and 300 mg
Applicant/Sponsor Name:	Novitium Pharma LLC
OSE RCM #:	2021-771-1
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on December 21, 2021 for hydroxychloroquine sulfate tablets. Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container labels for hydroxychloroquine sulfate tablets (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

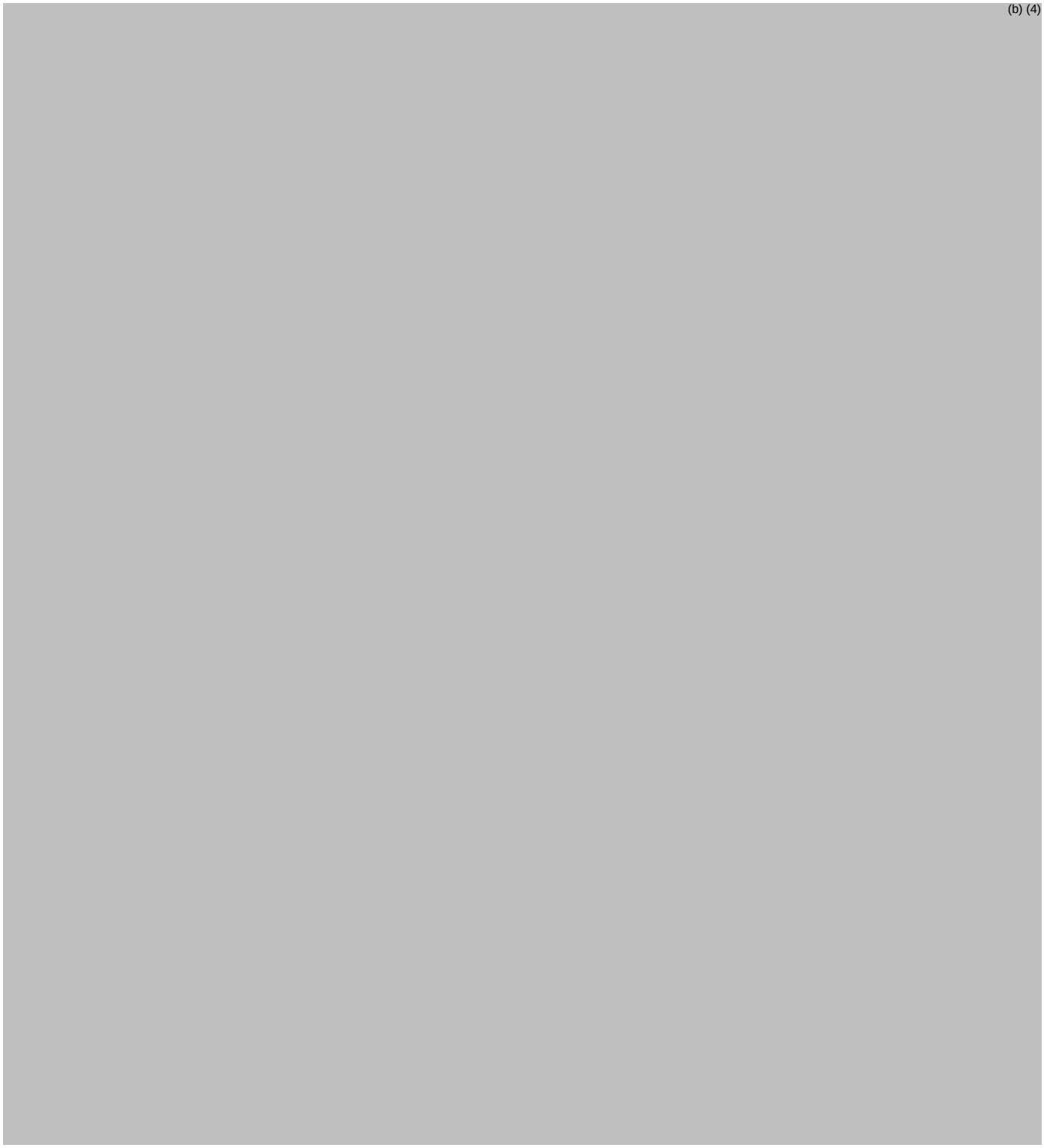
2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Vee, S. Label and Labeling Review for hydroxychloroquine sulfate tablets (NDA 214581). Silver Spring (MD): FDA, CDER, OSE, DEMPA 1 (US); 2021 SEP 29. RCM No.: 2021-771.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON DECEMBER 21, 2021

Container labels



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/s/

SARAH K VEE
01/03/2022 10:35:54 AM

IDALIA E RYCHLIK
01/03/2022 12:12:44 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 29, 2021
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	NDA 214581
Product Name, Dosage Form, and Strength:	Hydroxychloroquine sulfate Tablets, 200 mg and 300 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novitium Pharma LLC
FDA Received Date:	July 22, 2021
OSE RCM #:	2021-771
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Hydroxychloroquine sulfate Tablets, the Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the proposed prescribing information (PI) and container labels for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

Novitium submitted NDA 214581 on April 5, 2020 as a 505(b)(2) Application (RLD is Planquenil (Hydroxychloroquine Sulfate) (NDA N009768)). However, the Application received a Complete Response (CR) on February 12, 2021. Novitium submitted their response to the CR on July 22, 2021. DMEPA did not complete a labeling a review at the time.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed hydroxychloroquine PI and container labels and note that the indication and dosage and administration sections are identical to the RLD, Plaquenil. The proposed hydroxychloroquine has an additional strength of 300 mg in addition to the 200 mg strength. The two strengths are adequately differentiated in terms of the container labels. The recommended dosages for the proposed product support the 300 mg strength and may reduce the number of tablets that are needed in certain situations. Thus, the addition of the 300 mg strength is acceptable from a medication error perspective.

5 CONCLUSION & RECOMMENDATIONS

The proposed prescribing information (PI) and container label may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and the proposed recommendations to minimize the risk for medication error in Section 5.1 for the Division and in Section 5.2 for Novitium.

5.1 RECOMMENDATIONS FOR DIVISION OF RHEUMATOLOGY AND TRANSPLANT MEDICINE (DRTM)

A. Prescribing Information

1. How Supplied/Storage and Handling Section
    a. The storage statement in Section 16 How Supplied/Storage and Handling does not include units of measurement following the first numbers in the temperature ranges. Omission of the units of measure, could lead to confusion that may result in deteriorated drug product errors. Revise the storage information to include the Centigrade symbol (C) following 20° and Fahrenheit symbol (F) following 68°. For example, "Store at room temperature [20°C to 25°C (68°F to 77°F), allow excursions between 15°C and 30°C (59°F and 86°F)]".

5.2 RECOMMENDATIONS FOR NOVITIUM PHARMA LLC

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. To ensure consistency with the Prescribing Information, revise "(b) (4) (b) (4)" to read "Dosage: see prescribing information".
2. As currently presented, the format for the expiration date is not presented. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.
3. Storage information does not include units of measurement following the first numbers in the temperature ranges. Omission of the units of measure, could lead to confusion that may result in deteriorated drug product errors. Revise the storage information to include the Centigrade symbol (C) following 20° and Fahrenheit symbol (F) following 68°. For example, "Store at room temperature [20°C to 25°C (68°F to 77°F), allow excursions between 15°C and 30°C (59°F and 86°F)]".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for N/A received on July 22, 2021 from Novitium Pharma LLC, and the listed drug (LD).

Table 2. Relevant Product Information for Hydroxychloroquine and the Listed Drug		
Product Name	N/A	Plaquenil[a]
Initial Approval Date	N/A	04/18/1955
Active Ingredient	Hydroxychloroquine sulfate	
Indication	• Treatment of uncomplicated malaria due to Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale, and Plasmodium vivax in adult and pediatric patients. • Prophylaxis of malaria in geographic areas where chloroquine resistance is not reported in adult and pediatric patients. • Treatment of rheumatoid arthritis in adults. • Treatment of systemic lupus erythematosus in adults. • Treatment of chronic discoid lupus erythematosus in adults.	
Route of Administration	Oral	
Dosage Form	Tablets	
Strength	200 mg and 300 mg	200 mg
Dose and Frequency	Dosage for Malaria in Adult and Pediatric Patients <u>Prophylaxis</u> Treatment must start 2 weeks before travel to an endemic area. Advise the patient to take the prophylaxis dosage once a week, staring 2 weeks prior to travel to the endemic area, on the same day every week, continuing the same weekly dose while in the endemic area, and for 4 weeks after leaving the endemic area. The recommended prophylaxis dosage is: • Adult patients: 400 mg once a week • [redacted] (b) (4) pediatric patients: 6.5 mg/kg actual body weight (up to 400 mg) once a week <u>Treatment of Uncomplicated Malaria</u> The dosages for the treatment of uncomplicated malaria are: • Adult patients: Administer 800 mg initially; subsequently administer 400 mg at 6 hours, 24 hours, and 48 hours after the initial dose (total dosage = 2000 mg). • [redacted] (b) (4) pediatric patients:	

[a] Planquenil [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2021 AUG 18. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/009768s053lbl.pdf.

	Administer 13 mg/kg (up to 800 mg) initially; subsequently administer 6.5 mg/kg (up to 400 mg) at 6 hours, 24 hours, and 48 hours after the initial dose (total dosage = 31 mg/kg - up to 2000 mg). Dosage for Rheumatoid Arthritis in Adults The recommended dosage is: • Initial dosage: 400 mg to 600 mg daily as a single daily dose or two divided doses. The action of hydroxychloroquine is cumulative and may require weeks to months for maximum therapeutic effect. Daily doses exceeding 5 mg/kg (actual weight) of hydroxychloroquine sulfate increase the incidence of retinopathy. • Chronic dosage: 200 mg, 300 mg or 400 mg daily, as a single dose or two divided doses. Dosage for Systemic Lupus Erythematosus in Adults The recommended dosage is 200 mg, 300 mg or 400 mg daily, as a single dose or two divided doses. Dosage for Chronic Discoid Lupus Erythematosus in Adults The recommended dosage is 200 mg, (b) (4) or 400 mg daily, as a single dose or two divided doses.	
How Supplied	200 mg: Bottles of 30 and 100 tablets 300 mg: Bottles of 100 tablets	Bottles of 60 and 100 tablets
Storage	Dispense in a tight, light-resistant container as defined in the USP/NF. Keep out of the reach of children. Store at room temperature [20° to 25°C (68° to 77°F), allow excursions between 15° and 30°C (59° and 86°F)].	Dispense in a tight, light-resistant container as defined in the USP/NF. Store at room temperature up to 30°C (86°F) and allow for excursions between 15°C and 30°C (59°F and 86°F).

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following N/A labels and labeling submitted by Novitium Pharma LLC.

- Container label received on July 22, 2021.
- Prescribing Information (Image not shown) received on July 22, 2021, available from \\CDSESUB1\evsprod\nda214581\0012\m1\us\11413-draftpackageinsertword.docx

G.2 Label Images

(b) (4)

1 Page of Draft Labeling has been Withheld in Full Immediately Following this Page

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SARAH K VEE
09/29/2021 10:56:59 AM

IDALIA E RYCHLIK
09/29/2021 02:34:08 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 9/13/2021

TO: Division of Rheumatology and Transplant Medicine (DRTM)
Office of Immunology and Inflammation (OII)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 214581

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submissions: (b) (4).

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	(b) (4)

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/s/

FOLAREMI ADEYEMO
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