CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214581Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Clinical Pharmacology Review/Clinical Review/Division Summary

Date	See electronic stamp date
From	Qianni Wu, Pharm.D., Clinical Pharmacology Reviewer Jianmeng Chen, M.D., Ph.D., Clinical Pharmacology Team Leader Keith Hull, M.D., Ph.D., Clinical Reviewer Jane Filie, M.D., Associate Director for Labeling Nikolay Nikolov, M.D., Division Director/Signatory
Subject	Clinical Pharmacology Review/Clinical Review/Division Summary
NDA/BLA # and Supplement#	214581
Applicant	Novitium Pharma LLC
Date of Submission/Resubmission	April 15, 2020; July 22, 2021
PDUFA Goal Date	January 21, 2022
Proprietary Name	N.A.
Established or Proper Name	Hydroxychloroquine sulfate
Dosage Form(s)	Tablets
Applicant Proposed Indication(s)/Population(s)	• 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.
Applicant Proposed Dosing Regimen(s)	<u>Malaria in Adult and Pediatric Patients:</u> • Prophylaxis: Begin weekly doses 2 weeks prior to travel to the endemic area, continue weekly doses while in the endemic area, and continue the weekly doses for 4 weeks after leaving the endemic area: Adults: 400 mg once a week [redacted] (b) (4) pediatric patients: 6.5 mg/kg up to 400 mg, once a week • Treatment of Uncomplicated Malaria: See Full Prescribing Information (FPI) for complete dosing information. <u>Rheumatoid Arthritis in Adults:</u> • Initial dosage: 400 mg to 600 mg daily • Chronic dosage: 200 mg, 300 mg or 400 mg once daily (or in two divided doses) <u>Systemic Lupus Erythematosus in Adults:</u> • 200 mg, 300 mg or 400 mg once daily (or in two divided doses) <u>Chronic Discoid Lupus Erythematosus in Adults:</u> • 200 mg, [redacted] (b) (4) or 400 mg once daily (or in two divided doses)
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	Hydroxychloroquine Sulfate Tablets is an antimalarial and antirheumatic indicated for the:

	• 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. <u>Limitations of Use:</u> Hydroxychloroquine Sulfate Tablets is **not** recommended for the: • Treatment of complicated malaria. • Treatment of chloroquine or hydroxychloroquine-resistant strains of *Plasmodium* species. • Treatment of malaria acquired in geographic areas where chloroquine resistance occurs or when the *Plasmodium* species has not been identified. • Prophylaxis of malaria in geographic areas where chloroquine resistance occurs. Prevention of relapses of *P. vivax* or *P. ovale* because it is not active against the hypnozoite liver stage forms of these parasites. For radical cure of *P. vivax* and *P. ovale* infections, concomitant therapy with an 8-aminoquinoline drug is necessary.
Recommended Dosing Regimen(s) (if applicable)	<u>Malaria in Adult and Pediatric Patients:</u> • Prophylaxis: Begin weekly doses 2 weeks prior to travel to the endemic area, continue weekly doses while in the endemic area, and continue the weekly doses for 4 weeks after leaving the endemic area: Adults: 400 mg once a week Pediatric patients ≥ 23 kg: 6.5 mg/kg actual body weight up to 400 mg, once a week • Treatment of Uncomplicated Malaria: See Full Prescribing Information (FPI) for complete dosing information. <u>Rheumatoid Arthritis in Adults:</u> • Initial dosage: 400 mg to 600 mg daily • Chronic dosage: 200 mg, 300 mg or 400 mg once daily (or in two divided doses) <u>Systemic Lupus Erythematosus in Adults:</u> • 200 mg, 300 mg or 400 mg once daily (or in two divided doses) <u>Chronic Discoid Lupus Erythematosus in Adults:</u> • 200 mg or 400 mg once daily (or in two divided doses)

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Qianni Wu, Pharm D	OCP/DIIP	Section: 5	**Select one:** __x_ Authored Approved
	Signature: Qianni Wu -S Digitally signed by Qianni Wu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Qianni Wu -S, 0.9.2342.19200300.100.1.1=2002902901 Date: 2022.01.13 15:08:53 -05'00'			
Clinical Pharmacology Team Leader	Jianmeng Chen, MD, PhD	OCP/DIIP	Section: 5	**Select one:** ___Authored _x_ Approved
	Signature: Jianmeng Chen Digitally signed by Jianmeng Chen DN: cn=Jianmeng Chen, o=FDA/CDER/OTS/ OCP, ou, email=JIANMENG.CHEN@FDA.HHS.GOV, c=US Date: 2022.01.13 15:06:50 -05'00'			
Clinical Reviewer	Keith M. Hull, MD, PhD	OII/DRTM	Sections: 1, 2, 7, 8, 9, 10, 11, 12, 13, 14	**Select one:** _x_ Authored ___ Approved
	Signature: Keith M. Hull -S Digitally signed by Keith M. Hull -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Keith M. Hull -S, 0.9.2342.19200300.100.1.1=1300218445 Date: 2022.01.14 09:20:18 -05'00'			
Associate Director for Labeling	Jane Filie, MD	OII/ DRTM	Sections: 12	**Select one:** _X__Authored ___ Approved
	Signature: Jane Filie -S Digitally signed by Jane Filie -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jane Filie -S, 0.9.2342.19200300.100.1.1=1300218646 Date: 2022.01.13 16:17:25 -05'00'			
Cross-Discipline Team Leader/ Division Director/ Signatory	Nikolay Nikolov, MD	OII/ DRTM	Sections: All	**Select one:** ___ Authored X Approved
	Signature: Nikolay P. Nikolov -S Digitally signed by Nikolay P. Nikolov -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011314790, cn=Nikolay P. Nikolov -S Date: 2022.01.13 14:42:40 -05'00'			

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Hydroxychloroquine sulfate is a well-established medication that was originally synthesized in 1946 and first approved for medical use in the United States in 1955. The drug has been used for several decades to treat autoimmune-related rheumatic disease and is approved for multiple conditions of use, including in patients with RA and SLE. Over the last decade, hydroxychloroquine sulfate use has more than tripled and is considered a cornerstone of therapy in SLE, decreasing the risk of flare and progression to severe disease, as well as increasing patient survival.

Hydroxychloroquine sulfate is currently marketed as Plaquenil in a 200 mg tablet formulation. The proposed product is hydroxychloroquine sulfate as 200 mg and 300 mg tablets.

The submitted bioavailability data demonstrate bioequivalence between the proposed hydroxychloroquine product and the listed drug, Plaquenil. Consequently, the efficacy and safety of the Applicant's hydroxychloroquine product has been based on the Agency's previous findings of safety and effectiveness of the listed drug, Plaquenil (hydroxychloroquine sulfate) 200 mg tablets (NDA 009768).

The literature for the PK linearity of oral HCQ sulfate provided by the Applicant, supported the assessment of the adequacy of a waiver request for the new strength of 300 mg tablet. The Biopharmaceutics review of the resubmission focused on the dissolution method, dissolution data, and acceptance criterion as well as the biowaiver for 300 mg strength. The dissolution method was acceptable from a biopharmaceutics perspective and the biowaiver of 300 mg strength was granted supporting the approval of the new strength of 300 mg tablet.

In summary, the data submitted under NDA 214581, hydroxychloroquine sulfate 200 mg and 300 mg tablets, support the Approval action for the indications being sought, including rhematologic and non-rheumatologic indications, as determined by the collaborating review teams of the Division of Rheumatology and Transplant Medicine (DRTM), Division of Antiinfectives (DAI), and Division of Dermatology and Dentistry (DDD).

The proposed hydroxychloroquine sulfate 200 mg and 300 mg tablets will provide a more flexible dosing regimen for certain conditions of use.

2. Background

Novitium Pharma LLC (hereafter referred to as the Applicant) has submitted the current response to Complete Response for New Drug Application (NDA) 214581. On February 12, 2021, the Agency issued a Complete Response to the initial NDA submission due to biopharmaceutic deficiencies. The NDA was submitted via the 505(b)(2) pathway for Hydroxychloroquine Sulfate Tablets (b) (4) 200 mg and 300 mg for the treatment of acute attacks of malaria due to Plasmodium vivax, Plasmodium malariae, Plasmodium ovale, and susceptible strains of Plasmodium falciparum. Hydroxychloroquine sulfate is also indicated for the treatment of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

The Applicant is using Plaquenil (hydroxychloroquine sulfate) 200 mg tablets (NDA 009768; Concordia Pharmaceuticals Incorporated) as the listed drug (LD). Novitium's product contains the same active ingredient and are formulated in the same dosage form as the LD. Additionally, the route of administration and conditions of use, including therapeutic indications, are the same as the LD; however, the Applicant is introducing a new strength of the product, hydroxychloroquine sulfate 300 mg tablet.

Hydroxychloroquine sulfate is a well-established medication that was originally synthesized in 1946 and first approved for medical use in the United States in 1955. The drug has been used for several decades to treat autoimmune-related rheumatic disease and is approved for use in patients with RA and SLE. Over the last decade, hydroxychloroquine sulfate use has more than tripled and is considered a cornerstone of therapy in SLE, decreasing the risk of flare and progression to severe disease, as well as increasing patient survival[1,2].

The currently available formulation of the listed drug, Plaquenil (NDA 009768) consists of only 200 mg film-coated tablets. Since the tablets cannot be split, it is difficult to dose subjects weighing between 40 kg and 80 kg of body weight. Consequently, those patients are often prescribed dosing regimens of 200 mg and 400 mg on alternating days in an attempt to deliver an average daily dose of approximately 300 mg daily. With this submission, the Applicant is proposing both a 200 mg and 300 mg hydroxychloroquine tablet to be marketed to provide additional flexibility with dosing.

The current submission does not contain any clinical data and relies primarily on clinical pharmacology and bioequivalence data. From a clinical perspective, a 300 mg tablet of hydroxychloroquine sulfate would be advantageous in the management of patients with RA and SLE potentially allowing for more flexible dosing for certain conditions of use and patient populations. Review of the submission to support the non-rheumatologic indications was performed by the Division of Anti-Infectives (DAI) and Division of Dermatology and Denistry (DDD) and filed as separate documents. Both collaborative review Divisions agreed with the proposed respective indications, the revised dosing recommendations, and final agreed upon labeling.

[1] Wallace DJ et al. Nat Rev Rheumatol 2012; 8:522-33
[2] The Canadian Hydroxychloroquine Study Group. N Engl J Med 1991;324(3):150-4

3. Product Quality

The recommendation for the drug product section from the initial review of the NDA was that it was adequate. However, a complete response letter of February 12, 2021 was issued for the NDA and the main quality related deficiency (b) (4) (b) (4). As a result, a scientific bridge was not established to the listed drug, Plaquenil (NDA 009768). The complete response letter also included an additional non-approvability recommendation from the biopharmaceutics team requesting that the applicant adopt the standard dissolution method in the 2018 FDA guidance for highly soluble drugs. The Applicant has provided a new method and validation report and these have been evaluated in this review and are deemed adequate from a quality perspective. The new method differs from the dissolution method in the USP monograph for Hydroxychloroquine Sulfate Tablets, which will be reflected in the product labeling.

The container closure systems for the two strengths of the drug product are typical HDPE bottles with child-resistant closures and induction heat seals, (b) (4) As indicated in the first integrated quality assessment, the 200 mg strength drug product and the 300 mg strength product were not observed to have any trends for stability parameters under both accelerated and long term conditions for 6 months. The resubmission of July 22, 2021 did not include any updated stability data, however, the Applicant submitted updated 25°C/60%RH long term stability data for 24 months for all six registration batches (three from each strength) in the November 12, 2021 amendment. The Applicant had stated in the original submission that when updated data would be available, they would revise the expiry period to 24 months. The updated stability data were evaluated and as a result, an expiration dating period of 24 months is deemed acceptable.

In the original submission, (b) (4) (b) (4) the Biopharmaceutics team found major deficiencies (b) (4) of Hydroxychloroquine Sulfate. As a result, (b) (4) (b) (4) the submitted data were not adequate to support (b) (4) Hydroxychloroquine Sulfate (b) (4). In the resubmission, the Applicant (b) (4) (b) (4) conducted BE studies to bridge their proposed drug product and the listed drug, and requested a biowaiver for the higher strength-300 mg.

The Biopharmaceutics review of the resubmission focused on the dissolution method, dissolution data, and acceptance criterion as well as the biowaiver for 300 mg strength. The dissolution method was acceptable from a biopharmaceutics perspective and the biowaiver of 300 mg strength was granted based on the supporting data.

In conclusion, from a product quality perspective, the application is recommended for approval. The Division Signatory agrees with this recommendation.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted or required to support this application. Relevant pharmacology/toxicology information is contained in the listed drug, Plaquenil (hydroxychloroquine sulfate) 200 mg tablets (NDA 009768; Concordia Pharmaceuticals Incorporated).

5. Clinical Pharmacology

The Applicant, Novitium Pharma LLC, has submitted NDA 214581 for hydroxychloroquine (HCQ) sulfate oral tablet 200 mg and 300 mg under the 505(b)2 to rely on FDA's findings for the efficacy, safety as well as clinical pharmacology information of the listed drug, Plaquenil (hydroxychloroquine sulfate) tablet 200 mg (NDA 009768). In addition, the Applicant also relied on published PK studies to support the PK linearity of oral administration of HCQ sulfate substance.

The NDA was initially submitted on April 15, 2020. A Complete Response letter was issued (b) (4) (b) (4) (b) (4). The Applicant resubmitted the application on July 22, 2021 with two new bioequivalence (BE) studies (Study HYDR-21-029 and Study HYDR-21-030) in healthy volunteers. The focus of the clinical pharmacology review for this NDA was to assess the bioequivalence between proposed product and the listed drug with a strength of 200 mg in the two BE studies. In addition, the review also evaluated the Applicant's literature for the PK linearity of oral HCQ sulfate to support the final assessment of the adequacy of a waiver request for the new strength of 300 mg.

The following are the major clinical pharmacology findings from the current review:

1) Following 200 mg single-dose administration under fasted conditions in healthy male subjects, the 90% confidence interval (CI) for the test/reference (T/R) geometric mean ratio (GMR) of 200 mg HCQ tablet (proposed drug product, T) and 200 mg Plaquenil tablets (reference product, R) for systemic exposure (area under the curve (AUC)) and peak concentration (C_{max}) was within the bioequivalence limits of (b) (4) %. Therefore, the applicant could rely on Agency's previous findings of safety and effectiveness of HCQ in RA, SLE, and chronic discoid lupus eythematosus for the listed drug, Plaquenil (HCQ sulfate) tablet 200 mg (NDA 009768).

2) Following 200 mg single-dose administration of HCQ tablet under fed conditions in healthy male subject, the 90% CI for the test/reference GMR of 200 mg HCQ tablet (proposed drug product, T) and 200 mg Plaquenil tablets (reference product, R) for systemic exposure (area under the curve (AUC)) and peak concentration (C_{max}) was within the bioequivalence limits of (b) (4) %. Therefore, the food effect is expected to be consistent with the listed drug. The proposed labeling and the reference drug label (U.S. Prescribing Information (PI) for the reference drug, Plaquenil 200 mg tablets) advise the patient to take HCQ sulfate with food or milk.

3) Both product-specific literature describing Plaquenil and non-product specific literature supported the pharmacokinetic linearity for hydroxychloroquine sulfate administered via oral route. The Applicant adequately bridged s the proposed product via two aforementioned BE studies under both fast and fed contionto FDA's finding of safety and efficacy to justify the reliance on the listed drug under 505(b)2 pathway.

4) The Office of Study Integrity and Surveillance (OSIS) inspection was requested for the analytical site for Study HYDR-21-029 and HYDR-21-030 dated Aug. 11, 2021. The OSIS concluded dated Sep. 13, 2021 that an inspection is not warranted at this time, as OSIS inspected site in (b) (4), which falls within the surveillance interval.

Study HYDR-21-029 and HYDR-21-030

Study HRDR-21-029 and HYDR-21-030 have identical study designs, which are both open-label, randomized, single dose, two-treatment, single-period, parallel BE studies, to compare and evaluate the oral bioavailability of the proposed product (HCQ 200 mg tablet manufactured by Novitium Pharma LLC) with listed drug, Plaquenil 200 mg tablet, in healthy volunteers. Whole blood PK samples were collected at pre-dose (0 hours) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 48 and 72 hours following drug administration. Study HYDR-21-029 evaluated BE under fasted conditions in which subjects were fasted at least 10-hour prior to dosing and at least 4-hour after dosing, while Study HYDR-21-30 evaluated BE under fed conditions in which subjects received the dose 30 minutes after consumption of high-fat calorie breakfast.

Based on the study protocols, any post-dose blood sample collected after the window period of +2 minutes during housing will be noted as blood draw deviation. A total of 21 and 5 samples were reported in the blood sample deviations for Study HYDR-21-029 and HYDR-21-030, respectively. The maximum deviation from scheduled collection time was up to 15 minutes (Subject (b) (6) sample at 72 hours post-dose). The PK sampling deviation is acceptable with limited impact on PK results expected.

For both HYDR-21-029 and HYDR-21-30, 109 subjects were included in each study's PK statistical analysis. PK values were set to zero if below limit of quantification (LLOQ=2.034 ng/mL). In Study HYDR-21-29, one subject (b) (6) from the proposed product group was excluded due to consent withdrawal. In Study HYDR-21-30, two subjects from the proposed product group were excluded from the analysis (one subject (b) (6) due to inadequate consumption of high-fat-high-calorie breakfast and the other subject (b) (6) due to consent withdrawal) and were replaced by stand-by subjects (b) (6) respectively. Another subject (b) (6) from the Plaquenil group was excluded from analysis also due to inadequate consumption of high-fat-high-calorie breakfast but was not replaced by a stand-by subject. It was noted that the PK values of subjects (b) (6) from Study HYDR-21-029 and subjects (b) (6) from Study HYDR-21-30 were not reported in the Applicant's PK dataset. None of these subjects reported adverse events. All of them were considered as withdrawals by the Applicant and samples were not analyzed except (b) (6) from Study HYDR-21-029. The protocols for both studies Section 15.1 Analytical Procedure stated that "samples of all subjects who complete the study will be analyzed. In case of dropouts or withdrawals, sample of such subjects will not be taken

for analysis; however, the samples from subject withdrawn or dropped due to adverse events will also be analyzed and this data will not be included in pharmacokinetics and statistical analysis". Given that the decision to exclude samples from PK statistical analyses prior to samples being analyzed in the bioanalytical assay, the Applicant's approach to exclude PK samples from subject (b) (6) in Study HYDR-21-30 is acceptable.

The Applicant reported that samples from (b) (6) from Study HYDR-21-029 were analyzed "inadvertently". The reviewer looked at the reported PK values for (b) (6) from the bioanalytical assay report (Report Number HYDR-21-029) and found that the PK values were measured up to 24 hours. The value at each timepoint was within the range of values reported in the same dosing groups. The reviewer re-conducted the PK statistical analysis for Study HYDR-21-029 by including this subject and did not find much change in the final results. Thus, the reviewer determined that it is acceptable that the Applicant excluded this subject during their PK statistical analysis.

The Applicant's descriptive PK statistics summaries for Study HYDR-21-029 and Study HYDR-21-030 were shown in Table 1 and Table 2, respectively. The PK parameters, C_{max} and AUC_{0-72h}, were compared between the proposed product 200 mg and Plaquenil 200 mg. As oral HCQ has a long half-life of >120 days based on the approved PI of Plaquenil, it is reasonable to compare truncated AUC (AUC_{0-72h}) for BE evaluation in a parallel study design, given that the elimination phase of the proposed product and the listed drug were comparable based on the visual inspection of the concentration-time profiles under both fast and fed conditions (Figure 1). The 90% confidence interval (CIs) of test/reference GMR of C_{max} and AUC_{0-72h} were within the (b) (4) % in both fast and fed BE studies. The reviewer's analyses agreed with the Applicant's results.

Table 1. PK Statistical Result for Study HYDR-21-029 (Fasted) (n=110, including subject (b) (6))

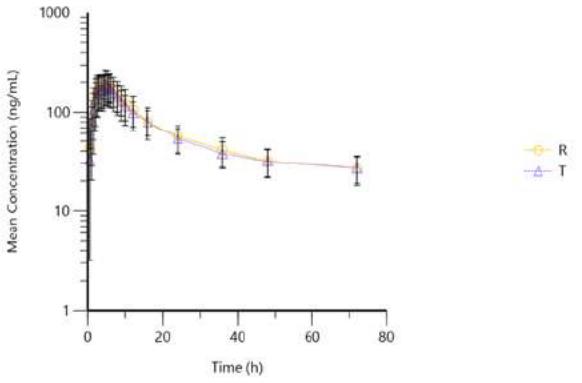
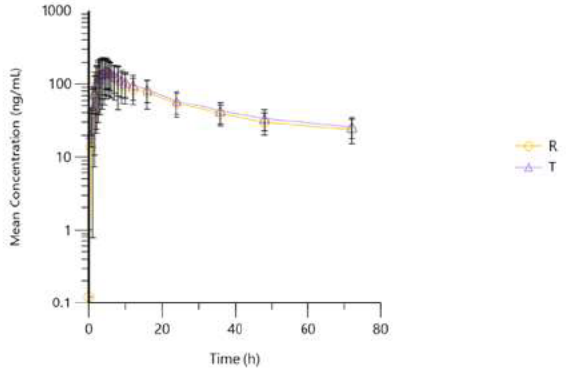
	Gemoetric Least Square Mean (T)	**Gemoetric Least Square Mean (R)**	**T/R Ratio**	**90% CI**
C_{max} (ng/mL)	198.69	196.76	100.98%	90.66-112.48%
AUC_{0-72h} (ng*h/mL)	3983.54	4065.82	97.98%	88.62- 108.32%

Source: Reviewer's analysis based on ADPC.xpt for Study HYDR-21-029 and Bioanalytical Assay Report (Report Number HYDR-21-029). Test: proposed product 200 mg tablet; Reference: Plaquenil 200 mg tablet.

Table 2. PK Statistical Result for Study HYDR-21-030 (Fed) (n=109)

	Gemoetric Least Square Mean (T)	**Gemoetric Least Square Mean (R)**	**T/R Ratio**	**90% CI**
C_{max} (ng/mL)	156.88	146.99	106.73%	91.27-124.81%
AUC_{0-72h} (ng*h/mL)	3814.33	3494.04	109.17%	97.50-122.22%

Source: Reviewer's analysis based on ADPC.xpt for Study HYDR-21-030. Test: proposed product 200 mg tablet; Reference: Plaquenil 200 mg tablet.

A. Study HYDR-21-029 (fasted) (Reference n=55; Test n=55. Subject (b) (6) Included)	B. Study HYDR-21-030 (fed) (Reference n=54; Test n=55)
	

Source: Reviewer's analysis based on ADPC.xpt for Study HYDR-21-029 and HYDR-21-030

Figure 1. Mean (SD) whole blood concentration-time profile following single dose of 200 mg proposed product (test) and 200 mg Plaquenil tablet (reference) under fasted (A) and fed (B) conditions

Dose proportionality

The relative BA/BE study was conducted at a lower dose of 200 mg whereas the proposed strenghth include 200 mg and 300 mg. According to the Plaquile package insert, HCQ exhibits linear PK with IV administration. An Information Request was sent to the Applicant for evidence to support linear PK with oral HCQ dated Oct. 8, 2021.

The Applicant provided a published literature to demonstrate the dose proportionality of Plaquenil tablet administered orally. One publication described the population PK model development for Plaquenil tablet on COVID-19 patients based on PK samples collected in an open-label, single-arm study with a dosing regimen of 400 mg BID on Day 1 followed by 200 mg BID subsequent days for a total of 5 days treatment.[3] Whole blood PK samples were collected within first 4 hours after dose administrations and at the end of treatment or at the time of treatment interruption. A one compartment model with first-order absorption and eliminiation was fitted to the data. The predictive performance was confirmed with an external set of data. This paper developed its PK model based on two other published population PK models for Plaquenil tablet using whole-blood concentrations for rheumatoid arthritis[4] and lupus erythematosus patients[5]. In the study for rheumatoid arthritis patients, 1 to 6 trough PK samples were collected between 22 and 192 days following multiple dose administration with

[3] Thémans P, Belkhir L, Dauby N, et al. Population Pharmacokinetics of Hydroxychloroquine in COVID-19 Patients: Implications for Dose Optimization. Eur J Drug Metab Pharmacokinet. 2020;45(6):703-713. doi:10.1007/s13318-020-00648-y

[4] Carmichael SJ, Charles B, Tett SE. Population pharmacokinetics of hydroxychloroquine in patients with rheumatoid arthritis. Ther Drug Monit. 2003;25(6):671–81.

[5] Morita S, Takahashi T, Yoshida Y, Yokota N. Population pharmacokinetics of hydroxychloroquine in Japanese patients with cutaneous or systemic lupus erythematosus. Ther Drug Monit. 2016;38:259–67.

daily doses ranging from 200 mg QD to 400 mg QD.[5] The observed concentrations were well described by a one-compartment model with first-order absorption. In the study for lupus erythematosus patients, multiple doses were administered with doses ranging from 200 mg QD to 200 mg and 400 mg every other day.[6] Three PK samples were collected at 3–5 hours, 7–11 hours, and 20–28 hours after or just before dosing during 36–48 weeks after initiation of HCQ therapy. The observed concentrations were also well described by a one compartment model with first-order absorption. All three studies for Plaquenil tablet demonstrated that PK data were well fitted to linear PK models, which supported the PK linearity of Plaquenil tablet following oral administration.

In addition, the Applicant provided one non-product specific literature[6], in which PK data from four clinical studies[7] [8] [9] [10] in cancer patients (more than 3 dose groups were studied in each clincial study) were used in this publication to validate the simulated steady state concentration (C_{ss}) for oral HCQ over a dose range 100 mg to 1200 mg/day from a PBPK model. A linear distribution of C_{ss} was described over the dose range based on the PBPK model which was confirmed by the patient data reported in these clinical trials. The PK of oral HCQ supplied by various generic products with daily doses ranging from 100 to 1200 mg/day following multiple doses administration in combination with various chemotherapies (i.e., bortezomib, temozolomide and temsirolimus) were evaluated in these four cancer studies. Although the HCQ products used in these trials were a variety of generic products available in the market, the HCQ PK in whole blood at steady state in all studies were described by two-compartment models with first order absorption, which suggested a linear PK of oral HCQ in the dose range studied. Although variabilities were noted in the dose proportionality results when comparing across different studies, the presence of variability is expected considering different populations were studied and different bioanalytical methods might have been used in each study. The observed HCQ PK data from these studies were well fitted to linear PK models, which increased the confidence of PK linearity of HCQ substance following oral administration.

A generic HCQ sulfate tablet product with additional new strengths, 100 mg, 300 mg and 400 mg manufactured by Accord Healthcare Inc. was approved in Aug. 2021 (ANDA 213342 Supplement 01) after this NDA was submitted. The reference listed drug (RLD) for this ANDA was also Plaquenil tablet (NDA 009768), which only had one strength, 200 mg. BE was demonstrated by two clinical studies on one tablet of 400 mg for test product and two

[6] Collins KP, Jackson KM, Gustafson DL. Hydroxychloroquine: A Physiologically-Based Pharmacokinetic Model in the Context of Cancer-Related Autophagy Modulation. *J Pharmacol Exp Ther*. 2018;365(3):447-459.
[7] Vogl DT, Stadtmauer EA, Tan KS, et al. Combined autophagy and proteasome inhibition: a phase 1 trial of hydroxychloroquine and bortezomib in patients with relapsed/refractory myeloma. Autophagy. 2014;10(8):1380-1390
[8] Rosenfeld MR, Ye X, Supko JG, et al. A phase I/II trial of hydroxychloroquine in conjunction with radiation therapy and concurrent and adjuvant temozolomide in patients with newly diagnosed glioblastoma multiforme. Autophagy. 2014;10(8):1359-1368.
[9] Rangwala R, Leone R, Chang YC, et al. Phase I trial of hydroxychloroquine with dose-intense temozolomide in patients with advanced solid tumors and melanoma. Autophagy. 2014;10(8):1369-1379.
[10] Rangwala R, Chang YC, Hu J, et al. Combined MTOR and autophagy inhibition: phase I trial of hydroxychloroquine and temsirolimus in patients with advanced solid tumors and melanoma. Autophagy. 2014;10(8):1391-1402.

tablets of 200 mg for reference product under fasting and fed conditions. The study results further demonstrated the dose proportionality of oral HCQ substance.

Bioanalytical Method

Both Study HYDR-21-029 and HYDR-21-030 used the same validated bioanalytical method (HC-AM rev.03) to assess the PK of HCQ in whole blood. The summary of the method validation (SPSHCMV01) was shown in Table 3.

Table 3. Validation Summary of Bioanalytical Method

Bioanalytical method review summary	Method Validation (b) (4) HCMV01 Method Number (HC-AM, rev.02)*		
Method description	Liquid/liquid extraction method with LC and Tandem Mass Spectrometry detection.		
Materials used for calibration curve/QC & concentration	HCQ sulfate (Lot: VL/S-HS-015) with methanol (250 µg/mL) spiked in human whole blood with K_2EDTA (lot: P-WB-0001/19)		
Validated assay range	2.034 (LLOQ) to 701.070 (ULOQ) ng/mL in human whole blood		
Minimum required dilutions (MRDs)	N/A		
Regression model & weighting	$1/X^2$ Linear regression analysis		
Validation parameters	**Method validation summary**		**Acceptability**
Calibration curve performance during accuracy & precision	No of standard calibrators from LLOQ to ULOQ	9	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1.65% to -0.02%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 4.67%	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	1.55% to 3.97%	Yes
	Inter-batch %CV	≤ 12.47%	Yes
	Percent total error (TE)	N/A	
Selectivity & matrix effect	6 whole blood lots were tested. At least 80% of the lots within 20% bias		Yes

Interference & specificity	Potential interfering substances (Acetaminophen, Caffeine, Ibuprofen, Nicotine, Cetirizine, Ranitidine, Diclofenac, Ondansetron and Pheniramine) in 6 replicates of PIS-LLOQ along with a standard curve and QCs: Mean %bias of LLOQ: 7.25% Mean %CV of LLOQ: 6.4%	Yes
Lipemic effect	One whole blood lot (WB-006/18) was tested and within 20% bias	Yes
Bench-top/process stability	Bench-top: 20.5 h at room temperature Process: 154 h at autosampler/refrigerator condition	Yes
Freeze-Thaw stability	Up to 5 cycles	Yes
Long-term storage	HCQ in whole blood: 177 days at -20°C set point freezer 177 days at -70°C set point freezer	Yes

Source: Reviewer's analysis based on Method Validation Report (b) (4) HCMV01).
*The method (HC-AM rev 02) was validated in the Method Validation Report. But method (HC-AM rev. 03) was used to analyze Study HYDR-21-029 and HYDR-21-030. No substantial change in method was identified. Method HC-AM rev.02 and HC-AM rev.03 were considered the same method.

Method Validation (Report Number (b) (4) HCMV01) and sample analyses for Study HYDR-21-029 (Report Number HYDR-21-029) and HYDR-21-030 (Report Number HYDR-21-030) were in line with the Agency's recommendations outlined in the Guidance For Industry Bioanalytical Method Validation (May 2018), and all acceptance criteria as specified in the guidance were met.

Recommendations
The Clinical Pharmacology review team deems that the bioequivalence is demonstrated between the proposed product 200 mg and the listed drug, Plaquenil 200 mg. The Applicant adequately bridged the proposed product to FDA's finding of safety and efficacy for Plaquenil to justify the reliance on the data and labeling of the listed drug. The dose proportionality of oral HCQ sulfate substance was supported by both the product-specific (i.e., Plaquenil tablet) and non-product-specific published literature provided by the Applicant. The proposed product of HCQ sulfate with a strength of 200 mg is acceptable for approval under 505(b)2 pathway from a Clinical Pharmacology perspective. The Division Signatory agrees with this recommendation. The final acceptance of the other strength (i.e., 300 mg) will depend on the adequacy of in-vitro dissolution studies and formulation proportional similarity assessment in support of the biowaiver request for 300 mg strength. See Integred Quality Assessment from Office of Pharmaceutical Quality dated Dec. 14, 2021 (DARRT Reference ID: 4904325).

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

To support the demonstration of substantial evidence of effectiveness for the approval of their product for the indications sought, including RA and SLE, the Applicant is relying on:

- The Agency's previous findings of safety and effectiveness of hydroxychloroquine in the indications sought for approval, including RA and SLE for the listed drug, Hydroxychloroquine Sulfate tablets (Plaquenil; NDA 009768)
- Two comparative bioequivalence studies that were conducted comparing the proposed product and the listed drug, Plaquenil
- Information in the published literature supporting the safety and efficacy of hydroxychloroquine in the indications sought for approval, including RA and SLE.

The primary data to support this NDA submission are derived from the BE studies comparing the proposed hydroxychloroquine tablets to the listed drug (Study HYDR-21-029 and Study HYDR-21-030). Based on these studies, the Cmax and AUC of the proposed hydroxychloroquine tablet (proposed product) was similar to Plaquenil (reference product) in both the fasted and fed states and was within the bioequivalence limits of (b) (4) %. Therefore, the data support the Applicant's reliance on the Agency's previous findings of safety and effectiveness of hydroxychloroquine in the indications sought for approval, including RA and SLE for the listed drug, Plaquenil (HCQ sulfate) tablet 200 mg (NDA 009768). The collaborating review Divisions, DAV and DDD, have also concluded that the

data support the effectiveness of the hydroxycholoroquine sulfate under this NDA for their respective indications. The Division Signatory agrees with these assessments and conclusions.

Hydroxychloroquine has been used for decades to treat autoimmune-related rheumatic disease and is approved for use in patients with RA and SLE. Over the last decade, hydroxychloroquine sulfate use has more than tripled and is considered a cornerstone of therapy in SLE, decreasing the risk of flare and progression to severe disease, as well as increasing patient survival[11,12]. The current submission does not contain any clinical data and relies on the clinical pharmacology and bioequivalence data.

8. Safety

The safety of hydroxychloroquine has been well-established and used for decades to treat autoimmune-related rheumatic disease, including patients with RA and SLE. As noted above in Section 7, the data derived from the two bioequivalence studies support the Applicant's reliance on the Agency's previous findings of safety and effectiveness of hydroxychloroquine in the indications sought for approval, including RA and SLE for the listed drug, Plaquenil (HCQ sulfate) tablet 200 mg (NDA 009768). Given the establishment of bioequivalence, the Applicant is relying on the safety data included in the Plaquenil package insert, which has been determined to be acceptable for approval. The collaborating review Divisions, DAV and DDD, have also concluded that the data support the safety of the hydroxycholoroquine sulfate under this NDA for their respective indications. The Division Signatory agrees with these assessments and conclusions.

With this NDA, the Applicant is proposing both a 200 mg and 300 mg hydroxychloroquine tablet, which while not changing the known safety profile of the drug, will allow for more flexible dosing options for patients weighing between 40 kg and 80 kg, and facilitate compliance with the current OAA dosing recommendations to limit retinal toxicity.

9. Advisory Committee Meeting

No Advisory Committee Meeting was necessary for this application.

[11] Wallace DJ et al. Nat Rev Rheumatol 2012; 8:522-33
[12] The Canadian Hydroxychloroquine Study Group. N Engl J Med 1991;324(3):150-4

10. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to the proposed product, this NDA is not a subject to PREA requirements.

11. Other Relevant Regulatory Issues

None.

12. Labeling

Prescribing Information
The Applicant has chosen not to use a proprietary name for their product and rather will use the established name of the drug, Hydroxychloroquine Sulfate, which is acceptable.

Given the demonstration of bioequivalence between the test product (hydroxychloroquine sulfate) and the reference listed product (Plaquenil; NDA 009768), the Applicant has relied on the Agency's previous findings of safety and effectiveness of hydroxychloroquine including very similar labeling language.

Major amendments to the proposed Hydroxychloroquine Sulfate Tablets label compared to the Plaquenil label include the following:

- Replacement of the drug name *Plaquenil* with *Hydroxychloroquine Sulfate*
- Addition of the 300 mg strength tablet
- Dosage recommendation for malaria for pediatric patients to reflect the body weight cut-off of ≥23 kg which differs from the reference listed product
- The DDD review team noted that the listed drug recommend dosage for discoid lupus erythematosus (DLE) is 200 mg given once daily or 400 mg given once daily or in two divided doses. The DDD team (b) (4) (b) (4) (b) (4) (b) (4) dosing recommendation for discoid lupus erythematosus (DLE) is 200 mg given once daily or 400 mg given once daily or in two divided doses.
- Change of inactive ingredients specific to the current product
- Replacement of Pharmacokinetics data to include the current bioequivalence studies

Other Labeling

Because the dissolution method and acceptance criterion utilized by the Applicant for Hydroxychloroquine Sulfate Tablets differ from the dissolution method in the USP monograph, the statement "FDA approved dissolution test and acceptance criterion differ from USP" will be included in section 11 DESCRIPTION of the Prescribing Information and in the carton labeling. (b) (4)

(b) (4)

All labeling has been reviewed by the labeling consultants and agreed upon with the Applicant.

13. Postmarketing Recommendations

No Risk Evaluation and Management Strategies (REMS) or Postmarketing Requirements (PMRs) and Commitments (PMCs) are required for this NDA.

14. Recommended Comments to the Applicant

None.

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/s/

NIKOLAY P NIKOLOV
01/14/2022 09:55:46 AM

JIANMENG CHEN
01/14/2022 09:58:56 AM

KEITH M HULL
01/14/2022 10:47:28 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Dermatology and Dental Products
Silver Spring MD 20993

Tel: 301 796-2110
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M E M O R A N D U M

Date:	07-DECEMBER-2021		
From:	Gary Chiang MD, MPH	Clinical Reviewer	OND/DDD
Through:	David Kettl MD	Clinical Team Lead	OND/DDD
	Kendall Marcus MD	Division Director	OND/DDD
To:	Keith Hull MD, PhD	Clinical Reviewer	OND/DRTM
	Anil Rajpal MD	Clinical Team Lead	OND/DRTM
Cc:	Susie Choi	Regulatory Project Manager	OND/DRTM
	Margie Kober	Acting Chief Project Management	OND/DDD

Re: NDA 214581

Material Reviewed:

- Original 505 (b)(2) NDA submission for hydroxychloroquine (HCQ) sulfate from Novitium Pharma LLC received 15-APRIL-2020
- Agency Complete Response 12-February-2021
- Novitium Pharma LLC resubmission of NDA on 22-JULY-2021
- Draft labeling for hydroxychloroquine sulfate, NDA 214581

Background:

Novitium Pharm LLC submitted an NDA 214581 via the 505 (b)(2) pathway for hydroxychloroquine (HCQ) sulfate tablets (b) (4) 200 mg, 300 mg, and (b) (4) 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 Division of Rheumatology and Transplant Medicine requested the Division of Dermatology and Dentistry to review the submission for HCQ indication for chronic discoid lupus erythematosus from Novitium Pharma LLC (hereon known as the applicant). The applicant references PLAQUENIL (hydroxychloroquine sulfate) 200 mg tablets (NDA 009768; Concordia Pharmaceuticals Inc) as the reference list drug (RLD). Novitium's HCQ product contains the same active ingredient and are formulated in the same dosage form as the referenced product. Additionally, the route of administration and conditions of use, including therapeutic indications are the same as Plaquenil; however, the applicant is introducing a new 300 mg strength.

Cutaneous lupus erythematosus (cutaneous LE) includes three subsets of LE-specific skin diseases: acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus erythematosus (CCLE). CCLE encompasses discoid lupus erythematosus (DLE), lupus erythematosus tumidus (LE tumidus), lupus profundus (also known as lupus panniculitis), chilblain lupus erythematosus (chilblain LE), and lichenoid cutaneous lupus erythematosus-lichen planus overlap syndrome (LE-LP overlap syndrome). Cutaneous LE can occur as a manifestation of systemic lupus erythematosus (SLE) or independent of SLE.

The classic findings of discoid lupus erythematosus (DLE) are discrete, erythematous, somewhat indurated plaques covered by a well-formed adherent scale that extends into dilated hair follicles (follicular plugging). The plaques tend to expand slowly with active inflammation at the periphery and then heal, leaving depressed central scars, atrophy, telangiectasias, and hyperpigmentation and/or hypopigmentation. DLE most often involves the face, neck, and scalp but may also occur on the ears (particularly conchal bowls) and, less frequently, on the upper torso. Localized DLE is limited to sites above the neck. Generalized DLE refers to DLE occurring both above and below the neck.

First line therapy typically involves:

- Photoprotection
- Use of topical or intralesional corticosteroids, topical calcineurin inhibitors, and/or systemic glucocorticoids.
- Systemic antimalarial agents (treatment with hydroxychloroquine or chloroquine, or with addition of quinacrine to either agents)

Hydroxychloroquine (HCQ) sulfate is a well-established medication that was synthesized in 1946 and first approved for medical use in the United States in 1955. The currently available presentation of PLAQUENIL consists only of film-coated 200 mg tablets. The recommended, labeled dosage for chronic discoid lupus erythematosus in adults in 200 mg given once daily, or 400 mg given once daily or in two divided doses.

Review:

NDA 214581 for hydroxychloroquine (HCQ) sulfate does not contain any clinical data and relies primarily on clinical pharmacology and bioequivalence data. For Dermatology, the 300 mg tablet is not a recommended dosage for chronic discoid lupus erythematosus (DLE) in currently approved labeling. The recommend dosage for DLE is 200 mg given once daily or 400 mg given once daily or in two divided doses. The applicant provided labeling (b) (4) for the treatment of DLE. (b) (4)

(b) (4)

Conclusions:

NDA 214581 for HCQ sulfate tablets from Novitium Pharma LLC is approvable from the clinical perspective of DDD. DDD recommends that for the indication of treatment of chronic discoid lupus erythematosus (DLE) for this application, the language in the currently approved Plaquenil labeling of only 200 mg and 400 mg be included in labeling for this new NDA product.

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/s/

GARY T CHIANG
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DAVID L KETTL
12/07/2021 09:45:25 AM

Cross-Discipline Team Leader / Division Summary Memo

Date	February 10, 2021
From	Anil Rajpal, MD, MPH; Clinical Team Leader (Acting) Nikolay Nikolov, MD; Division Director
Subject	Cross-Discipline Team Leader / Division Director Memo
NDA/BLA # and Supplement#	NDA 214581
Applicant	Novitium Pharma LLC
Date of Submission	April 15, 2020
PDUFA Goal Date	February 15, 2021
Proprietary Name	Not applicable*
Established or Proper Name	Hydroxychloroquine Sulfate
Dosage Form(s)	Tablets (200 mg and 300 mg)
Applicant Proposed Indication(s)/Population(s)	• Malaria ("treatment of uncomplicated malaria due to P. falciparum, P. malariae, P. ovale, and P. vivax" and "prophylaxis of malaria in geographic areas where chloroquine resistance is not reported") • Lupus Erythematosus ("treatment of chronic discoid lupus erythematosus and systemic lupus erythematosus in adults") • Rheumatoid Arthritis ("treatment of acute and chronic rheumatoid arthritis in adults")
Applicant Proposed Dosing Regimen(s)	• Malaria (Prophylaxis): o Adults: 400 mg once weekly on the same day of each week starting 2 weeks prior to exposure, and continued for 4 weeks after leaving the endemic area. o [redacted (b) (4)] pediatric patients: 6.5 mg/kg ([redacted (b) (4)], not to exceed 400 mg, once weekly on the same day of the week starting 2 weeks prior to exposure, and continued for 4 weeks after leaving the endemic area. • Malaria (Treatment of Uncomplicated Malaria): o Adults: 800 mg [redacted (b) (4)] followed by 400 mg [redacted (b) (4)] at 6 hours, 24 hours and 48 hours after the initial dose (total 2000 mg [redacted (b) (4)]). o [redacted (b) (4)] pediatric patients: 13 mg/kg [redacted (b) (4)], not to exceed 800 mg [redacted (b) (4)] followed by 6.5 mg/kg [redacted (b) (4)], not to exceed 400 mg [redacted (b) (4)], at 6 hours, 24 hours and 48 hours after the initial dose. • Lupus Erythematosus

	○ The recommended adult dosage is 200, 300 or 400 mg daily, administered as a single daily dose or in two divided doses. (b) (4) . • Rheumatoid Arthritis ○ The recommended adult dosage is 200, 300 or 400 mg daily, administered as a single daily dose or in two divided doses. (b) (4)
Recommendation on Regulatory Action	Complete Response

*The applicant does not intend to request a proprietary name for this drug product.
(b) (4)

Summary: This is a 505 (b)(2) new drug application (NDA) submitted by Novitium Pharma LLC for hydroxychloroquine sulfate which references the listed drug NDA 009768 for Plaquenil. This application was submitted (b) (4) (b) (4) (b) (4). However, the Biopharmaceutics review team concluded that (b) (4) (b) (4) (b) (4) a scientific bridge has not been established to the relied-upon listed drug. The deficiencies are shown below. To support the application, the Applicant needs to either address each of these deficiencies (b) (4) (b) (4) or conduct appropriate *in vivo* bioavailability or bioequivalence studies to bridge the proposed drug product to the listed drug. The CDTL and the Division Director agree with this assessment and recommendations.

Regulatory Action: The regulatory action is Complete Response (CR) based on the deficiencies outlined below.

Deficiencies: The deficiencies below should be communicated in the CR Letter.

DRUG PRODUCT QUALITY

Biopharmaceutics Deficiencies

(b) (4)

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(b) (4)

Information needed to address the above deficiencies:

To support your application, you should (1) address the above deficiencies (b) (4) (b) (4), or (2) conduct appropriate in vivo bioavailability or bioequivalence studies to bridge your proposed drug product to the listed drug.

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/s/

ANIL K RAJPAL
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NIKOLAY P NIKOLOV
02/10/2021 08:42:16 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES PUBLIC HEALTH SERVICE

Memorandum

Food and Drug Administration
Center for Drug Evaluation and Research
CDER/OND/DRTM

Date: January 06, 2021

From: Keith Hull, MD, PhD
Medical Officer

Through: Anil Rajpal, MD
Clinical Team Leader

Product: Hydroxychloroquine Sulfate

Subject: Primary Clinical Review

Sponsor: Novitium Pharma LLC

Application: NDA 214581/01

Novitium Pharma LLC (hereafter referred to as the Applicant) has submitted a New Drug Application (NDA) 214581 via the 505(b)(2) pathway for Hydroxychloroquine Sulfate Tablets (b) (4) 200 mg and 300 mg for the treatment of acute attacks of malaria due to Plasmodium vivax, Plasmodium malariae, Plasmodium ovale, and susceptible strains of Plasmodium falciparum. Hydroxychloroquine sulfate is also indicated for the treatment of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

The Applicant is using PLAQUENIL (hydroxychloroquine sulfate) 200 mg tablets (NDA 009768; Concordia Pharmaceuticals Incorporated) as the reference listed drug (RLD). Novitium's product contains the same active ingredient and are formulated in the same dosage form as the RLD. Additionally, the route of administration and conditions of use, including therapeutic indications, are the same as the RLD; however, the Applicant is introducing a new strength of product, hydroxychloroquine sulfate 300 mg tablet.

Hydroxychloroquine sulfate is a well-established medication that was originally synthesized in 1946 and first approved for medical use in the United States in 1955. The drug has been used for several decades to treat autoimmune-related rheumatic disease and is approved for use in patients with RA and SLE. Over the last decade, hydroxychloroquine sulfate use has more than tripled and is considered a cornerstone of therapy in SLE, decreasing the risk of flare and progression to severe disease, as well as increasing patient survival[1,2].

[1] Wallace DJ et al. Nat Rev Rheumatol 2012; 8:522-33

[2] The Canadian Hydroxychloroquine Study Group. N Engl J Med 1991;324(3):150-4

In 2016, the American Academy of Ophthalmology (AAO) revised their treatment guidelines to limit dosing of hydroxychloroquine not to exceed 5 mg/kg/day due to the potential for retinal damage. As treatment with hydroxychloroquine often continues for the lifetime of the patient it is therefore critical to use the lowest effective dose from initiation of therapy to reduce the cumulative dose. Other risk factors for developing ocular toxicity include obesity and age > 60 years, pre-existing retinal disease and in those patients taking tamoxifen. Previously a dose of HCQ < 6.5mg/kg/day was considered safe. With the 2016 AAO guidelines recommending a lower maximum dose of 5 mg/kg/day it is inevitable that many patients will be receiving doses exceeding the new recommendations.

The currently available formulation of PLAQUENIL consists only film-coated 200 mg tablets. Since the tablets cannot be split, it is difficult to dose subjects weighing between 40 kg and 80 kg of body weight. Consequently, those patients are often prescribed dosing regimens of 200 mg and 400 mg on alternating days in an attempt to deliver an average daily dose of approximately 300 mg daily. With this submission, the Applicant is proposing both a 200 mg and 300 mg hydroxychloroquine tablet to be marketed.

The current submission does not contain any clinical data and relies primarily on clinical pharmacology and bioequivalence data. From a clinical perspective, a 300 mg tablet of hydroxychloroquine sulfate would be advantageous in the management of patients with RA and SLE potentially allowing for better medication compliance and optimization of dosing. The clinical review team will defer to the other review disciplines regarding the approvability of the Applicant's new drug formulation.

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/s/

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