CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214952Orig1s000

SUMMARY REVIEW

DIVISION OF CARDIOLOGY AND NEPHROLOGY

Divisional Memorandum

NDA: 214952 (LIQREV, sildenafil oral suspension)

Sponsor: CMP Development

Reviewer: N. Stockbridge, M.D., Ph.D.

The product is sildenafil oral suspension 10 mg/mL. The scientific basis for approval is provided in the OPQ review (Carver, 4 Feb 2023). Approval follows several Complete Response actions for manufacturing issues.

DCN determined that LIQREV could be approved as safe and effective for the 20-mg TID dosing regimen, carving out information from the AFFILIATE study and information related to the 80-mg TID dosing regimen. A1481324 trial data for the secondary efficacy endpoints showed a trend for improved efficacy of 80 mg over 20 mg for clinical worsening (HR 0.71, p 0.195). Additionally, there was a dose-dependent improvement in 6MWD for 80 mg over 20 mg at month 6, but no difference at month 12. These differences did not meet the pre-specified criteria for significance. Therefore, the new data from A1481324 did not demonstrate, and we did not conclude, that the 80 mg is superior to 20 mg for mortality, clinical worsening, or function. Safety and efficacy for the 20 mg TID dosing regimen is supported by the SUPER-1 (NCT006644605) study, approved in NDA 021845 and described in the REVATIO labeling. The omission of information from the AFFILIATE study and related 80-mg dosing information thus does not render this 505(b)(2) product unsafe or ineffective.

DCN, in consultation with DPMH, determined that the pediatric information can be omitted from the labeling; and the 505(b)(2) NDA product is safe and effective for the remaining adult use.

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/s/

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Cross-Discipline Team Leader Review

Date	August 4, 2021
From	Manoj Khurana
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 214952
Type	505(b)(2)
Applicant	CMP Development LLC
Date of Submission	October 3, 2020
PDUFA Goal Date	August 5, 2021
Proprietary Name / Established (USAN) names	Liqrev® (Sildenafil Oral Suspension)
Dosage forms / Strengths	Oral Suspension / 10 mg/mL
Proposed Indication(s)	Treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability
Action:	*'Complete Response'*

Material Reviewed/Consulted	
Integrated Quality Review (7/26/21)	Zhengfu Wang (Drug Substance), Ali Mohamadi (Drug Product), Carl Lee (Process and Facility), Nadia Ahmed (Biopharmaceutics), Denise Miller, Daniel Schu (Microbiology), Mohan Sapru (Application Technical Lead)
Pharmacology-Toxicology Review (06/30/2021)	Xi Yang, Jean Wu
Clinical Pharmacology Review (6/11/2021)	Brianna Cote, Manoj Khurana
Clinical Review	NA
Division of Pediatric and Maternal Health Review (04/01/2021; 07/16/2021)	Catherine Roca, Miriam Dinatale, Lynne Yao; Meshaun Payne
Division of Medication Error Prevention and Analysis Reviews (03/22/2021, 04/16/2021, 07/02/2021)	Danielle Harris, Mariette Aidoo, Hina Mehta
Office of Study Integrity and Surveillance Review (5/27/2021)	Melkamu Getie-Kebtie, Kara Scheibner, Stanley Au, Seongeun Cho
Office of Prescription Drug Promotion Reviews (04/30/2021)	Zarna Patel, James Dvorsky

1. Introduction

On October 3, 2020, CMP Development LLC submitted a New Drug Application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Liqrev® (the final agreed upon tradename), an oral suspension of sildenafil, for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability.

The application relies on the Agency's previous finding of safety and effectiveness for the reference listed drug, REVATIO® tablets (NDA 021845, approved 1998). No new clinical efficacy data are submitted in this application and no new claims are being sought with this application.

2. Background

Sildenafil is an inhibitor of cGMP specific phosphodiesterase type-5 (PDE-5) in the smooth muscle of the pulmonary vasculature, where PDE-5 is responsible for degradation of cGMP. Sildenafil, therefore, increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. In patients with PAH, this can lead to vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation.

The recommended dose of sildenafil per the REVATIO label is (b) (4) mg or 20 mg three times a day taken 4-6 hours apart.

3. Product Quality

Office of Product Quality (OPQ) does not recommend approval of the application due to deficiencies identified in the drug product manufacturing and testing facilities remain currently unresolved.

Following is the summary of quality assessment from OPQ's Integrated Quality Review:

Drug substance
Sildenafil citrate, a white to off-white hygroscopic crystalline powder, is a compendial drug substance. The release specifications of the drug substance comply with current USP monograph. Particle size distribution is routinely tested on release. The CMC details about the drug substance such as structural characterization, manufacture and control strategies are cross-referenced to DMF (b) (4), which has been reviewed and found adequate. The drug substance exhibits polymorphism, which is controlled and tested by the drug substance manufacturer. Based on information provided in the NDA, the drug substance release specification includes testing the critical quality attributes (CQAs) and conforms to USP monograph.

The drug substance (b) (4) (b) (4) (b) (4) The container closure is suitable for intended use and provides adequate protection over the proposed retest period. The retest period of (b) (4) is supported by stability data.

Drug product
The drug product is a new formulation of sildenafil. Pharmaceutical development studies adequately support the formulation design, including excipient selection and excipient levels. No

novel or human/animal origin excipients are used in the formulation. Except strawberry flavor, all excipients are compendial (USP-NF) and their levels are within limits of approved drugs. All ingredients contained in strawberry flavor are approved for use by the Agency or are considered as being generally recognized as safe (GRAS). Three excipients, sodium benzoate, citric acid monohydrate, and tri-sodium citrate dihydrate contain (b) (4) The calculated maximum amount of (b) (4) mg/day stays within the FDA's limit for (b) (4) mg/day, per CFR 73 (b) (4)

The product release specification, involving testing of all the product critical quality attributes (CQAs), is adequate to ensure the consistent product quality. The unspecified and specified impurities are controlled per ICH Q3B; calculated based on the maximum daily dose of 60 mg/day. (b) (4) are used to manufacture the drug product. The Applicant has provided risk assessment analyses for (b) (4) and results show that the drug product complies with ICH Q3C. Therefore, a (b) (4) test is not included in the drug product specification. Sodium benzoate levels are controlled at (b) (4)%, which is adequate (b) (4) (b) (4) The non-compendial analytical procedures used for testing the drug product have been validated according to ICH guidelines. A risk assessment, per ICH guideline Q3D, regarding levels of elemental impurities in the drug product has been provided. The elemental impurities in the proposed product do not exceed the ICH Q3D-compliant permitted daily exposure (PDE) limits. Hence, no release testing for elemental impurities is required. In conclusion, the product design, selection of excipients and control of product quality via release testing are adequate.

The product manufacturing includes (b) (4) Adequate information has been provided about incoming materials and unit operations. The critical process parameters and in-process control limits for different unit operation are adequate. The level of viscosity is controlled with the viscosity limit of (b) (4) cps at the (b) (4) Process scale-up is < (b) (4) for the (b) (4) L batch size. Equipment used for submission batch manufacturing will be used for commercial manufacturing, and the process parameters and controls are similar. Overall, the manufacturing process is well-controlled.

Microbiology
The proposed microbiological tests, test methods, and acceptance criteria are consistent with regulatory expectations for a preserved, non-sterile, aqueous drug product for oral administration.

Biopharmaceutics
According to Biopharmaceutics review, although the applicant claimed (b) (4) solubility for sildenafil citrate, the data provided demonstrate that the drug substance belongs to BCS Class II. The applicant has conducted comparative dissolution studies between the proposed product and the LD. Per revised dissolution method, the applicant has demonstrated the discriminating ability of the dissolution method and proposed acceptance criteria are adequate. No bridging of formulations is necessary because the currently proposed drug product formulation is the same formulation used in the in vivo clinical studies. Additionally, the proposed commercial manufacturing sites is the same as the used for clinical and registration batches.

Container Closure System
Each mL of sildenafil oral suspension contains 10 mg of sildenafil (equivalent to 14 mg sildenafil citrate). The suspension is packaged in (b) (4) mL Amber Colored (b) (4) glass bottles with a (b) (4) 28 mm white child-resistant closures. Each bottle of the proposed drug product contains 122 mL of sildenafil suspension i.e., 1.22 g sildenafil (equivalent to 1.71 g sildenafil citrate) per bottle. The results from leachables and extractables studies and associated justifications are acceptable. The proposed container closure system is appropriate for the intended use.

Expiration Date and Storage Conditions
Based on the OPQ's assessment of stability data, the proposed product shelf-life of 24 months, when stored at controlled room temperature of 20 to 25°C (68 to 77°F) in commercial packaging, is acceptable. Excursions are permitted to 15°C to 30°C (59°F to 86°F)

Facilities review/inspection
The Office of Process and Facilities recommends a 'withhold' status for this NDA due to the 'out of compliance' status for the drug substance manufacturing facility - (b) (4) product testing facility - (b) (4) and drug product manufacturing and testing facility, (b) (4) A 704(a)(4) review of the facility has identified significant CGMP deficiencies, including deficient records of process parameters and in-process controls for certain unit operations. The firm's responses to 704(a)(4) deficiencies, which include lack of microbial controls and cross-contamination concerns, have been reviewed but critical outstanding concerns remain unresolved.

4. Nonclinical Pharmacology/Toxicology

No additional nonclinical studies were submitted to the current application. All excipients used in the formulation are compendial. The flavoring substances used in the strawberry flavor are considered generally recognized as safe (GRAS), have Joint Expert Committee on Food Additives (JECFA) status, and are present below (b) (4)%. The amounts of other excipients present in sildenafil oral suspension are below the maximum daily intake listed in Inactive Ingredient Report (IIR) for chronic oral administration. Overall, there are no safety concerns regarding the amount of the excipients in the proposed formulation for the intended use. Pharm-tox considered the application approvable from a nonclinical perspective.

5. Clinical Pharmacology

Office of Clinical Pharmacology (OCP) recommends approval of the sildenafil 10 mg/mL oral suspension with or without food. The applicant conducted an open-label, balanced, randomized, single-dose two-treatment, three-sequence, three-period, crossover, oral bioequivalence study of sildenafil 10 mg/mL oral suspension with REVATIO 20 mg tablets in healthy, adult, human subjects under fasting condition (Study 19-014). The study also assessed the effect of food for the sildenafil 10 mg/mL oral suspension.

The results show that for the prespecified primary PK assessments, peak concentration (Cmax) and the area under the curve measurements (AUC0-t and AUC0-inf) for sildenafil and the metabolite, piperazine N-desmethyl sildenafil, bioequivalence was demonstrated between the oral suspension and REVATIO, thus establishing a bridge to borrow Agency's previous finding of safety and effectiveness for REVATIO.

When sildenafil 10 mg/mL oral suspension was administered with high-fat meal the Cmax of sildenafil and piperazine N-desmethyl sildenafil were decreased by 52.9% and 49.5%, respectively compared to fasted state, however, without any changes in the AUC0-t and AUC0-inf of sildenafil and the metabolite, piperazine N-desmethyl sildenafil. The modest decrease in peak exposure with food without any change in the total exposure renders the effect of food as clinically insignificant. The lack of no significant food effect for the oral suspension is consistent with the food effect results reported earlier for REVATIO.

Site Inspection:
OCP requested inspection of the clinical and bioanalytical sites at (b) (4)

where the clinical study and bioanalysis of samples were conducted. OSIS inspection identified select subjects for which the bioanalytical data was unreliable for the metabolite, piperazine N-desmethyl sildenafil concentrations. OSIS concluded that the "objectionable conditions were isolated in nature," and recommended excluding objectionable samples from the assessment of piperazine N-desmethyl sildenafil PK.

OCP reviewer's reanalysis after excluding the questionable data did not change the conclusion of the original analysis further assuring the bridging study results.

6. Clinical/Statistical- Efficacy

As discussed under Clinical Pharmacology, the relative bioavailability study provides the bridge to the efficacy findings of the listed drug, REVATIO.

7. Safety

This application primarily relies on the Agency's previous determination of safety for the listed drug, REVATIO.

8. Advisory Committee Meeting

The application does not raise significant issues regarding the safety or effectiveness of the drug; hence, no Advisory Committee Meeting was held or needed.

9. Pediatrics

This application triggers Pediatric Research Equity Act (PREA) because it is a new dosage form. The applicant requested a request a partial waiver for pediatric patients from birth to less than 1 year of age because the product would be ineffective and/or unsafe.

The label for the reference product (REVATIO, sildenafil) contains the following Warning and Precaution: "In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing REVATIO dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of REVATIO, particularly chronic use, is not recommended in children." Section 8.4 of the reference product label includes further details. This language will be included in the label for the oral suspension. Although pediatric patients < 1 year of age were not studied in the trial, the warning on the mortality risk in REVATIO labeling was intended to be inclusive of the entire pediatric age range.

PeRC agreed with the partial waiver as requested and that pediatric patients 1 to less than 17 years of age have been fully assessed. The product labeling will be updated accordingly at appropriate time pending resolution of the issues leading to Complete Response.

10. Other Relevant Regulatory Issues

None.

11. Labeling

A final agreement on labeling was not reached with the applicant because of the planned 'Complete Response' action at the end of the review cycle. The proposed proprietary name,

LIQREV, is accepted by DMEPA.

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
Complete Response – Due to deficiencies identified in the drug product manufacturing and testing facilities.

Risk Benefit Assessment
For the indications sought, the risk-benefit of LIQREV when used as directed in the proposed label is not expected to be different compared to REVATIO.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
None

Recommendation for other Postmarketing Requirements (PMR) and Commitments
None

Recommended Comments to Applicant
Comments related to appropriate resolution of deficiencies noted for the drug substance manufacturing facility, product testing facility, and drug product manufacturing and testing facility should be sent along with the Complete Response Letter.

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

/s/

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