CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215602Orig1s000

SUMMARY REVIEW

Summary Review

Date	January 19, 2022
From	Laura Jawidzik, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 215602
Applicant	Azurity Pharmaceuticals
Date of Submission	April 5, 2021
PDUFA Goal Date	February 5, 2022
Proprietary Name	Fleqsuvy
Established or Proper Name	Baclofen oral suspension
Dosage Form/strength	Oral suspension 5 mg/ml
Applicant Proposed Indication(s)/Population(s)	Treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity
Applicant Proposed Dosing Regimen(s)	Initiate with a low dosage, preferably divided doses. The maximum dosage is 80 mg daily.
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	Treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity
Recommended Dosing Regimen(s) (if applicable)	Initiate with a low dosage, preferably divided doses. The maximum dosage is 80 mg daily.

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Susanne Goldstein
Pharmacology Toxicology Review	N/A
OPQ Review	Integrated review
Clinical Pharmacology Review	Adarsh Gandhi/Bilal AbuAsal
OPDP	Lynn Panholzer/Aline Moukhtara
OSE/DMEPA	Beverly Weitzman/Stephanie DeGraw

1. Background

The Applicant has submitted a 505(b)(2) New Drug Application (NDA) for Fleqsuvy (baclofen oral suspension 5 mg/ml). The recommended indication is for the treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity. The proposed dosing regimen is the same as baclofen tablets: 5 mg (1mL) three times a day (TID) for three days, 10 mg (2 mL) TID for three days, 15 mg (3 mL) TID for three days, and 20 mg (4 mL) TID for three days. The maximum recommended dosage is 80 mg daily (20 mg four times a day). The product is a grape flavored oral suspension.

Baclofen is approved under several dosage forms for the treatment of spasticity resulting from multiple sclerosis: intrathecal, oral tablets, oral disintegrating tablets, oral solution (1 mg/ml), and oral granuales.

The Applicant had a preIND meeting with the Division in February 2017. At that time the Applicant was advised that a 505(b)(2) pathway appeared acceptable. The Applicant notified the Agency that the listed drug Lioresal (baclofen tablets) was discontinued. The Applicant asked about the appropriateness of relying on FDA's finding of safety and/or effectiveness for a discontinued listed drug. The Applicant was advised to use the ANDA product designated as the reference standard (RS) in the Orange Book to establish a bridge between the proposed drug product and the specified listed drug.

The Applicant was advised that no additional nonclinical studies would be needed to a support clinical development or a 505(b)(2)NDA.

The Applicant is relying on baclofen tablets (Teva ANDA-A072235) as the RS to support the safety and efficacy of their product. This product is identified in the Orange Book as a RS for baclofen tablets.

The Applicant submitted a clinical pharmacology study to establish a pharmacokinetic bridge to the RS.

2. Product Quality

The final recommendation from the Office of Pharmaceutical Quality (OPQ) review team is to approve the application. From a quality perspective, the review team finds that the application provides for adequate assurance that the product will be suitable for use by the intended patient population

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann. The OPQ integrated review lists the entire OPQ team that was involved with the review of this application. Please refer to the OPQ review for details of the product quality assessment.

According to the OPQ review, the drug substance is produced with adequate quality for use as an oral suspension. No deficiencies were identified by the drug substance reviewers. The proposed specification is adequate to ensure the identity, strength, quality, purity, and potency of the product for the proposed shelf-life.

The drug product is an orange to yellow suspension with artificial grape flavoring that will be marketed in bottles containing 120 mL or 300 mL of the suspension. Although the formula is a suspension, approximately (b)(4)% of the drug substance is fully dissolved. According to the OPQ drug product reviewers, stability and release testing were found to be acceptable. The stability data provides adequate support for a shelf-life of 24 months at controlled room temperature.

OPQ determined that the manufacturing processes for the drug product were acceptable. The manufacturing and test facilities for this application were found to be acceptable based on prior compliance history or a recent 704(a)(4) assessment.

The biopharmaceutics reviewers found the dissolution method and acceptance criterion acceptable. Bridging studies were not needed for the proposed product as there were no changes in the composition of the proposed product between the clinical batches and the proposed commercial batches nor where there changes in the product manufacturing site or manufacturing process in the scale-up.

There were no outstanding issues identified in the integrated OPQ review.

3. Nonclinical Pharmacology/Toxicology

The Applicant is relying on the nonclinical information in the oral baclofen tablet label (Lioresal NDA 017851) and the FDA's finding of safety and effectiveness for oral baclofen with no new studies needed to support the NDA. No nonclinical data were submitted for this application; therefore, a nonclinical review was not needed for this application.

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was performed by clinical pharmacology reviewer Dr. Adarsh Gandhi with Dr. Bilal AbuAsal as the team leader. OCP has concluded that the pharmacokinetic study conducted by the Applicant provides an adequate scientific bridge for this application to rely on the labeling information of the listed drug, Lioresal.

The Applicant conducted a pharmacokinetic (PK) study in adult healthy volunteers to demonstrate the bioequivalanece between baclofen oral suspension and the reference standard baclofen tablets. Study RM-05-PK001 was a phase 1 pivotal bioequivalence and food effect study that demonstrated the bioequivalence (BE) of baclofen oral suspension 20 mg (4 mL of 5mg/mL) to 20 mg of the reference standard. As per Dr. Gandhi's review, BE was established between baclofen oral suspension and the RS for 20 mg single doses where the geometric least squares mean ratio (90% confidence interval) for C_{max} was 99.20 (92.17 – 106.77), AUC_{0-t} was

100.87 (95.29 – 106.77) and $AUC_{0-□}$ was 101.91 (96.99 – 107.08). This study also evaluated the effect of high-fat meal on the PK of baclofen oral suspension, where the high-fat meal decreased the AUC by 10% and C_{max} by 33%. This finding is comparable to the effect of high-fat meal on the RS based on previous ANDA submissions (ANDA 212067, ANDA 074584, and ANDA 211659).

The Office of Study Integrity and Surveillance (OSIS) was consulted for clinical and bioanalytical site inspections for the pivotal bioavailability/bioequivalence study RM-05-PK001. OSIS determined that the inspections at the sites were previously conducted for other applications within the surveillance interval, and therefore not warranted at this time.

5. Clinical Microbiology

The integrated OPQ reviews notes that the microbiology assessment was adequate.

6. Clinical/Statistical- Efficacy

The clinical effectiveness of baclofen oral suspension was established through the demonstration of bioequivalence to the reference standard baclofen product.

7. Safety

The safety of baclofen oral suspension was established through the demonstration of bioequivalence to the reference standard baclofen product. Dr. Susanne Goldstein reviewed safety data in the application from the bioequivalence study, RM-05-PK001, which was conducted under fed and fasted conditions.

There were no deaths or serious adverse events in the study. There was one discontinuation due to the adverse event of increased creatinine and increased creatine kinase (CK). The subject had a mildly elevated creatinine. The CK was noted to be elevated after receiving a single dose of baclofen, but there was no baseline CK available for comparison. There were no adverse events related to the local tolerability of the baclofen oral suspension.

Dr. Goldstein did not identify any new safety concerns with the use of baclofen oral suspension.

8. Advisory Committee Meeting

N/A

9. Pediatrics

The listed drug Lioresal is approved for patients age 12 and older. The efficacy of Fleqsuvy in pediatric patients age 12 and older was established through bioequivalence to the reference standard baclofen product. For pediatric patients less than age 12, the Pediatric Research

Committee (PeRC) concurred with the Division's recommendation to grant a partial waiver for children ages 0 to <12 years old for the treatment of spasticity caused by multiple sclerosis.

10. Other Relevant Regulatory Issues

The Applicant submitted the proposed proprietary name, Fleqsuvy. DMEPA found the name to be acceptable.

11. Labeling

The labeling for Fleqsuvy will be similar to the approved labeling for the listed drug. The approval of Ozobax (baclofen oral solution) included labeling revisions needed to comply with the Physician's Labeling Rule (PLR) and sections that comply with the Pregnancy and Lactation Labeling Final Rule (PLLR). The Ozobax label is being used as the base for the Flequsvy label because it has already been converted into the required format.

12. Postmarketing Recommendations

Not Applicable

13. Recommended Comments to the Applicant

I recommend approval of this NDA for Fleqsuvy based on the finding that Fleqsuvy 20 mg meets the bioequivalence criteria to the 20 mg dose of baclofen oral tablets, which the Division has previously determined to be safe and effective for the treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity.

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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01/31/2022 12:59:40 PM

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