CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215422Orig1s000

SUMMARY REVIEW

Summary Review

Date	November 12, 2021
From	Laura Jawidzik, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 215422
Applicant	Saol Therapeutics Research Limited
Date of Submission	January 22, 2021
PDUFA Goal Date	November 22, 2021
Proprietary Name	Lyvispah
Established or Proper Name	Baclofen oral granules
Dosage Form(s)	Oral granules 5 mg, 10 mg, and 20 mg packets
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, in adults and pediatric patients age 12 years and older particulary 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	Richard Siarey/Lois Freed
OPQ Review	Integrated review
Clinical Pharmacology Review	Yifei Zhang/Bilal AbuAsal
OPDP/DMPP	LaShawn Griffiths/Marcia Williams/Mary Carroll/Domenic D'Alessandro
OSE/DMEPA	Beverly Weitzman/Stephanie DeGraw/Danielle Harris

1. Background

The Applicant has submitted a 505(b)(2) New Drug Application (NDA) for Lyvispah (baclofen oral granules). Lyvispah is administered orally and is presented in packets containing orally dissolvable granules. The recommended indication is for the treatment of spasticity resulting from multiple sclerosis in patients age 12 years and older. The proposed dosing regimen is the same as baclofen tablets: 5 mg three times a day (TID) for three days, 10 mg TID for three days, 15 mg TID for three days, and 20 mg TID for three days. The maximum recommended dosage is 80 mg daily (20 mg four times a day).

Baclofen is approved under several dosage forms for the treatment of spasticity resulting from multiple sclerosis: intrathecal, oral tablets, oral disintegrating tablets, and oral solution,

The Applicant had a preIND meeting with the Division in February 2019. 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 in the Orange Book to establish a bridge between the proposed drug product and the specified listed drug.

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

The Applicant submitted clinical pharmacology studies to establish a pharmacokinetic bridge to the reference standard.

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 in the oral granules formulation. No deficiencies were identified by the drug substance reviewers.

The drug product is a white to off-white, free-flowing granule containing baclofen with strawberry flavoring in a packet. The proposed container closure system is an (b) (4)

packet. 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 (b) (4) months at controlled room temperature. In-use stability results confirm that the drug product can be administered with soft foods such as apple sauce, yogurt, and pudding. The Applicant also monitored the stability of the drug product in apple juice and milk. In-use stability also confirmed that the drug product can be administered via feeding tubes.

OPQ determined that the manufacturing process for the drug product were acceptable. The manufacturing and test facilities for this application were found to be acceptable based on prior history.

The biopharmaceutics reviewers found the dissolution method and acceptance criterion acceptable. The Applicant did not need to bridge the to-be-marketed formuation as the to-be-marketed formuation was utilitized in the pivotal bioavailablity studies. All three strengths of baclofen granules were studied in bioavailability studies so a biowaiver was not required.

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 additions to the nonclinical section of labeling are recommended. The nonclinical review team recommends approval.

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was performed by clinical pharmacology reviewer Dr. Yifei Zhang with Dr. Bilal AbuAsal as the team leader. OCP has concluded that the pharmacokinetic studies conducted by the Applicant provide an adequate scientific bridge for this application to rely on the labeling information of the reference standard (RS).

The Applicant conducted two pharmacokinetic (PK) studies in healthy volunteers to demonstrate the bioequivalanece between Lyvispah and the reference standard baclofen tablets. Study Saol 1001-01 was a phase 1 bridging study that demonstrated the bioequivalence of baclofen granules 20 mg to 20 mg of the reference standard. This study also evaluated the PK of Lyvispah when administered with or without water, or in soft food. When Lyvispah was taken with or without water or soft food, the baclofen exposure metrics (AUC and C_{max}) were all within the bioequivalence criteria compared with the exposure of the RS after administration with water under fasted conditions.

Study Saol 1001-02 demonstrated dose-proportionality of the granule formation across the dose range of 5 mg, 10mg, and 20 mg. This study also evaluated the effect of a high-fat meal on the PK of the granules. Administration of high fat meal led to decrease in AUC by 10% and C_{max} by 29%, which is comparable to the effect of high fat meal on the RS.

The Office of Study Integrity and Surveillance (OSIS) was consulted for clinical and analytical site inspections for the pivotal relative bioavailability study Saol 1001-01. OSIS determined that the inspections 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 Lyvispah was established through the demonstration of bioequivalence to the reference standard baclofen product.

7. Safety

The safety of Lyvispah was established through the demonstration of bioequivalence to the reference standard baclofen product. Dr. Susanne Goldstein reviewed new safety data in the application. The safety review focused on the two clinical studies submitted with the applications: Saol 1001-01 and Saol 1001-02. Study 01 was a single dose fasted comparative bioavailability study of baclofen granuels and baclofen oral tablets. Study 02 was a single-dose bioavailabity study. As part of the study design,

There were no deaths in either study. There was one serious adverse event (SAE) of thrombotic stroke that occurred four days after a single dose of baclofen granules. Dr. Goldstein felt this SAE was unrelated to the use of baclofen. There was one discontinuation due to the adverse event of pruritus. Pruritis is already included in Section 6 of the FDA label.

The Applicant included a specific assessment of the local tolerability of the oral granules. This included a visual assessment of the tongue, palate, and buccal mucosa. These assessments were performed at screening, prior to dosing, and at approximately 2 and 24 hours after dosing. No alteration in the appearance of the oral mucosa was noted. Two patients reported dry mouth and three patients reported a oropharyngeal pain (sore throat). Of the three patients reporting oropharyngeal pain, one had received the reference product and one reported the pain during the washout period. It is unlikely that oropharyngeal pain was related to the use of baclofen granules. Dry mouth and taste disorders are already included in the labeling for baclofen.

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

8. Advisory Committee Meeting

N/A

9. Pediatrics

The listed drug Lioresal is approved for patients age 12 and older. The efficacy of Lyvispah 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 previously submitted the proposed proprietary name, (b) (4) DMEPA found the name (b) (4) to be unacceptable due to orthographic similarities and shared product characteristics with the proprietary name, (b) (4) The Applicant subsequently submitted the proposed name, (b) (4) which was also found to be unacceptable. The Applicant ultimately submitted the name Lyvispah which was found to be acceptable.

11. Labeling

The labeling for Lyvispah 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 Lyvispah 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 Lyvispah based on the finding that Lyvispah 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.

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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