DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

DATE: June 14, 2024

FROM: Roselyn E. Epps, M.D., FAAP, FAAD, Clinical Reviewer, Division of Dermatology and Dentistry (DDD), Office of Immunology and Inflammation (OII)
David Kettl, M.D., Clinical Team Leader, DDD, OII

SUBJECT: Sofpironium Bromide 15% topical gel (NDA 217347) Class 2 resubmission

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On September 23, 2022, Botanix SB submitted NDA 217347 sofpironium topical gel 15% for the treatment of primary axillary hyperhidrosis in patients 9 years and older to the US FDA.

After review, on September 22, 2023, the Agency issued a Complete Response (CR) for NDA 217347 for the following reasons:

> *Based on the evaluation of the human factors (HF) study results, the user interface does not support the safe and effective use of the proposed product.*
> *The results of the HF validation study demonstrated several use errors/close calls/use difficulties with critical tasks that may result in harm to the patient or others, or compromised efficacy.*

The Agency informed the Applicant that the information needed to resolve the deficiencies included the following:

1. *Review the HF study results and subjective feedback to identify potential areas of optimization.*
2. *Implement additional design modifications and user interface revisions identified in item #1 above, along with the following:*
    a. *Label the applicator with the applicator's intended use/purpose because several users in the HF validation study indicated that they did not understand what the applicator was, or how to use it.*
    b. *Revise the instructions for use (IFU) to address the subjective feedback that:*
        i. *The IFU has too much information*
        ii. *Certain information in the IFU lacks salience*
        iii. *The IFU was folded which may have contributed to missed steps*
    c. *Place the statement "wash hands with soap and water immediately after use" on the principal display panel of the carton and container labeling to emphasize this important information, based on the residual risk and subjective feedback related to the task of washing hands.*
3. *Consider implementing a mitigation to address the foreseeable use issue of users of this product tilting the applicator to apply to the underarm(s) and spilling the gel, as observed in the HF validation study.*
4. *Conduct another HF validation study to demonstrate that the revised user interface supports the safe and effective use of the product.*

Also, with the response to the above deficiencies, the Applicant was to include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

The review team did not identify any other CR issues for the initial review cycle, and the team concluded that the safety and efficacy had been acceptably demonstrated. The risks of the product could be described in labeling and followed with routine pharmacovigilance. Addressing the HF study results was the only item to be addressed in the second cycle review.

On December 20, 2023, Botanix provided a resubmission of their NDA (SDN 24) which included the following:

- Updated draft label including proprietary name and revised IFU.
- Updated Carton and Container labeling including proprietary name.
- Proposed proprietary name, Sofdra (resubmission of the conditionally approved tradename package).
- Pharmacovigilance report from Japan.
- Safety findings from scientific literature.
- Human factors (HF) validation study clinical study report (CSR).

Human Factors

After the December 2023 resubmission, the Agency interacted with the Applicant on multiple occasions. Highlights of the interactions follow.

- On February 28, 2024, the Agency sent a Discipline Review letter informing the Applicant of concerns regarding the HF validation study methodology. The Agency recommended conducting a new HF validation study.
- On March 7, 2024, the Applicant responded, addressed the deficiencies, and requested a meeting. The Agency granted a type C written response only (WRO) meeting on March 21, 2024.
- On March 25, 2024, the Agency sent written response clarifying the specific concerns with the HF validation study methodology.
- On March 28, 2024, the Applicant submitted additional information to address concerns regarding methodology.
- On April 15, 2024, the Agency sent an advice letter which reiterated our concerns and requested that they conduct and a new HF validation study and submit the results for review.
- On April 18, 2024, the Applicant submitted results from a new HF validation study, which were reviewed by the Division of Medication Error and Analysis 1 (DMEPA).

On May 20, 2024, DMEPA concluded their review of the HF validation study results submitted in response to the CR [Reference # 5384146]. Reviewer Matthew J. Barlow provided the following conclusion and recommendation:

> *The results of the HF validation study demonstrated use issues with critical tasks that may result in harm. However, based on our review of the available participants' subjective feedback and root cause analysis, we did not identify additional risk controls to address the use issues at this time. We find the risks gave been mitigated to an acceptable level. As such, we have no recommendations for this NDA.*

Safety

In the December 20, 2023, submission, the Applicant submitted Periodic Adverse Drug Experience Report (PADER) for sofpironium bromide (Investigational New Drug [IND] 121256). The PADER reporting period is January 28, 2023, to December 14, 2023. The Applicant stated that there were no plans to update and integrate the clinical safety sections of the NDA (Module 2.7.4 and the ISS) in the resubmission.

The following safety information was provided:

- No new clinical trials were conducted by Kaken or Botanix since January 27, 2023 (PADER).
- No other clinical studies of sofpironium bromide were ongoing or completed during the reporting period.
- Sofpironium bromide gel, 5% is approved for marketing in Japan under the tradename ECCLOCK®. No new safety findings were reported from marketing experience in Japan during the reporting period, and those occurring were consistent with the currently approved labeling.
- The Applicant submitted two publications published since the NDA submission.
  - Efficacy of sofpironium bromide gel on clozapine-induced hypersalivation in patients with treatment-resistant schizophrenia: double-blind, controlled crossover study (Amano 2023)
  - Efficacy of 5% sofpironium bromide gel in Duchenne muscular dystrophy with palmoplantar hyperhidrosis: A retrospective case study (Funato 2023)

Both articles concern sofpironium gel of 5%, a strength with differs from the formulation under Agency review. Additionally, the articles describe use in clozapine-induced hypersalivation and palmoplantar hyperhidrosis, indications other than the proposed axillary hyperhidrosis indication.

Labeling

- On June 6, 2024, the Office of Prescription Drug Promotion (OPDP) review of the proposed PI was based on the draft labeling emailed to OPDP on May 23, 2024.
- On June 4, 2024, a combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI/IFU, and comments were sent.
- On June 7, 2024, the Applicant submitted revised IP, IFU, container label and carton labeling.
- On June 11, 2024, DMEPA 1 reviewer Madhuri R. Patel, PharmD concluded that the Applicant had implemented all container label and carton labeling recommendations and there were no additional recommendations. [Reference ID: 5384146]

The final labeling will be attached to the Action Letter.

Other Disciplines

- March 13, 2024: DMEPA completed the review of the proposed proprietary name, Sofdra, and concluded that it is conditionally acceptable. [Reference ID: 5345963]
- June 11, 2024: The Chemistry Manufacturing and Controls (CMC) Team recommended that all Office of Pharmaceutical Quality (OPQ) disciplines are adequate. CMC.
  Action recommended: Approval [Reference ID: 5396090]

Conclusions and Recommendation:

The Applicant has responded to Agency concerns cited in the CR. No new safety signals or concerns were identified during the interim period.

The Clinical discipline recommends approval.

References

Amano Y, Mazda J, Amano K, Ohi K, Shioiri T. Efficacy of sofpironium bromide gel on clozapine-induced hypersalivation in patients with treatment-resistant schizophrenia: double-blind, controlled crossover study. BJPsych Open. 2023;9(1):e14. Published 2023 Jan 13. doi:10.1192/bjo.2022.630

Funato M, Iwata R, Iimoto M. Efficacy of 5% sofpironium bromide gel in Duchenne muscular dystrophy with palmoplantar hyperhidrosis: A retrospective case study. J Dermatol. 2024;51(1):135-139. doi:10.1111/1346-8138.16990

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