

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217347Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	217347
PDUFA Goal Date	June 20, 2024
Nexus TTT #	2022-1830
Reviewer Name(s)	Donella Fitzgerald, PharmD
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	June 14, 2024
Subject	Evaluation of Need for a REMS
Established Name	Sofpironium bromide
Trade Name	Sofdra
Name of Applicant	Botanix SB, Inc.
Therapeutic Class	Anticholinergic
Formulation(s)	Topical gel, 12.45%
Dosing Regimen	Apply 1 pump per underarm once a day at bedtime

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1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Sofdra (sofipronium bromide) is necessary to ensure the benefits outweigh its risks. Botanix SB, Inc. (hereafter referred to as the Applicant) submitted a New Drug Application (NDA) 217347 for sofipronium topical gel 15% (12.45% free base) with the proposed indication for the topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older. This application is under review in the Division of Dermatology and Dentistry (DDD). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Sofipronium bromide (sofipronium), a new molecular entity^a, [REDACTED] (b) (4) [REDACTED] is proposed for the topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older. It reduces the rate of sweating by preventing stimulation of acetylcholine receptors in sweat glands.¹

Sofipronium is proposed to be marketed as a topical gel in a 50 mL bottle with a multi-dose metered pump and applicator containing 12.45% (w/w) of sofipronium. Each pump delivers 72 mg of sofipronium in 0.67 mL of gel. The proposed dose is one pump actuation per underarm administered once a day at bedtime, for a daily dose of 144 mg of sofipronium. It should not be used more frequently than once every 24 hours. Sofipronium may be used chronically and is expected to be administered in the outpatient setting.^b Sofipronium 5% gel (ECCLOCK®) is currently marketed in Japan; it was approved in September 2020 for the treatment of primary axillary hyperhidrosis.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 217347 relevant to this review:

- **09/23/2022:** NDA 217347 submission for the topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age received.
- **03/07/2023:** A mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that no major safety issues have been identified at this stage of the review and that a REMS will likely not be required.
- **09/22/2023:** Complete Response Letter (CRL) issued due to Human Factors deficiencies.
- **12/20/2023:** Applicant resubmitted NDA 217347 in response to the CRL issued September 22, 2023.

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- **05/20/2024:** Human Factors Study Report review concluded that the sofipironium device administration risks have been mitigated to an acceptable level.²

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Hyperhidrosis is a common condition of excessive sweating beyond what is physiologically required to regulate a normal body temperature.^{3,4} It can be divided into primary and secondary. Primary hyperhidrosis is a chronic, idiopathic condition without another underlying cause. Secondary hyperhidrosis may be associated with a variety of endocrine, neurologic, cardiovascular, and metabolic disorders and with a number of medications. The pathophysiology is not completely understood; however, the sweat glands are histologically and functionally normal and the excessive sweating appears to be caused by an exaggerated stimulation of the eccrine sweat glands and lower threshold for response to normal stimuli, such as emotional and physical stress.^{5,6} The prevalence of hyperhidrosis has been estimated to be around 1-5% of the population.⁷ According to a study published in 2016, the estimated prevalence of hyperhidrosis was 4.8%, or about 15.3 million people based on the current United States population.⁸ In this study, the highest prevalence rate was among people 18 to 30 years old.

Primary hyperhidrosis is generally localized and symmetric, most often affecting the axillae, palms, and soles but may also involve the face, scalp, trunk and intertriginous area. Primary hyperhidrosis symptoms typically start in late childhood or adolescence following puberty and may persist into adulthood.⁹ The severity can range from mild dampness to severe dripping.¹⁰ Hyperhidrosis negatively impacts daily life, especially mental health, self-esteem, interpersonal relationships, and work/school life and productivity.^{11,12} Studies have found that the prevalence of anxiety and depression was higher in patients with hyperhidrosis compared to those without.^{13c}

3.2. Description of Current Treatment Options

Treatment selection depends on factors such as the location of involvement, patient preferences, severity, safety concerns, cost, and availability.¹⁴ Treatment options for primary axillary hyperhidrosis include antiperspirants, botulinum toxin, topical glycopyrronium, thermolysis, iontophoresis and surgery.

Topical antiperspirants are considered first-line treatments. They are readily available, inexpensive, and well tolerated. Most patients with hyperhidrosis will require higher dose prescription antiperspirants

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

such as 6.25% aluminum chloride hexahydrate. These products may not be effective and can cause skin irritation which limits their use.

There are two prescription products for the treatment of primary hyperhidrosis. Onabotulinumtoxin A (Botox) was approved in 2004 for the treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients. Qbrexza (glycopyrronium cloth 2.4%) was approved in 2018 for the treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older. Botox treatment can be costly and burdensome as it requires numerous injections (20-40 per axilla) and may be painful. QBrexza treatment may be more convenient as it is administered with a single-use cloth, however use may be limited by systemic anticholinergic effects.

In addition to the drugs approved for the treatment of primary hyperhidrosis, there are also FDA-cleared medical devices. MiraDry® is a microwave-based thermolysis device that works by destroying axillary sweat glands. There are multiple approved iontophoresis devices (Dermadry, Drionic, RH-900) that use an electrical current to temporarily inactivate the sweat glands. In April 2023, the FDA approved the Brella SweatControl patch that uses alkali thermolysis to decrease sweat production. An alternate treatment option patients may consider is a sympathectomy, which involves surgical removal of the nerves responsible for stimulation of the sweat glands.

As current therapies for primary hyperhidrosis may have limited efficacy, can be burdensome, invasive and/or costly, there is an unmet need for additional treatment options for this condition.

4. Benefit Assessment

The efficacy of sofipirionium for the topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age was demonstrated in two pivotal phase 3 studies (BBI-4000-CL-301/Study 301 [NCT03836287] and BBI-4000-CL-302/Study 302 [NCT03948646]). The studies were identical in design: multicenter, randomized, double-blind, and vehicle controlled. Study 301 enrolled 350 subjects at 35 centers in the United States (US) and Study 302 enrolled 351 subjects in the US. In each study subjects were randomized in a 1:1 ratio to sofipirionium bromide gel 15% or vehicle. Subjects were instructed to apply treatment once daily at bedtime to each axilla for 42 days. Efficacy was assessed using the Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) scale and gravimetric sweat assessments (5 minutes at room temperature) on both axillae. The studies had the same co-primary efficacy endpoints: The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-7 scale score from baseline to end of treatment (EOT) and secondly, the change in gravimetric sweat production (GSP) from baseline to EOT. The primary analysis population was the intent to treat (ITT) population which was defined as all randomized subjects. Table 1 outlines the efficacy results based on the ITT population in subjects who were ≥ 12 years of age.^d

^d Because different versions of the HDSM-Ax scale were used for children <12 years of age and adolescents and adults ≥ 12 years of age, the recommended presentation of results is to use the analysis including subjects ≥ 12 years of age. Across the two studies, only 5 subjects <12 years of age were enrolled.

Table 1: Co-primary Efficacy Results in Studies 301 and 302 (ITT)

	Study 301		Study 302	
	SB Gel 15% (N=173)	Vehicle (N=177)	SB Gel 15% (N=180)	Vehicle (N=171)
≥2 point improvement in HDSM-Ax-7 (≥12 years)	N=172	N=177	N=178	N=169
Estimated proportion (adjusted ¹) (%)	48.8	29.3	64.2	47.7
p-value	0.0005		0.0040	
Estimated proportion (unadjusted ²) (%)	50.4	32.1	63.3	47.1
Treatment difference (95% CI)	18.3 (8.0, 28.7)		16.2 (5.4, 26.9)	
Change from Baseline³ in GSP	N=173	N=177	N=180	N=171
Difference in Ranks ⁴				
LS Means [Ranks] (SE)	-14.9 (6.8)	14.8 (6.7)	-9.9 (7.1)	11.8 (7.5)
p-value	0.0019		0.0296	
Values ⁵				
Median	-127.8	-100.3	-142.6	-134.2
25 th percentile, 75 th percentile	-200.5, -52.4	-227.5, -28.5	-260.1, -75.0	-230.0, -59.5

¹ Estimates and p-value from logistic regression adjusted for baseline and analysis center (multiple imputation).

² Estimates and CI using Wald method (multiple imputation)

³ Baseline value calculated from the median GSP value from Visits 2, 3, and 4; EOT value calculated from the median GSP value from Visits 10, 11, and 12.

⁴ ANOVA on the difference in ranks adjusted for baseline rank and analysis center (multiple imputation).

⁵ Medians and quartiles averaged over the 20 multiply imputed datasets.

CI= confidence interval; LS=Least squares; SE= standard error

Source: Division of Dermatology and Dentistry. Multidisciplinary Review and Evaluation for sofipironium bromide, NDA 217347, September 22, 2023.

The applicant reported that both studies met the co-primary endpoints, demonstrating statistically significant efficacy results. The DDD concluded that the applicant provided substantial evidence of effectiveness of sofipironium gel 15% versus vehicle in the treatment of primary axillary hyperhidrosis.^{15e}

5. Risk Assessment & Safe-Use Conditions

The primary safety analysis consists of data from 701 subjects treated with sofipironium during the Phase 3 clinical trials (Study 301, Study 302). Supportive safety data from a long-term, multicenter (US), randomized, open-label, safety study of sofipironium bromide gel, 5% and 15% in subjects with axillary hyperhidrosis (BBI-4000-CL-303/Study 303) is also included.

No deaths were reported in the pivotal Phase 3 studies; however, one death was reported in Study 303. The patient was a 57-year-old African American male who received sofipironium 5% gel, 285 doses (40 weeks, 5 days). The subject died of septic shock secondary to pneumonia. The Applicant reported that the death was not related to sofipironium use. The medical officer concluded that it is unlikely that the pneumonia and septic shock events were related to study drug.

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

One serious adverse event (SAE) was reported in each Phase 3 study. In Study 301 one patient who was randomized to the sofipirionium gel group and completed treatment through Day 43, experienced a small bowel obstruction and was hospitalized for treatment. The small bowel obstruction was considered resolved on Day 75. The subject completed the study on day 98. The clinical reviewer noted in the Multidisciplinary Review for NDA 217347 that ileus and bowel symptoms are known adverse events which can be related to anticholinergic medications; however, the half-life of sofipirionium is brief and it was unlikely to be present at the time of the patient’s symptom onset. Therefore, it is unlikely that the serious AE was related to study drug. The SAE that occurred in Study 302 was a case of appendicitis on Day 11 of sofipirionium treatment in a subject. The subject underwent an appendectomy and sofipirionium treatment resumed following surgery. The clinical reviewer concluded that the appendicitis was not likely related to sofipirionium.

5.1. Anticholinergic Effects

Due to the excess blockade of cholinergic receptors within the central nervous system and blockade of exocrine glandular secretion and muscle contraction, anticholinergic drugs have the potential to cause central and peripheral adverse reactions that affect multiple organ systems including gastrointestinal, genitourinary and head, ears, eyes, nose and throat (HEENT). Anticholinergic adverse reactions were observed in the clinical trials for sofipirionium. Table 2 summarizes the most frequent anticholinergic adverse reactions occurring in $\geq 2\%$ of subjects:

Table 2: Anticholinergic Adverse Reactions Occurring in $\geq 2\%$ of Subjects		
Adverse Reactions	Sofipirionium gel, 12.45% (N = 353) n (%)	Vehicle (N = 347) n (%)
Dry mouth	51 (14.4%)	2 (0.6%)
Vision blurred	30 (8.5%)	1 (0.3%)
Mydriasis	23 (6.5%)	0
Urinary retention	8 (2.3%)	0

None of the anticholinergic adverse reactions was reported to be serious, however, treatment discontinuations occurred in the sofipirionium treatment groups. In Study 301 five subjects reported discontinuation due to eight treatment emergent adverse events (TEAE). The AEs as reported (#subjects) were: blurred vision (1); application site dermatitis, bilateral (2); urinary retention (1); mydriasis (1); dry mouth (1); application site pain, bilateral (2). In Study 302, nine subjects reported discontinuation due to fourteen TEAEs. The AEs as reported (#subjects) were: blurred vision (2); mydriasis (4); application site dermatitis (3); application site pain (1); application site erythema (1); dry eye (1); dry mouth (2). The medical officer concluded that the reported AEs leading to study discontinuation were consistent with anticholinergic effects and likely related to study drug use. She stated that “overall, adverse events were reversible and mild to moderate in severity.”¹⁶

Draft labeling for sofipronium includes a Contraindication for patients with medical conditions that can be exacerbated by the anticholinergic effect of sofipronium, as well as Drug Interaction language stating that coadministration of sofipronium with anticholinergic medications may result in additive interaction leading to an increase in anticholinergic adverse effects. The proposed Warnings and Precautions include worsening of urinary retention, decreased control of body temperature and operating machinery or an automobile as transient blurred vision may occur with sofipronium use.

6. Expected Postmarket Use

If approved, sofipronium is expected to be prescribed for use by patients in the outpatient setting. The likely prescribers include dermatologists, primary care providers, and pediatricians. These prescribers should be familiar with the associated risks of anticholinergic medications and how to manage them. Providers can counsel patients and/or caregivers at the point of care regarding the potential risks of anticholinergic effects. The patients (or caregivers) should be able to take the necessary action of reporting to their healthcare provider symptoms suggestive of anticholinergic effects such as increased urinary retention and blurred vision.

As sofipronium 5% gel was approved in Japan in September 2020, there is foreign postmarketing experience with its use in treatment of primary axillary hyperhidrosis. According to the Applicant, they did not identify new safety findings after marketing in Japan.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for sofipronium beyond routine pharmacovigilance and labeling. Proposed labeling for sofipronium includes a Patient Information Sheet and Instructions for Use (IFU) that detail the administration instructions.

8. Discussion of Need for a REMS

Based on the efficacy and safety information currently available, the Clinical Reviewer recommends approval of sofipronium gel for the topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older.¹⁷

The benefits of treatment with sofipronium was demonstrated by meeting the co-primary endpoints of the proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-7 scale score from baseline to end of treatment and the change in gravimetric sweat production (GSP) from baseline to end of treatment.

The safety profile for sofipronium is consistent with drug products that have anticholinergic pharmacologic activity.¹⁸ Blurred vision, urinary retention, mydriasis, dry mouth and dry eye were observed during the clinical trials. Draft labeling for sofipronium includes a Contraindication for patients

with medical conditions that can be exacerbated by the anticholinergic effect of sofipironium, as well as Drug Interaction language stating that coadministration with anticholinergic medications may result in additive interaction leading to increased anticholinergic adverse effects. The proposed Warnings and Precautions include worsening of urinary retention, decreased control of body temperature and caution when operating machinery or an automobile as transient blurred vision may occur with sofipironium use. No postmarketing requirements or commitment are recommended at this time.

The healthcare providers who are likely to prescribe sofipironium should be familiar with the risks associated with anticholinergic medications and how to manage them. Proposed labeling includes Instructions for Use and a Patient Information sheet. The patients and caregivers will likely be able to identify anticholinergic adverse reactions and report symptoms to their provider. Postmarketing data for sofipironium 5% gel currently marketed in Japan did not identify new safety findings. The DDD is not recommending postmarketing requirements or commitments for sofipironium topical gel 15% at this time.

Therefore, based on the data currently available, DRM and DDD agree that a REMS is not necessary to ensure the benefits outweigh the risks of sofipironium treatment.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for sofipironium to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

¹ Botanix SB, Inc. Draft Prescribing Information for sofipironium gel (NDA 217347), August 28, 2023.

² Barlow M, Flint J. Division of Medication Error Prevention and Analysis 1 Human Factors Study Report Review for sofipironium bromide, NDA 217347, May 20, 2024.

³ Smith CC, Pariser D. (2022). Primary focal hyperhidrosis. *UpToDate*. Retrieved April 6, 2023 from <https://www.uptodate.com/contents/primary-focal-hyperhidrosis>.

⁴ Doolittle J, Walker P, Mills T, Thurston J. Hyperhidrosis: an update on prevalence and severity in the United States. *Arch Dermatol Res* (2016) 308:743-749.

⁵ Smith CC, Pariser D. (2022). Primary focal hyperhidrosis. *UpToDate*. Retrieved April 6, 2023 from <https://www.uptodate.com/contents/primary-focal-hyperhidrosis>.

⁶ McConaghy JR, Fosselman D. Hyperhidrosis: Management Options. American Family Physician (2018) Vol 97:11. Retrieved April 6, 2023 from <https://www.aafp.org/afp>.

⁷ Smith CC, Pariser D. (2022). Primary focal hyperhidrosis. *UpToDate*. Retrieved April 6, 2023 from <https://www.uptodate.com/contents/primary-focal-hyperhidrosis>.

⁸ Doolittle J, Walker P, Mills T, Thurston J. Hyperhidrosis: an update on prevalence and severity in the United States. *Arch Dermatol Res* (2016) 308:743-749.

⁹ Glaser DA, Ballard AM, Hunt NL, Pieretti LJ, Pariser DM. Prevalence of Multifocal Primary Hyperhidrosis and Symptom Severity Over Time: Results of a Targeted Survey. *Dermatol Surg* (2016) 42(12):1347-1353.

¹⁰ Doolittle J, Walker P, Mills T, Thurston J. Hyperhidrosis: an update on prevalence and severity in the United States. *Arch Dermatol Res* (2016) 308:743-749.

¹¹ McConaghy JR, Fosselman D. Hyperhidrosis: Management Options. American Family Physician (2018) Vol 97:11. Retrieved April 6, 2023 from <https://www.aafp.org/afp>.

¹² Lenefsky M, Rice ZP. Hyperhidrosis and Its Impact on Those Living With It. *Am J Manag Care* (2018) 24:-S0).

¹³ Glaser DA, Ballard AM, Hunt NL, Pieretti LJ, Pariser DM. Prevalence of Multifocal Primary Hyperhidrosis and Symptom Severity Over Time: Results of a Targeted Survey. *Dermatol Surg* (2016) 42(12):1347-1353.

¹⁴ Smith CC, Pariser D. (2022). Primary focal hyperhidrosis. *UpToDate*. Retrieved April 6, 2023 from <https://www.uptodate.com/contents/primary-focal-hyperhidrosis>.

¹⁵ Division of Dermatology and Dentistry. Multidisciplinary Review and Evaluation for sofipronium bromide, NDA 217347, September 22, 2023.

¹⁶ Division of Dermatology and Dentistry. Multidisciplinary Review and Evaluation for sofipronium bromide, NDA 217347, September 22, 2023.

¹⁷ Epps R, Kettle D. Division of Dermatology and Dentistry. Clinical Memorandum for sofipronium bromide, NDA 217347, June 14, 2024.

¹⁸ Division of Dermatology and Dentistry. Multidisciplinary Review and Evaluation for sofipronium bromide, NDA 217347, September 22, 2023.

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Name of Applicant	Botanix SB Inc
Therapeutic Class	Anticholinergic
Formulation(s)	Topical gel, 12.45%
Dosing Regimen	Apply one pump actuation per underarm topically once daily at bedtime

This memo is to defer the Division of Risk Management’s (DRM’s) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for new drug application (NDA) 217347 sofipirionium bromide. Sofipirionium bromide is a small molecule, quaternary ammonium analogue of the anticholinergic drug glycopyrrolate. The Division of Dermatology and Dentistry (DDD) received the NDA for sofipirionium bromide on September 23, 2022. The proposed indication is for primary axillary hyperhidrosis in adult and pediatric patients 9 years and older.

The applicant proposes to manufacture sofipirionium bromide in a metered pump bottle, with an applicator cap over the dispenser and a covering cap. Results of a Human Factors validation study demonstrated several use errors and/or difficulties with critical tasks that could lead to potential underdose, overdose and inadvertent drug exposure to others.¹ The review division concluded that “despite the overall conclusion that effectiveness was adequately demonstrated, and that safety events in the clinical trial were not substantial, the deficiencies in the human factors information does not support an approval of this application due to the risks of medication errors and adverse reactions due to inappropriate drug administration”.² Due to the outstanding deficiencies, DDD plans to issue a Complete Response letter.

Therefore, DRM defers comment on the evaluation of the need for a REMS for NDA 217347 during this review cycle. The evaluation of the necessity for a REMS for NDA 217347 will be undertaken by DRM when the applicant resubmits the NDA for review. Please send DRM a new consult at such time.

This memo serves to close the existing consult request to DRM for sofipirionium bromide under NDA 217347.

¹ Barlow M. Division of Medication Error Prevention and Analysis 1 Human Factors Study Report and Labels and Labeling Review for sofipirionium bromide, NDA 217347, September 15, 2023.

² Division of Dermatology and Dentistry. Draft Multidisciplinary Review and Evaluation for sofipirionium bromide, NDA 217347, September 19, 2023.

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