Sofpironium Bromide (SOFDRA) Topical Gel 12.45% in Primary Axillary Hyperhidrosis National Drug Mini-Monograph

November 2024

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: 1L, first-line; 2L, second-line; CFB, change from baseline; DB, double-blind; DLQI, Dermatology Life Quality Index; EG, extension group; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; GSP, gravimetric sweat production; HDSM-Ax, Hyperhidrosis Disease Severity Measure – Axillary; HDSM-Ax-7, 7-item HDSM-Ax; HDSS, Hydrosis Disease Severity Score; MC, multicenter; pp, percentage point; PAxH, primary axillary hyperhidrosis; Q, GRADE quality of evidence; RCT, randomized clinical trial; SG, switching group; TEAE, treatment-emergent adverse event; TGWS, total gravimetric weight of sweat; VC, vehicle-controlled

FDA APPROVAL INFORMATION

Description / MOA	Sofpironium is an anticholinergic agent that competitively inhibits stimulation of acetylcholine receptors located on certain peripheral tissues including sweat glands
Indication Under Review[1]	Treatment of primary axillary hyperhidrosis in adults
Dosage Regimen	Apply a single pump actuation to each armpit once daily at bedtime. (One pump is dispensed onto the top of the applicator then the gel applied to each armpit.) See application requirements in the prescribing information. Renal Impairment: Not studied. Hepatic Impairment: Not studied. Geriatric Use: Insufficient data. In general, dosage should usually start at the low end.
Dosage Forms Under Review	Topical gel 12.45% (w/w) in 50-mL bottle with metered dose pump and applicator

EFFICACY CONSIDERATIONS

General Considerations	No published clinical trial has evaluated sofpironium topical gel at the approved strength of 12.45%.
Phase 2 US Trial	A 42-day, phase 2, U.S., multicenter, double-blind, dose- and vehicle-controlled, randomized clinical trial (RCT) (N = 227) supported the efficacy of sofpironium topical gel 5%, 10%, and 15% in the change in Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) score from baseline.[2] The HDSM-Ax is a validated patient-reported measure of symptom severity and frequency that was developed to satisfy U.S. FDA requirements. Based on the 5% concentration showing efficacy with a lower incidence of systemic anticholinergic adverse effects, 5% sofpironium was recommended as the clinical dose and subsequently studied in phase 3 trials.[3]
Unpublished US Trials	**Study BBI-4000-CL-301 (Cardigan I) and BBI-4000-CL-302 (Cardigan II): A Multicenter, Randomized, Double-Blinded, Vehicle Controlled Study to Evaluate the Safety and Efficacy of Topically Applied Sofpironium Bromide Gel 15% in Subjects with Axillary Hyperhidrosis**[4]
Design	42-day, phase 3, MC DB VC RCT, stratified by study site Co-primary Efficacy Endpoints: At least a 2-point improvement in the HDSM-Ax-7 scale score (HDSM-Ax-7-2) and CFB in gravimetric sweat production (GSP)
Population	Adult and pediatric ≥ 9 years with PAxH; HDSM-Ax-7 scale score of 3–4; ≥ 50 mg GSP at rest per axilla with total 2-axilla combined score of ≥ 150 mg; symptoms of axillary hyperhidrosis for ≥ 6 months *Baseline Characteristics, Study 301 (N = 350)*: Mean age 32.6 years; 2 (1%) ≥ 65 years; 43% male; 77% White; 21% Black or African American; mean HDSM-Ax-7 score 3.5; mean GSP 297 mg; mean duration of symptoms 172 months *Baseline Characteristics, Study 302 (N = 351)*: Mean age 31.9 years; 7 (4%) ≥ 65 years; 45% male; 78% White; 19% Black or African American; mean HDSM-Ax-7 score 3.6; mean GSP 310 mg; mean duration of symptoms 198 months
Intervention	Sofpironium topical gel 15% once daily at bedtime for 42 days
Comparator	Vehicle topical gel

Results

Efficacy Results at Week 6 (Intent-to-treat Population, Unadjusted)

Measure	Study	SOF15%	VEH	Relative Risk (95% CI)	Diff or AAE, pp (95% CI)	Q
HDSM-Ax-7-2, n/N (%)	301	88/173 (50.7)	57/177 (32.1)	1.6 (1.22, 2.05)	18.6 (8.3, 28.9)	ID
	302	114/180 (63.1)	80/171 (46.6)	1.4 (1.11, 1.64)	16.6 (5.9, 27.2)	ID
Mean CFB in GSP, mg [N]	301	−14.9 [173]	14.8 [177]	—	−29.7 (−48.4, −11.0)	ID
	302	−9.9 [180]	11.8 [171]	—	−21.8 (−41.4, −2.2)	ID

Q, GRADE quality of evidence (ID, insufficient data

Dermatology Life Quality Index (DLQI) was not evaluated.

Subgroup Analyses: Treatment differences were smaller in males (11.5; 95% CI −3.9, 26.8) than females (24.0; 10.0, 38.0); however, there were fewer males (n = 153 and 156, respectively) than females (n = 197 and 195, respectively) in Study 301 and Study 302.

Onset of Effects: Separation between the sofpironium gel 15% and vehicle groups in the rates of HDSM-Ax-7-2 seems to occur by Day 8.[4]

Duration of an Adequate Therapeutic Trial: The peak HDSM-Ax-7-2 effect was apparently not reached by Day 42.[4] The mean change from baseline in GSP reached a maximal reduction at about Day 29.[4]

Published JP Trial	**A phase 3, multicenter, randomized, double-blind, vehicle-controlled, parallel-group study of 5% sofpironium bromide (BBI-4000) gel in Japanese patients with primary axillary hyperhidrosis**[3]
Design	6-week, phase 3, MC DB VC RCT; dynamic allocation based on sex, total gravimetric weight of sweat (TGWS), HDSS, and medical site. *Primary Efficacy Measure*: Hyperhidrosis Disease Severity Score of 1 or 2 (HDSS-1/2) at end of treatment and ≥ 50% reduction in TGWS (TGWS-50) from baseline
Population	Japanese patients ≥ 12 years of age diagnosed with PAxH and had ≥ 2 of the following 6 conditions: onset at age ≤ 25 years; bilateral symmetrical sweating; no sweating during sleep; ≥ 1 episode of heavy sweating per week; family history of axillary hyperhidrosis; and excessive sweating interfering with daily activities. Also had to have HDSS of 3 or 4 at baseline-1 to -3; HDSM-Ax score of ≥ 2 at baseline-1 to -3; gravimetric weight of sweat per side of ≥ 50 mg at two or more of baseline-1 to -3; and subjective symptoms persisting for ≥ 6 months. *Main Exclusion Criteria*: Secondary hyperhidrosis; heavy sweating triggered or worsened by menopause; thoracic sympathectomy was indicated; current or past treatment that might affect the efficacy and/or safety evaluations; and current or past disease that might affect efficacy and/or safety evaluation. *Baseline Characteristics (N = 281)*: Mean age 35.8 y; male 84%; HDSS grade 3 | 4, 67.3% | 32.7%; mean Dermatology Life Quality Index (DLQI) total score 11.3. (DLQI range, 0–30. Higher scores indicate worse impact on quality of life. Scores > 10 indicate the patient's life is severely affected by their skin disease. A minimal clinically important difference is ≥ 4 points.)

Intervention	Sofpironium 5% applied with an applicator to both axillae once daily at bedtime
Comparator	Vehicle
Results	**Efficacy Results at Week 6 (Full Analysis Set)**

Measure	SOF15%	VEH	Relative Risk (95% CI)	Diff or AAE, pp (95% CI)	Q
HDSS-1/2 + TGWS-50, n/N (%)	76/141 (53.9)	51/140 (36.4)	1.5 (1.13, 1.93)	17.5 (6.02, 28.93)	L[α,β]
Mean CFB in DLQI (SD)	−6.8 (4.94)	−4.5 (4.54)	—	−2.3	M[β]

Q, GRADE quality of evidence (L, low; M, moderate)
[α] Downgraded for indirectness (surrogate measure for final clinical outcome)
[β] Downgraded for imprecision (optimal information size not met)

Published JP Long-term Extension Study	A phase III, 52-week, open-label study to evaluate the safety and efficacy of 5% sofpironium bromide (BBI-4000) gel in Japanese patients with primary axillary hyperhidrosis[5]
Design	52-week, phase 3, MC OL noncontrolled observational study; extension of the 6-week phase 3 RCT Previous vehicle patients switched to sofpironium (Switching Group [SG]) and active-treatment patients continued sofpironium (Extension Group [EG]).
Intervention	Sofpironium – one actuation per axilla at bedtime
Results	At Week 52 for SG (N = 94) and EG (N = 91), respectively: • HDSS-1/2 + TGWS-50, 57.4% and 58.2% • CFB in DLQI score, –8.8 and –9.7 • Serious Adverse Events, 2.1% and 1.1% • Adverse Drug-related Reactions, 39.4% and 45.1%

SAFETY CONSIDERATIONS

Boxed Warnings	None
Contraindications	Medical conditions that can be exacerbated by anticholinergic effects (e.g., glaucoma, paralytic ileus, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis, Sjögren's syndrome)
Other Warnings	Urinary retention, control of body temperature, operating machinery or an automobile
Top Adverse Events (≥ 2%)	Dry mouth, blurred vision, mydriasis, urinary retention Local Skin Reactions: Pain, erythema, dermatitis, pruritus, irritation, exfoliation
Phase 2 and Phase 3 RCT Safety Results[4]	For sofpironium 15% (N = 353) vs vehicle (N = 347): • Serious Adverse Events, 143 (40.5%) vs 46 (13.3%) • Severe Treatment-Emergent Adverse Event (TEAE), 9 (2.5%) vs 0 (0%) • Any Treatment-related TEAE, 114 (32.3%) vs 18 (5.2%)
Drug Interactions	Concomitant anticholinergics Strong inhibitors of CYP2D6 (avoid)
Pregnancy	Insufficient human data; no significant embryofetal developmental adverse effects in animals. No specific recommendations about use in pregnancy.
Lactation	Insufficient human data; detected in animal milk; likely to be present in human milk. Consider risks vs benefits.

OTHER CONSIDERATIONS

Systemic Drug Exposure	Systemic exposure to sofpironium and its metabolite BBI-4010 were low, mostly < 1 ng/mL or below the detectable limit of 0.05 ng/mL. [4] There was no accumulation with multiple dosing, making the risks of anticholinergic adverse effects from overdose / overuse less likely, per the U.S. FDA.[4]

PHARMACOTHERAPEUTIC OPTIONS				
DRUG	**VANF**	**CFU**	**FDA**	**UpToDate[6]**
OTC Topical Antiperspirants				
Aluminum chloride, low-strength	NA	NA	Not FDA approved	1L for very mild PAxH
Prescription Topical Antiperspirants				
Aluminum chloride hexahydrate, topical (DRYSOL, DRYSOL DAB-O-MATIC)	Yes	No	Not FDA approved	1L for PAxH
Topical Anticholinergics				
Glycopyrronium tosylate (QBREXZA) cloth / wipe 2.4%	No	NA	Topical treatment of PAxH in adults and pediatric patients ≥ 9 years of age No recommended prerequisite therapies	1L alternative and 2L for inadequate responders to prescription antiperspirants. Can be used as an adjunct to prescription antiperspirants
Sofpironium bromide topical gel 12.45%	TBD	TBD	Same as glycopyrronium	Not mentioned
Botulinum Toxins				
OnabotulinumtoxinA	Yes / PA-F	Severe focal hyperhidrosis and inadequate response or unmanageable intolerance to a prescription topical therapy	Severe PAxH inadequately managed with topical agents in adults	2L for inadequate responders to prescription antiperspirants
AbobotulinumtoxinA	Yes / PA-F		Off label	
Systemic Anticholinergics				
Glycopyrrolate	Yes (inj) No (oral soln, tab, ODT)		Off label for PAxH	For refractory PAxH (Used more than oxybutynin but not evaluated in RCTs.)
Oxybutynin Oxybutynin chloride	Yes (tab, SA/XL; tab) No (syrup, patch, gel)		Off label for PAxH	For refractory PAxH (Evaluated in RCTs.)

ODT, oral disintegrating tablet

There are no current American clinical practice guidelines covering PAxH.

POTENTIAL PLACE IN THERAPY IN VHA	
2L in PAxH	1. There were no active-controlled trials to inform the place in therapy of sofpironium topical gel in primary axillary hyperhidrosis. 2. Sofpironium topical gel may be used as a second-line treatment for patients with primary axillary hyperhidrosis who have an inadequate response or intolerance to an aluminum chloride hexahydrate antiperspirant or for whom a prescription antiperspirant is medically inadvisable.

Prepared November 2024.

Contact person: Francine Goodman, PharmD, BCPS, National Program Manager, Formulary Management, VA Pharmacy Benefits Management Services (12PBM)

References

1 SOFDRA (sofpironium) topical gel 12.45% [prescribing information online]. Wayne, PA: Botanix SB, Inc. 06/2024. Available at: prescribing-information.pdf (sofdra.com). Accessed 08/21/2024.

2 Kirsch B, Smith S, Cohen J, DuBois J, Green L, Baumann L, Bhatia N, Pariser D, Liu PY, Chadha D, Walker P. Efficacy and safety of topical sofpironium bromide gel for the treatment of axillary hyperhidrosis: A phase II, randomized, controlled, double-blinded trial. J Am Acad Dermatol. 2020 Jun;82(6):1321-1327. doi: 10.1016/j.jaad.2020.02.016.

3 Yokozeki H, Fujimoto T, Abe Y, Igarashi M, Ishikoh A, Omi T, Kanda H, Kitahara H, Kinoshita M, Nakasu I, Hattori N, Horiuchi Y, Maruyama R, Mizutani H, Murakami Y, Watanabe C, Kume A, Hanafusa T, Hamaguchi M, Yoshioka A, Egami Y, Matsuo K, Matsuda T, Akamatsu M, Yorozuya T, Takayama S. A phase 3, multicenter, randomized, double-blind, vehicle-controlled, parallel-group study of 5% sofpironium bromide (BBI-4000) gel in Japanese patients with primary axillary hyperhidrosis. J Dermatol. 2021 Mar;48(3):279-288. doi: 10.1111/1346-8138.15668.

4 Center for Drug Evaluation and Research (CDER). Multi-discipline review of sofpironium (SOFDRA). Food and Drug Administration (FDA). September 2023.

5 Fujimoto T, Abe Y, Igarashi M, Ishikoh A, Omi T, Kanda H, Kitahara H, Kinoshita M, Nakasu I, Hattori N, Horiuchi Y, Maruyama R, Mizutani H, Murakami Y, Watanabe C, Kume A, Hanafusa T, Hamaguchi M, Yoshioka A, Egami Y, Matsuo K, Matsuda T, Akamatsu M, Yorozuya T, Takayama S, Yokozeki H. A phase III, 52-week, open-label study to evaluate the safety and efficacy of 5% sofpironium bromide (BBI-4000) gel in Japanese patients with primary axillary hyperhidrosis. J Dermatol. 2021 Aug;48(8):1149-1161. doi: 10.1111/1346-8138.15927.

6 Smith CC, Pariser D. Primary focal hyperhidrosis. In: UpToDate. Dellavalle RP, Owen C (Eds), Wolters Kluwer. (Accessed on August 23, 2024.)