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ADISINSIGHT REPORT

Sofpironium Bromide: First Approval

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Abstract
Sofpironium bromide (ECCLOCK® in Japan) gel is a topical anticholinergic agent developed by Bodor Laboratories and licenced to Brickell Biotech for the treatment of hyperhidrosis. The drug is designed to reduce sweating by inhibiting M3 muscarinic receptors in eccrine glands at the application site. In September 2020, sofpironium bromide gel 5% received its first approval in Japan for the treatment of primary axillary hyperhidrosis (PAH). Clinical studies are currently ongoing in the USA to assess the safety and efficacy of sofpironium bromide gel 15% in PAH. This article summarizes the milestones in the development of sofpironium bromide gel leading to this first approval for the treatment of PAH.

Sofpironium bromide (ECCLOCK® gel): Key points

A topical anticholinergic agent is being developed by Bodor Laboratories and licenced to Brickell Biotech for the treatment of hyperhidrosis

Received its first approval on 25 September 2020 in Japan

Approved for the treatment of PAH

1 Introduction

Hyperhidrosis is characterized by excessive sweating beyond the physiologically required amount [1] and may significantly impact the affected individual's quality of life and mental and emotional wellbeing [2, 3]. Primary hyperhidrosis is idiopathic and may occur as a result of aberrant sympathetic and parasympathetic nervous activity overstimulating the sweat glands [4], which include eccrine glands (distributed all over the body) and apocrine glands (localized in the axillae and urogenital region); these are regulated via cholinergic and adrenergic neurotransmission, respectively [1]. Apoeccrine sweat glands, which are regulated largely through cholinergic activity, are also present in adult axillae and may have a significant role in axillary hyperhidrosis [1]. Topical aluminium chloride antiperspirants are typically the first-line treatment option for axillary hyperhidrosis but may lead to skin irritation, particularly with more potent doses [4]. Later-line options for patients not responding to topical aluminium chloride include botulinum toxin A injections and surgery (local surgery or endoscopic thoracic sympathectomy) [4].

Sofpironium bromide gel is a topical anticholinergic agent developed by Bodor Laboratories and licenced to Brickell Biotech for the treatment of hyperhidrosis. On 25 September 2020, sofpironium bromide gel 5% received its first approval in Japan as ECCLOCK® gel 5% for the treatment of primary axillary hyperhidrosis (PAH) [5]. The gel is recommended to be applied at an appropriate amount to the axillae once a day [6]. It should not be applied to broken skin (e.g. wounds, eczema, dermatitis) due to an increased likelihood of anticholinergic adverse events; mydriasis and/or irritation may also occur with drug contact with the eyes. Due to its anticholinergic effects, sofpironium bromide is contraindicated in patients with angle-closure glaucoma (symptoms may worsen from potential increases in intraocular pressure) and in those with dysuria due to benign prostatic hyperplasia

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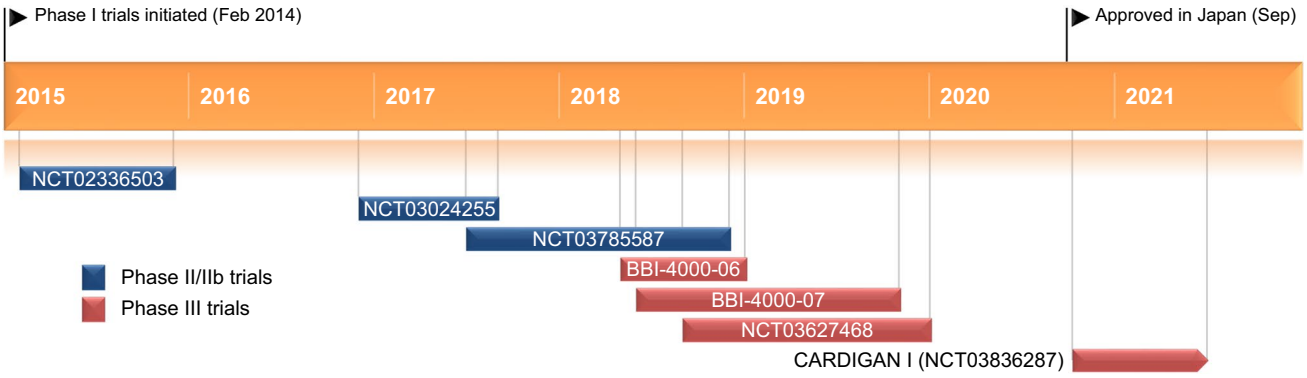


Key milestones in the development of sofpironium bromide gel in primary axillary hyperhidrosis

(urinary retention may occur) [6]. Clinical studies of sofpironium bromide gel 15% for the treatment of PAH are ongoing in the USA.

1.1 Company Agreements

In February 2020, Brickell Biotech and Bodor Laboratories entered into a settlement agreement and an amended license agreement, resolving the dispute related to the sofpironium bromide license agreement (arbitration proceeding initiated in October 2019 [7]) [8]. Pursuant to the settlement, the parties agreed to dismiss the related litigation and arbitration with prejudice. The Amended and Restated License Agreement retains with the Company a worldwide, exclusive license to develop, manufacture, market, sell, and sublicense products containing sofpironium bromide (the proprietary compound) based upon the patents referenced in the Amended and Restate License Agreement for a defined field of use [8].

In April 2015, Brickell Biotech entered into a licensing agreement with Kaken Pharmaceutical for the development and commercialization of sofpironium bromide for the treatment of hyperhidrosis [9]. Under the terms of the agreement, Kaken gained exclusive rights to develop and commercialize sofpironium bromide in Japan and certain other Asian countries [9].

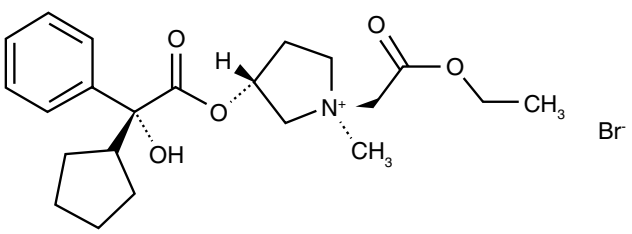
2 Scientific Summary

2.1 Pharmacodynamics

Sofpironium bromide is a structural analogue of the potent anticholinergic glycopyrrolate [10] and is present in the formulation in its two stereoisomeric forms (at the N+ position) [6]. Formulated in a topical gel, sofpironium bromide reduces sweating by inhibiting M3 muscarinic receptors in eccrine glands at the application site [6]. In vitro data showed that while sofpironium bromide had the highest affinity for the M3 receptor subtype, it also had a high affinity for the M1, M2, M4 and M5 subtypes. Sofpironium bromide exhibited anticholinergic activity by inhibiting the contractile activity of guinea pig ileal tissue in a concentration-dependent manner. In a rat model, sofpironium bromide reduced footpad sweating induced by pilocarpine (a muscarinic receptor agonist) [6].

2.2 Pharmacokinetics

As a retrometabolic drug based on glycopyrrolate, sofpironium bromide was designed to undergo rapid metabolism to reduce its systemic presence once absorbed into the skin [10]. Following two weeks of once-daily application of sofpironium bromide to each axillae (≈ 27 mg of drug per application), patients with PAH (aged ≥ 20 years) experienced a mean maximum plasma concentration (C_{max}) of 0.17 ng/mL after a mean time of 3.6 h (t_{max}), with an area under the concentration-time curve over 24 h ($AUC_{0–24}$) of 2.2 ng·h/mL [6]. Sofpironium bromide did not appear to accumulate in the system; after four and six weeks of once-daily topical application, the mean C_{max} were 0.14 ng/mL (t_{max} 2.7 h, $AUC_{0–24}$ 1.6 ng·h/mL) and 0.098 ng/mL (t_{max} 2.6 h, $AUC_{0–24}$ 0.87 ng·h/mL). In an in vitro analysis, sofpironium bromide was bound 34.8–37.8% to human plasma protein over drug



Chemical structure of sofpironium bromide (one epimer; the drug contains an additional stereoisomer at the N+ position)

concentrations of 20–2000 ng/mL (equivalent concentrations to free form) [6].

In vitro data have also demonstrated that sofpironium bromide is metabolized mainly through non-enzymatic hydrolysis, and also through oxidative metabolism via CYP2D6 and CYP3A4 [6]. In PAH patients receiving sofpironium bromide in a 28-day repeated dose study, de-ethylated forms of the drug were found to be the main metabolites in plasma and urine samples. In rats, ≈ 54% and ≈ 45% of radiolabeled sofpironium bromide were found in urine and faeces, respectively, 168 h after subcutaneously administering the drug. When applied to the axillae for 28 days in PAH patients, < 0.5% of the applied amount of sofpironium bromide was detected in the urine [6].

2.3 Therapeutic Trials

2.3.1 Phase III Trials

In the pivotal phase III trial conducted in Japanese PAH patients (BBI-4000-06), sofpironium bromide gel 5% was effective in reducing excessive sweating [11]. Patients (n = 281) were aged > 12 years and randomized 1:1 to receive sofpironium bromide gel 5% or vehicle, which were applied to the axillae once daily for 42 days [11, 12]. At baseline, all patients had a Hyperhidrosis Disease Severity Scale (HDSS) score of ≥ 3, Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) score of ≥ 2, and gravimetric sweat production (GSP) of ≥ 50 mg/5 min per axilla [11, 12]. A significantly higher proportion of sofpironium bromide gel 5% recipients than vehicle recipients (53.9 vs 36.4%; p = 0.003) achieved an HDSS score of 1 or 2 at the end of treatment and also a ≥ 50% reduction in GSP rate at the end of treatment (primary endpoint) [11, 12]. Relative to vehicle, sofpironium bromide gel 5% significantly improved the individual endpoints of the proportion of patients achieving an HDSS score of 1 or 2 (60.3 vs 47.9%; p = 0.036) and those achieving a ≥ 50% reduction from baseline in GSP rate (77.3 vs 66.4%; p = 0.042) after the 42 days of treatment [12]. Sweat production was also significantly reduced with sofpironium bromide gel 5% than with vehicle [change in total GSP mean value (i.e. across both axillae) from baseline − 157.6 vs − 127.6 mg; p = 0.015]; similarly, sweating severity as per HDSM-Ax scoring was improved (change in score from baseline − 1.41 vs − 0.93; p = 0.001) [12].

Findings from another phase III study (BBI-4000-07) conducted in Japanese PAH patients (aged > 12 years) suggested that the therapeutic benefits from sofpironium bromide gel 5% were sustained for 52 weeks of treatment; 57.8% of patients who received once-daily sofpironium bromide gel 5% (n = 185) both achieved an HDSS score of 1 or 2 and a ≥ 50% reduction in GSP rate at the end of treatment [6].

2.3.2 Phase II Trials

In a double-blind phase IIb trial conducted in the USA (NCT03024255), once-daily sofpironium bromide gel applied over 42 days was effective in treating PAH in adults over three different dose strengths (5%, 10% and 15%) [13]. Patients (aged ≥ 18 years; n = 227) had PAH symptoms for 6 months prior to the study and an HDSM-Ax score of ≥ 3 and an HDSS score of 3 or 4 at baseline, with no other skin or subcutaneous conditions in either axilla. Patients were

Features and properties of sofpironium bromide

Alternative names	BBI-4000; ECCLOCK®; ECCLOCK® Gel 5%
Class	Cyclopentanes; phenylacetates; pyrrolidines, skin disorder therapies; small molecules
Mechanism of Action	Cholinergic receptor antagonist
Route of Administration	Topical
Pharmacodynamics	Potently inhibits M3 muscarinic receptors in eccrine glands to reduce sweating
	High affinity for all of the M1–M5 receptor subtypes; highest affinity for M3
Pharmacokinetics	No systemic drug accumulation apparent after once-daily application for 6 weeks; mean time to peak plasma concentration 2.6–3.6 h, mean peak plasma concentration 0.098–0.17 ng/mL
Adverse events	
Most frequent	Nasopharyngitis, application site events (dermatitis, erythema, pruritus, eczema, burning, itching, dryness, scaling)
Occasional	Dry mouth, blurred vision, mydriasis, constipation
ATC codes	
WHO ATC code	D11 (other dermatological preparations); R03 (drugs for obstructive airway diseases)
EphMRA ATC code	D11 (other dermatological preparations); R3 (anti-asthma and COPD products)
Chemical Name	1-*ambo*-(3*R*)-3-{[(*R*)-(cyclopentyl)hydroxy(phenyl)acetyl]oxy}-1-(2-ethoxy-2-oxoethyl)-1-methylpyrrolidinium bromide

randomized 1:1:1:1 to the sofpironium bromide gel 5%, 10%, and 15% and vehicle groups. Efficacy endpoints were assessed hierarchically among the sofpironium bromide gel groups in the order of 15%, 10%, and 5%. Relative to vehicle, a significantly greater proportion of patients in each of the sofpironium bromide 5%, 10% and 15% gel groups improved their HDSM-Ax score by ≥1 (70%, 79% and 76%, respectively, vs 54% of vehicle recipients; all $p \leq 0.0387$) [co-primary endpoint] or ≥2 (47%, 49% and 50% vs 23%; all $p \leq 0.0068$). The least square mean change in HDSM-Ax score from baseline was also noted to be significantly improved relative to vehicle for all three sofpironium bromide groups (−2.02, −2.09 and −2.10 for 5%, 10% and 15% gel, respectively, vs −1.30 with vehicle; all $p \leq 0.0001$) [co-primary endpoint] [13].

These findings were consistent with those of an earlier, vehicle-controlled phase IIb trial (NCT02336503), which also assessed the efficacy of once-daily sofpironium bromide gel 5%, 10% and 15% in adult PAH patients [14]. All patients ($n = 189$) had HDSS scores of 3 or 4, and a sweat production rate of ≈50 mg/5 min per axilla at baseline. After 28 days of treatment, significantly higher proportions of patients in each sofpironium bromide gel group achieved a 2-grade improvement in HDSS score relative to the vehicle group (primary endpoint); similarly, a significantly greater proportion of patients in each sofpironium bromide gel group than in the vehicle group achieved a 1- and 2-grade improvement in HDSM-Ax score. Among sofpironium bromide gel 15% recipients, 38.3% achieved a ≥2-grade improvement in HDSS score (vs 12.2% of vehicle recipients; $p < 0.01$) and 44.7% achieved a ≥2-grade improvement in HDSM-Ax score (vs 19.5%; $p < 0.01$) [14].

2.4 Adverse Events

Once-daily sofpironium bromide gel 5% was generally well tolerated in patients with PAH in Japanese phase III clinical trials [6, 12]. Most treatment-emergent adverse events (TEAEs) in BBI-4000-06 were reported to be mild or moderate in severity, and no serious TEAEs were reported in the sofpironium bromide gel 5% group [12]. The most common TEAEs among sofpironium bromide gel 5% recipients in this study were nasopharyngitis (14.2%), application site dermatitis (8.5%) and application site erythema (5.7%) [12]. Treatment-related adverse events (TRAEs) in BBI-4000-06 and BBI-4000-07 mainly occurred at the application site and included dermatitis (6.4% and 27.6%), erythema (5.7% and 5.9%) and pruritus (2.1% and 3.2%); application-site eczema (7.0%) was also reported in BBI-4000-07 as a TRAE [6]. Other TRAEs in BBI-4000-07 included mydriasis (1.6%) and blurred vision (0.5%) [6]. In BBI-4000-06, 2.8% of sofpironium bromide gel 5% recipients experienced anticholinergic TEAEs, including dry mouth (1.4%), constipation (0.7%) and mydriasis (0.7%) [12].

Preliminary findings from a US open-label phase III trial assessing safety in PAH patients aged >9 years ($n = 300$; NCT03627468) indicated that once-daily sofpironium bromide gel 5% and 15% were generally well tolerated for 52 weeks of treatment in patients aged >9 years with PAH [15]. No serious TRAEs were reported [15].

Key clinical trials of sofpironium bromide

Drug(s)	Indication	Phase	Status	Location(s)	Identifier	Sponsor
Sofpironium bromide gel (5, 15%)	Primary axillary hyperhidrosis	III	Completed	USA	NCT03627468	Brickell Biotech
Sofpironium bromide gel (5%), vehicle	Primary axillary hyperhidrosis	III	Completed	Japan	BBI-4000-06	Brickell Biotech, Kaken Pharmaceutical
Sofpironium bromide gel (5%), vehicle	Primary axillary hyperhidrosis	III	Completed	Japan	BBI-4000-07	Brickell Biotech, Kaken Pharmaceutical
Sofpironium bromide gel (15%), vehicle	Primary axillary hyperhidrosis	III	Recruiting	USA	NCT03836287 (CARDIGAN I)	Brickell Biotech
Sofpironium bromide gel (15%), vehicle	Primary axillary hyperhidrosis	III	Not yet recruiting	USA	NCT03948646 (CARDIGAN II)	Brickell Biotech
Sofpironium bromide gel (5, 10, 15%), vehicle	Primary axillary hyperhidrosis	II	Completed	USA	NCT03024255 (BBI4000CL203)	Brickell Biotech
Sofpironium bromide gel (5, 10, 15%), vehicle	Primary axillary hyperhidrosis	II	Completed	USA	NCT02336503 (BBI4000CL201)	Brickell Biotech
Sofpironium bromide gel (15%), vehicle	Palmar hyperhidrosis	II	Completed	USA	NCT02682238 (BBI4000CL202)	Brickell Biotech
Sofpironium bromide gel (15%)	Primary axillary hyperhidrosis in paediatric patients	II	Active, no longer recruiting	USA	NCT03785587 (BBI4000CL108)	Brickell Biotech

Most TEAEs occurring in US phase IIb studies (NCT03024255 [13] and NCT02336503 [14]) were mild or moderate in severity and resolved after stopping study treatment [13] or spontaneously [14]. In NCT03024255, TEAEs were reported in 30%, 33% and 52% of sofpironium bromide gel 5%, 10% and 15% recipients, respectively (vs 16% of vehicle recipients); 21%, 30% and 37% of TEAEs occurring in the sofpironium bromide groups were considered to be treatment related [13]. Application site TEAEs with sofpironium bromide gel 5%, 10% and 15% that required additional (concomitant) treatment or treatment interruption or discontinuation included burning (incidences 42%, 47% and 48%, respectively, vs 40% with vehicle), erythema (49%, 47% and 56% vs 28%), itching (39%, 37% and 41% vs 37%), dryness (28%, 37% and 33% vs 11%), and scaling (18%, 30% and 28% vs 4%). Eight severe TEAEs occurred in the study, seven of which were associated with anticholinergic effects (dry mouth and blurred vision). One serious TEAE of myocardial infarction occurred, which was not considered to be treatment related [13]. In NCT02336503, 11.2% of sofpironium bromide gel recipients experienced anticholinergic TRAEs, most of which were mild and transient [14].

2.5 Ongoing Clinical Trials

Two pivotal phase III trials have been planned to assess the safety and efficacy of sofpironium bromide gel 15% in patients (aged ≥ 9 years) with PAH in the USA [16]; one study has commenced recruitment (CARDIGAN I) [17] while the other (CARDIGAN II) is yet to be initiated. Both studies will enrol ≈ 350 patients each [16]. The co-primary efficacy endpoints in CARDIGAN I will be the proportion of patients achieving a ≥ 2-point improvement in HDSM-Ax score and the change in GSP from baseline, both assessed after 6 weeks of treatment [17]. In addition, an open-label phase II trial assessing the long-term safety, pharmacokinetics and efficacy of sofpironium bromide gel 15% in PAH patients aged 9–17 years ($n = 25$) is currently ongoing in the USA [18]. Interim findings have suggested that after 24 weeks of treatment, once-daily sofpironium bromide gel 15% was well tolerated, with consistent pharmacokinetic findings to previous studies in adults. Clinically meaningful improvements in HDSM-Ax score were also observed [18].

3 Current Status

Sofpironium bromide (ECCLOCK® in Japan) gel 5% received its first approval on 25 September 2020 in Japan for the treatment of PAH [5].

Declarations

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Authorship and conflict of interest During the peer review process the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made by the authors on the basis of scientific completeness and accuracy. Julia Paik is a salaried employee of Adis International Ltd/Springer Nature, and declares no relevant conflicts of interest. All authors contributed to the review and are responsible for the article content.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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