Health Technology Briefing
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Glycopyrronium bromide cream for treating severe primary axillary hyperhidrosis

Company/Developer	Leith Healthcare / Dr. August Wolff GmbH & Co. KG Arzneimittel

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28731	NICE ID: Not available	UKPS ID: 672993

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

One percent glycopyrronium bromide (GPB) cream has been developed for the treatment of severe primary axillary hyperhidrosis (severe underarm sweating, which has no obvious cause). Patients with primary axillary hyperhidrosis (PAHH), suffer from an excessive amount of sweat production in the armpits when the body does not need to cool down. Severe PAHH strongly affects the patient's quality of life, interfering with daily activities and causing anxiety and embarrassment. Current treatment options are associated with considerable adverse events such as skin irritation, dry mouth, and compensatory sweating. There is therefore a need for additional treatments which avoid these whilst improving quality of life.

One percent GPB cream works by blocking a type of receptor (structures capable of recognising and receiving messages) that is predominantly responsible for mediating the secretion of sweat from the sweat glands. This blocking means the volume of sweat produced is reduced. One percent GPB cream is applied to each armpit. If licensed, 1% GPB cream will provide an additional treatment option for patients with severe primary axillary hyperhidrosis.

Proposed Indication

For the treatment of severe primary axillary hyperhidrosis (PAHH).[1]

Technology

Description

One percent glycopyrronium bromide (GPB) cream (Axhidrox®, WO3970) contains the active substance glycopyrronium (GP) as bromide GPB.[2] Eccrine sweat glands express various muscarinic acetylcholine (ACh) receptor subtypes and can therefore be activated by ACh and effectively blocked by muscarinic antagonists.[3] GPB is a muscarinic antagonist with a high affinity for M3 receptors. Secretion of sweat from the sweat glands is predominantly mediated by the M3 receptors. Antagonism of these receptors decreases the volume of sweat secretion.[4]

One percent GPB cream has been developed for the treatment of patients with severe PAHH. In the phase III clinical trial (NCT03658616), 0.54g of 1% GPB cream was administered topically to both axillae once per day for the first 4 weeks, followed by flexible use (maximum once per day and minimum twice per week) from week 5 onwards.[1,3]

Key Innovation

Hyperhidrosis (HH) is a potentially debilitating illness that affects multiple domains of patients' lives including their psychological, physical, and social functioning.[5] Additionally, current treatment options for severe PAHH are associated with adverse events. Antiperspirants containing aluminium salts applied in high concentrations (the only topical formulations available in the EU up to June 2022) commonly cause skin irritation and show limited effects, especially in severe PAHH.[3] Compensatory sweating is a common side effect of endoscopic thoracic sympathectomy, the standard surgical treatment for axillary HH.[6] Oral use of anticholinergic substances including GP is associated with improvements in quality of life and clinical symptoms but at the cost of considerable systemic adverse events such as dry mouth, which cause patients to cease therapy.[7,8] Other common adverse events include constipation, dry eyes, and urinary retention.[9] There is therefore a need for additional treatment options for severe PAHH which improve clinical outcomes and quality of life for patients without considerable adverse events.

In the phase III clinical trial (NCT03658616), treatment with 1% GPB cream was shown to significantly reduce sweat production and improve quality of life in patients with severe PAHH, while being well-tolerated with only few mild to moderate adverse drug reactions.[3] One percent GBP cream may therefore present a potentially more long-term treatment option for patients with severe PAHH.[10]

Regulatory & Development Status

One percent GPB cream is licensed for the topical treatment of severe PAHH in adults in 23 Member States of the European Economic area following completion of a Decentralised Procedure in 2022 and 2023 (repeat use procedure), with Sweden acting as the reference member state.[11]

Patient Group

Disease Area and Clinical Need

Hyperhidrosis (HH) is a chronic condition characterised by disproportionate and excessive sweating.[7] HH is a common disease of unknown aetiology in which a complex dysregulation of the sympathetic nervous

system leads to excessive sweat production.[3] Primary HH refers to when there is no obvious cause. It is thought to be the result of a problem with the part of the nervous system that controls sweating.[12] HH can be localised (affecting specific sites) or generalised (affecting most or all of the body).[13] Axillary HH means the armpits are affected.[7] HH can develop at any age, although primary axillary HH (PAHH) typically starts soon after puberty.[12] Typically, sweating in primary HH is bilaterally symmetrical and localised, and patients do not sweat during sleep. Patients with PAHH suffer from an excessive amount of sweat production in the armpits beyond what is needed for thermoregulation.[7] Excessive sweating can have a profound effect on quality of life, interfering with daily activities and causing anxiety and embarrassment.[14]

HH has been estimated to affect between 1 and 3 in every 100 people.[12] An estimated 90% of these are primary and more than half affect the axilla.[15] In England (2022-23), there were 2,109 finished consultant episodes (FCEs) and 2,065 admissions for HH (ICD-10 code R61), which resulted in 1,639 day cases and 1,501 FCE bed days.[16] For localised HH specifically (ICD-10 code R61.0), there were 1,168 FCEs and 1,167 admissions resulting in 1,150 day cases and 30 FCE bed days.[16]

Recommended Treatment Options

Treatments for HH offered in secondary care include:[14]

- Topical therapies (including emollients, antiperspirants and antimuscarinic medicines)
- Iontophoresis (with tap water or glycopyrronium)
- Botulinum toxin type A injections
- Systematic therapies (for example oral antimuscarinics [such as oxybutynin, propantheline and glycopyrronium], clonidine, diltiazem, benzodiazepines)
- Surgery

NICE guidelines recommend endoscopic thoracic sympathectomy for primary HH of the upper limb including the axillae.[17]

Clinical Trial Information

Trial	NCT03658616; EudraCT 2017-004534-28; Combined Randomized, Double-blind, Dose-confirming Phase 3a Study in Parallel Design to Assess the Efficacy and Safety of Topical 4-week Treatment With 1% GPB Cream vs Placebo and Open-label Phase 3b Study to Assess Long-term Efficacy and Safety in Patients With Primary Axillary Hyperhidrosis Treated With 1% GPB Cream **Phase III –** Completed **Location(s):** Five EU countries and UK **Study completion date (actual):** February 2022
Trial Design	Randomised, parallel assignment, quadruple masking (participant, care provider, investigator, outcomes assessor)
Population	N=518 (actual); aged 18 years to 65 years; body mass index of 18-32 kg/m^2; diagnosis of severe primary axillary hyperhidrosis with a hyperhidrosis disease severity scale score of 3 or 4.
Intervention(s)	WO3970 (formulation containing WO3970 for topical application)
Comparator(s)	Placebo (WO3988) (formulation containing placebo of WO3988 for topical application)

Outcome(s)	Primary outcomes: • Dose-confirming part: Absolute change in sweat production assessed by gravimetric measurement [Time frame: baseline (day 1a), to day 29] • Long-term part (only for newly recruited patients): Absolute change in sweat production assessed by gravimetric measurement [Time frame; baseline (day 1b) to week 12] See trial record for full list of other outcomes.
Results (efficacy)	**Phase 3a [Time frame: 4-week treatment]:** Absolute change in sweat production from baseline to day 29 in logarithmic values was significantly larger in the GPB 1% group compared with the placebo group (P = 0004). The improvement in HidroQoL exceeded the minimal clinically important difference of 4. The proportion of responders was twofold higher for sweat reduction (−19708 mg GPB 1% vs. −8349 mg placebo), Hyperhidrosis Disease Severity Scale (HDSS) (23% GPB 1% vs. 12% placebo) and HidroQoL (60% GPB 1% vs. 26% placebo).[7] **Phase 3b [Time frame: 72-week treatment period with additional 4-week follow-up]:** Total median sweat production decreased by 119.30mg (−65.6%) until week 12. Absolute change in sweat production from baseline to week 12 in logarithmic values was statistically significant (p <0.0001). Patients' quality of life was improved at all study time points compared to baseline, as assessed by Hyperhidrosis Quality of Life Index and Dermatology Life Quality Index (p <0.0001).[3]
Results (safety)	**Phase 3a [Time frame: 4-week treatment]:** Treatment was safe: most treatment-emergent adverse effects were mild or moderate, and transient. Local tolerability was very good, with 9% of patients having only mild or moderate application-site reactions. The most reported adverse drug reaction was dry mouth (16%), an expected anticholinergic effect of the treatment.[7] **Phase 3b [Time frame: 72-week treatment period with additional 4-week follow-up]:** Treatment was safe and locally well-tolerated with only few mild to moderate adverse drug reactions (ADRs). Dry mouth and application site erythema were the most common reported ADRs.[3]

Estimated Cost

The cost of 1% GPB cream is not yet known.

Relevant Guidance

NICE Guidance

- NICE interventional procedures guidance. Transcutaneous microwave ablation for severe primary axillary hyperhidrosis (IPG601). December 2017.
  NICE interventional procedures guidance. Endoscopic thoracic sympathectomy for primary hyperhidrosis of the upper limb (IPG487). May 2014.
- NICE evidence summary (ES10). Hyperhidrosis: oxybutynin. March 2017.

- NICE evidence summary (ESUOM16). Hyperhidrosis: oral glycopyrronium bromide. July 2013.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- Primary Care Dermatology Society. Hyperhidrosis (excessive sweating). 2024.[18]
- International Hyperhidrosis Society. Primary Focal Axillary Hyperhidrosis. 2018.[19]
- B Rzany, FG Bechara, K Feise, M Heckmann, S Rapprich, B Wörle. Update of the S1 Guidelines on the Definition and Treatment of Primary Hyperhidrosis. 2018.[20]
- J McConaghy and D Fosselman. Hyperhidrosis: Management Options. 2018.[21]

Additional Information

References

1 Clinicaltrials.gov. *Assessment of Efficacy and Safety of Topical Administration of 1% Glycopyrronium Bromide (GPB) in Patients With Primary Axillary Hyperhidrosis and the Assessment of Long-term Efficacy and Safety of Topical Administration of 1% GPB Cream in Patients With Primary Axillary Hyperhidrosis*. *Trial ID: NCT03658616*. 2018. Status: Completed. Available from: https://clinicaltrials.gov/study/NCT03658616 [Accessed 07 Mar 2024].

2 Swedish Medical Products Agency. *Summary Public Assessment Report: Axhidrox (glycopyrronium bromide)*. 2022. Available from: https://docetp.mpa.se/LMF/Axhidrox%202,2%20mg_pumpning%20Cream%20ENG%20sPAR_09001bee82a09cba.pdf [Accessed 07 Mar 2024].

3 Szeimies RM, Abels C, Kilic A, Reich H, Berger B, Schulze zur Wiesche E, et al. Long-term efficacy and safety of 1% glycopyrronium bromide cream in patients with severe primary axillary hyperhidrosis: Results from a Phase 3b trial. *Journal of the European Academy of Dermatology and Venereology*. 2023;37(4):823-30. Available from: https://doi.org/10.1111/jdv.18843.

4 DrugBank Online. *Glycopyrronium*. 2024. Available from: https://go.drugbank.com/drugs/DB00986 [Accessed 12 Mar 2024].

5 Parashar K, Adlam T, Potts G. The Impact of Hyperhidrosis on Quality of Life: A Review of the Literature. *American Journal of Clinical Dermatology*. 2023;24(2):187-98. Available from: https://doi.org/10.1007/s40257-022-00743-7.

6 Loizzi D, Mongiello D, Bevilacqua MT, Raveglia F, Fiorelli A, Congedo MT, et al. Surgical management of compensatory sweating: A systematic review. *Front Surg*. 2023;10:1160827. Available from: https://doi.org/10.3389/fsurg.2023.1160827.

7 Abels C, Soeberdt M, Kilic A, Reich H, Knie U, Jourdan C, et al. A glycopyrronium bromide 1% cream for topical treatment of primary axillary hyperhidrosis: efficacy and safety results from a phase IIIa randomized controlled trial. *British Journal of Dermatology*. 2021;185(2):315-22. Available from: https://doi.org/10.1111/bjd.19810.

8 Cruddas L, Baker D. Treatment of primary hyperhidrosis with oral anticholinergic medications: a systematic review. *Journal of the European Academy of Dermatology and Venereology*. 2017;31(6):952-63. Available from: https://doi.org/10.1111/jdv.14081.

9 National institute for Health and Care Excellence (NICE). *Hyperhidrosis: oxybutynin*. 2017. Available from: https://www.nice.org.uk/advice/es10/resources/hyperhidrosis-oxybutynin-pdf-1158108623557.

10 Dermatoloy Times. *Don't Sweat It: Glycopyrronium Bromide Cream Decreases Hyperhidrosis by 66%*. Press release 1 Mar 2023. Available from: https://www.dermatologytimes.com/view/don-t-sweat-it-glycopyrronium-bromide-cream-decreases-hyperhidrosis-by-66- [Accessed 12 Mar 2024].

11 Swedish Medical Products Agency. *Package leaflet: Axhidrox 2.2 mg/pump actuation cream*. 2023. Available from: https://docetp.mpa.se/LMF/Axhidrox%20cream%20ENG%20PL_09001bee827198bb.pdf [Accessed 24 Apr 2024].

12 NHS Inform. *Hyperhidrosis*. 2023. Available from: https://www.nhsinform.scot/illnesses-and-conditions/skin-hair-and-nails/hyperhidrosis/ [Accessed 07 Mar 2024].

13 DermNet. *Hyperhidrosis*. 2015. Available from: https://dermnetnz.org/topics/hyperhidrosis [Accessed 22 May 2024].

14 National Institute for Health and Care Excellence (NICE). *Hyperhidrosis: oxybutynin* (*ES10)*. Available from: https://www.nice.org.uk/advice/es10/chapter/Introduction-and-current-guidance [Accessed 07 Mar 2024].

15 National Institute for Health and Care Excellence (NICE). *Hyperhidrosis: How common is it?* 2023. Available from: https://cks.nice.org.uk/topics/hyperhidrosis/background-information/prevalence/ [Accessed 07 Mar 2024].

16 NHS England. *Hospital Admitted Patient Care Activity, 2022-23: Diagnosis*. 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2022-23.

17 National Institute for Health and Care Excellence (NICE). *Endoscopic thoracic sympathectomy for primary hyperhidrosis of the upper limb (IPG487)*. 2014. Available from: https://www.nice.org.uk/guidance/ipg487 [Accessed 07 Mar 2024].

18 Primary Care Dermatology Society (PCDS). *Hyperhidrosis (excessive sweating)*. 2024. Available from: https://www.pcds.org.uk/clinical-guidance/hyperhidrosis [Accessed 24 Apr 2024].

19 International Hyperhidrosis Society. *Primary Focal Axillary Hyperhidrosis*. 2018. Available from: https://www.sweathelp.org/treatments-hcp/clinical-guidelines/primary-focal-hyperhidrosis/primary-focal-axillary.html [Accessed 05 Mar 2024].

20 Rzany B, Bechara FG, Feise K, Heckmann M, Rapprich S, Wörle B. Update of the S1 guidelines on the definition and treatment of primary hyperhidrosis. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*. 2018;16(7):945-52. Available from: https://doi.org/10.1111/ddg.13579.

21 McConaghy JR, Fosselman D. Hyperhidrosis: management options. *American Family Physician*. 2018;97(11):729-34. https://pubmed.ncbi.nlm.nih.gov/30215934/.

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