LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Axhidrox
(glycopyrronium bromide)

SE/H/2141/01/DC

This module reflects the scientific discussion for the approval of Axhidrox. The procedure was finalised on 2022-03-10. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Axhidrox, 2,2 mg/ pump actuation, Cream.

The active substance is glycopyrronium (GP) as glycopyrronium bromide (GPB). One gram cream contains 8 mg GP, corresponding to 10 mg GPB per gram cream. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Axhidrox 2.2 mg/pump actuation, cream, is submitted according to Article 8(3) of Directive 2001/83/EC. The applicant, Dr. August Wolff GmbH & Co Arzneimittel applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, DE, DK, EE, FI, HR, LT, LV, NL, NO as concerned member states (CMS).

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

Paediatric Regulation
The applicant has obtained a partial PIP waiver from the PDCO/EMA for some subsets of the paediatric population (<12 years) for Axhidrox in the treatment of hyperhidrosis.

In accordance with article 7 of Regulation 1901/2006, as amended, the applicant has submitted a paediatric investigation plan EMEA-002383-PIP01-18 for adolecents from 12 years to less than 18 years of age. The European Medicines Agency's decision P/0420/2020 was provided on 23 October 2020. The European Medicines Agency has deferred the obligation to submit the results of studies with Axhidrox. Furthermore, the agreed Paediatric Investigation Plan is not completed yet as none of the measures are completed.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology

Hyperhidrosis results from overstimulation of the eccrine sweat glands. Five muscarinic acetylcholine receptors (mAChR M1-M5) have been identified in the basolateral membrane of the sweat gland cells. Glycopyronium bromide (GPB) is in clinical use since early 1960s. Since then, oral and inhalation formulations have been developed as therapeutic agents inhibiting the muscarinic acetylcholine receptor in various indications including chronic obstructive pulmonary disease (COPD), excessive salivation, and peptic ulcers. As a competitive inhibitor of the mAChRs, glycopyrronium (GP) inhibits ACh-driven sympathetic actions on various exocrine glands, including sweat glands. The Applicant has provided literature data showing that GP as GPB is a competitive inhibitor of the mAChRs. The substance has a high binding affinity to all five muscarinic mAChR subtypes and *in vitro* inhibitory dissociation constants (Ki) in the lower nanomolar range for human isoforms of the mAChR subtypes. The Applicant has also submitted a study evaluating GPB binding to the five recombinant mACh receptor subtypes expressed on CHO-K1 cells. However, the study submitted was not well described in the study report.While the lack of further information rendered it impossible to fully assess the relevance of the study data, the results provided are in line with data from studies in the publication domain evaluating the issue (i.e. Gavaldà et al. (https://doi.org/10.1016/j.pupt.2014.05.005)). Therefore, the issue was not further pursued. Based on the results, GPB had the highest binding affinity for the M1- receptor (IC50=1.53 nM) followed by the M4 (IC50=1.89 nM), M5 (IC50=2.11 nM), M3 (IC50=2.71 nM), and M2 (IC50=3.29 nM) suggesting that the affinities for all five receptors are in the low nanomolar range.
One secondary pharmacodynamics study has been referenced by the Applicant, which showed that GPB had no effect on neurokinin-A-induced contraction of isolated tracheal smooth muscle. While of limited relevance for the present Application, the overall impression is that the lengthy clinical experience of GP limits the usefulness of further secondary pharmacodynamics studies.

No safety pharmacology studies have been performed with Axhidrox. The Applicant has referenced the safety pharmacology studies for GPB in the Seebri Breezhaler EPAR. hERG inhibition was noted only at GPB concentrations sufficiently above MHRD. However, in beagle dogs, transient effects were noted on heart rate, blood pressure and QT-interval. Further, in the 4-week study, tachycardia was a frequent finding at doses ≥0.077 mg/kg/day. Potential cardiovascular effects of GPB are clinically recognized according to the Seebri SmPC.
Passage of GPB to CNS is considered limited and given the low systemic exposure of GP after dermal exposure CNS effects are not likely. Likewise, since there is only low systemic exposure following topical application of GPB 10 mg/g cream, an impact on the resopiratory system is not likely. Further, the safety pharmacology studies for the inhaled Seebri breezhaler did not reveal any treatment-related effects on the respiratory system in rats at an inhaled dose of 0.168 mg/kg GPB. Collectively, while cardiovascular effects have been shown for another GPB product, the limited systemic exposure after

dermal use of Axhidrox is unlikely to result in effects on safety pharmacology parameters in the clinical setting.

No pharmacodynamic drug interaction studies have been performed. However, in line with SmPC documents of previously approved GP products, an interaction with other anticholinergic medical drugs is possible.

Collectively, the pharmacology studies presented and referenced are considered sufficient to support the present Application for Axhidrox.

Pharmacokinetics

The Applicant has not performed any pharmacokinetics studies with Axhidrox to support the present Application. Referenced data from EPARs of previously approved products have been included. However, the Applicant presented a validation report he LC-MS/MS method developed for determination of GP concentrations in minpig plasma and buffer which was considered adequate for the purpose.

The Applicant has provided absorption study data for previously approved (EU or US) products. No separate pharmacokinetic studies of absorption have been performed with Axhidrox. However, the toxicokinetics from the 7-day repeated dose study in minipigs where 0.5% to 2% GPB in cream wasused (see toxicology section) revealed that Cmax and AUClast values increased with increasing dose in a largely dose-dependent manner on Days 1 and 7. Further, the Cmax and AUClast noted on Day 7 following topical daily treatment with 1% GPB (10 mg/g) cream were Cmax = 56.6 pg/mL and AUClast = 569 h*pg/mL. Collectively the data show that low systemic GP exposures are expected after dermal Axhidrox administration.

Referenced studies from previously approved GP products show that 14C-labeled GPB was taken up and retained in melanin-containing structures following oral or intravenous administration. Further, in the mouse, peak 14C-labeled GPB radioactivity was found in all organs at 5-10 minutes except brain whereas liver, kidney and intestines showed traces of activity at 24 hours. Of relevance for reproductive toxicity, no or limited placenta transfer was observed in pregnant mice, rabbits, dogs and humans but GP and its metabolites distributed to milk and reached a milk-plasma ratio of 11. Referenced studies on metabolism of GPB from public literature and public assessment reports show that GPB is mainly metabolized via cytochrome P450 (CYP)–mediated oxidative metabolism. No unique human metabolites were identified in liver microsomes and hepatocytes. It is also noted that the expression of CYP enzymes seem to be at least 300-fold lower in skin microsomal fraction compared to liver microsomal fraction.

Excretion of GP is dependent on the route of administration. Studies using i.v. administration have shown that excretion was mainly via urine (60%) and bile/faeces (40%), wheres p.o. administration of GP was mainly excreted via faeces (>90%), suggesting that the swallowed dose is not absorbed. No data on excretion after dermal administration is available. However, while low systemic concentrations are expected after dermal administration, it is assumed that faeces and urine represent major excretion pathways.

Toxicology

In support of the present application, the applicant is referring to both published data and original non-clinical studies. The toxicity of GP-containing products has been characterized in various non-clinical programs supporting approval of GP-containing products (Seebri, Cuvposa and Qbrexza). In addition, the applicant has performed new studies for this application which included a 7-day dermal local tolerance study in minipig, QSAR analyses of impurities, In Vitro Bovine Corneal Opacity and Permeability Test, In Vitro EpiOcular and an In Vivo Local Lymph Node Assay. The clinical formulation was used in the studies.

No single-dose studies have been performed by the applicant, and they are not considered warranted. However, the Applicant has referenced LD50-data from previous GP products. While these studies are old, it is stressed that LD50-data is of limited regulatory relevance.

The applicant refers to several published repeat-dose toxicity studies for other GP-containing products (oral, inhalative and topical) that supported marketing approvals. Studies were performed in rats, dogs, mice and minipigs. GP-induced toxicities were mainly related to the pharmacology of the substance as a mACh antagonist with effects such as mydriasis, reduced excretion from exocrine glands and tachycardia. Hence, dry oral mucosa or gums, reduced lacrimal gland secretions, hypertrophy of the salivary or lacrimal glands and mild inflammation, dilation of the ducts and/or alveoli of the sub mucosal glands in the pharynx were observed. Further, effects were noted on body weight. Reduced food intake and reduced body weight gain were observed in rats while reduced food intake was seen in dogs when treated by inhalation. Repeat-dose studies in mice and rats with oral administration of GPB revealed a reduction in mean weight gain for both species. Survival was reduced in a 13-week repeated dose studies in mice, this was not seen in any other species. The causes of the treatment-related mortality and reduced body weight gain were unclear. Regarding studies with dermal application, rats treated with 20% solution showed induced excessive local irritation at the treatment site, resulting in premature sacrifice or cessation of dosing of several animals. Reduced mean body weight and mean body weight change (gain) were observed in groups treated with ≥6% solution in male rats but not in female. In a 39-week study in minipigs, no adverse toxicities were noted despite exposures up to 44mg/kg daily. Collectively, GPB is well-tolerated with mainly pharmacology-related toxicities.

Published literature from other GP-containing drug products that supported marketing approval of oral, inhalative and topical drug products have not shown any genotoxicity.

Other approved GP-containing products have not presented any carcinogenic effects; hence, no carcinogenic risk is expected for topical use. The Applicant’s justification for not having conducted carcinogenicity studies is acceptable.

Reproductive and developmental toxicity of GPB has been studied in already approved GPB-containing products. Subcutaneous and inhalation routs of administration of GPB revealed no effects on male rat fertility parameters (including sperm counts and sperm motility) at 1.5 mg/kg GP. In female rats, decreases in the number of corpora lutea and implantation sites were observed with a NOAEL of 0.5 mg/kg/day GP. No effects on embryo-foetal development were observed in pregnant rats exposed to GPB via inhalation during gestation days 6 to 17 and in pregnant rabbits inhaling GPB during gestation days 7 through 19. Pre- and postnatal development was not affected in a study applying s.c. GPB dosing of pregnant rats. Oral administration of 100 mg/kg/day in a study assessing effects on fertility or general reproductive function in rats revealed no treatment-related effects. Based on the low systemic exposure after dermal application, the risk for foetal exposure and consequently an impact on foetal development is low. The applicant’s justification for not having conducted Reproductive and developmental toxicity studies is acceptable.

The labelling in section 4.6 has been written in accordance with the data presented and the perceived risk. It takes into account the DART data available and the clinical systemic exposure to GPB during Axhidrox use. The contact of the suckling child with the cream or Axhidrox-treated skin should be avoided. Furthermore, any skin to skin contact between treated skin area with other areas including skin of others should be avoided (not only during breast-feeding). Therefore, information regarding the risk associated with any skin to skin contact has been included in 4.4.
Regarding studies in juvenile animals, dermal application with 1% GPB (10 mg/g) cream resulted in a much lower systemic exposure compared to treatment with already approved GPB products. The 7-day dermal local tolerance and toxicity study in minipigs (discussed below) showed that all tested concentrations and formulations were well tolerated and there were no adverse findings at the application sites. Further, there is considerable clinical experience from treating juvenile patients with other topical GPB products, why no additional non-clinical studies are considered needed.

The applicant has conducted a 7-Day dermal local tolerance and toxicity study in minipigs to investigate the local and systemic tolerability. The test item was administered daily for 7 consecutive days at local concentrations of 0%, 0.5%, 1%, 2% GPB in cream, and 4% GPB in gel corresponding to daily doses of 0, 0.11, 0.22, 0.45, 0.89 mg/kg GPB (corresponding to 0.09, 0.18, 0.36, 0.71 mg/kg GP, respectively). Blood was sampled for toxicokinetic evaluation at pretest and Days 1, 3, 5 and 7 and formulations in the syringe were analyzed on Days 1 and 7. The study shows that the GPB cream and gel were well tolerated at all concentrations tested. There were no test item-related mortalities, clinical signs, findings at the application site, changes in body weight, food consumption and clinical laboratory parameters or test item-related pathomorphologic findings. There were no signs of local intolerance at macroscopic or microscopic evaluations. GP was absorbed slowly and to a limited extent, i.e. systemic exposure was low.

The applicant has conducted a local tolerance study to evaluate the eye hazard potential of 1% GBP cream using the bovine corneal opacity and permeability test. 1% GBP cream did not induce ocular irritation through both endpoints (opacity and permeability) and therefore, it was concluded that 1% GPB cream is not classified as eye irritant.

In addition, the applicant has conducted a local tolerance study to evaluate the eye hazard potential of GBP cream using the Reconstructed Human EpiOcular™ Model. The study concluded that 1% GPB cream is not classified as eye irritant.

The Local Lymph Node Assay (OECD 429, Study No. 20241154) was designed to evaluate whether the test item induces skin sensitization. The study concluded that GPB cream would be regarded as having potential as very weak skin sensitizer. However, the 7-day dermal local tolerance and toxicity study in minipigs (Study No. 509876) showed that all tested concentrations and formulations were well tolerated after repeated administrations and there were no adverse findings at the application sites. Considering the unclear clinical relevance of the findings, the Applicant has included the information in section 5.3 of the SmPC.

The lack of studies on antigenicity, immunotoxicity, dependence, metabolism and phototoxicity is considered acceptable.

The applicant has provided an *in silico* toxicology analysis with the parent compound GPB and both hydrolysis products ((2RS)-2-cyclopentyl-2-hydroxy-2-phenylacetic acid and (3RS)-3-hydroxy-1,1-dimethyl-pyrrolidinium) in order to reveal any statistical alerts and predictions of those compounds over a range of end points by comparing the chemical structure with an empirical database. The analysis indicated that all three compounds should be considered negative for bacterial mutagenicity. Benzaldehyde is a well-known and naturally occurring substance. Based on available data and experience with benzaldehyde no health risk is expected at concentrations of 0.0065% as contained in the drug product 1% GPB cream (Axhidrox).

Taken together, topical treatment with GPB up to 2% in creams and 4% in gel was well tolerated locally and no systemic adverse effects were found. In conclusion, there are no non-clinical toxicology concerns regarding the proposed clinical use of Axhidrox.

Environmental Risk Assessment (ERA)

A fragmented ERA has been provided by the Applicant which is not considered sufficient for conclusions on the potential environmental risks posed by Axhidrox. The log K_{ow} has been determined experimentally to -1.32 at a single pH. As the substance will be in the non-ionized form across all relevant pH levels it was considered appropriate that measurements were only performed at a single pH (5.7).

The ERA Phase II programme is not complete and thus no conclusions can be made regarding the potential environmental risks posed by Axhidrox. The Applicant has presented the studies planned for completion of the ERA in Table 9 of the AR. Further studies may also be needed pending the results of the above studies, in accordance with the ERA guideline.
The completed studies, including an updated ERA, should be provided as a Type II variation. The applicant provided a commitment letter including a list of planned ERA studies. The commitment letter also included timelines for each individual study and a statement that relevant documents will be updated and submitted via Type II variation asap, but not later than Q2 2024. The issue is considered resolved in current procedure. The ERA studies will be assessed in indicated Type II variation.

Summary of main study results

Substance (INN/Invented Name):					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log K_{ow} = -1.32 at pH 5.7			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}				B/not B
	BCF				B/not B
Persistence	DT50 or ready biodegradability				P/not P
Toxicity	NOEC or CMR				T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)		µg/L			> 0.01 threshold (Y/N)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} =			List all values
Ready Biodegradability Test	OECD 301B				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = $DT_{50,\ sediment}$ = $DT_{50,\ whole\ system}$ = % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	species
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:

Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/ kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/ kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/ kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/ kg	
Sediment dwelling organism		NOEC		mg/ kg	species

IV. CLINICAL ASPECTS

Pharmacokinetics
In one of the three clinical studies (Phase 1b, Hyp-02/2015) the applicant investigated the pharmacokinetics of GPB creams (0.5%, 1% and 2% GPB). The systemic plasma exposure is relevant for safety but do not correlate to efficacy since the GPB cream is locally applied and locally acting. The in vivo study was supported with literature data on absorption, distribution, metabolism, excretion, special populations, interactions and for comparison of systemic exposure with other routes of administration as well as another topically applied GP product.

Absorption:

Study Hyp-02/2015
The study was a single-center, double-blind, randomized, placebo-controlled, phase Ib, single and multiple dose escalation study to assess safety, local tolerability, PK and efficacy of GP in male and female subjects with moderate to severe axillary hyperhidrosis. The PK of GPB creams containing different concentrations, i.e. 0.5%, 1%, 2%, (corresponding to 4.3 mg, 8,6 mg and 17.3 mg, respectively) was investigated in 30 adult patients with moderate to severe primary axillary hyperhidrosis. Patients were treated with ascending doses of GPB in 3 cohorts, where Cohort 1 received 0.5% GPB cream, Cohort 2 received 1% GPB cream, and Cohort 3 received 2% GPB cream. Each cohort also included placebo patients and consisted of 10 patients (8 active and 2 placebo [=vehicle]). Study drug was administered as single daily doses of 0.54 g cream to each axilla (total 1.08 g cream) for 14 days. Blood samples for assessment of plasma GP concentrations were collected up to 7 days after the first dose, on Day 14 up to 8 hours post- dose, and on Day 21 (i.e. 7 days post last dose).

Results:

Table. Pharmacokinetic parameters of GP on Day 1 (calculated by non-compartmental methods) (n=8)

Dose	**0.5%**	**1%**	**2%**
AUCz (h*pg/mL)	45.331±24.0830 (19.84/50.994/79.77)	105.833±77.2494 (36.19/92.661/270.21)	373.032±345.4567 (79.94/235.290/1103.22)
AUC_8 (h*pg/mL)	12.728±4.0737 (6.85/12.235/16.91)	40.243±25.0212 (19.85/34.490/93.75)	142.478±119.6182 (27.06/87.130/344.00)

AUC_{24} (h*pg/mL)	45.560±24.2740 (19.97/51.115/80.43)	106.513±77.7982 (36.36/93.216/272.07)	375.346±347.6475 (80.50/236.315/1110.40)
C_{max} (pg/mL)	2.234±1.3496 (0.50/2.395/4.04)	10.763±7.2854 (4.22/7.435/23.50)	29.330±26.2451 (5.21/14.300/71.20)
T_{max} (h)	7.6±10.11 (1/2.5/24)	4.0±1.60 (2/3.5/7)	2.9±1.68 (1/2.0/6)
T_z (h)	17.93±9.325 (4.0/23.83/24.0)	21.86±5.599 (8.0/23.83/23.9)	23.84±0.006 (23.8/23.83/23.9)

mean±SD (min/median/max)

Table. Pharmacokinetic parameters of GP on Day 14 (calculated by non-compartmental methods) (n=8)

Dose	**0.5%**	**1%**	**2%**
AUC_z (h*pg/mL)	78.577±74.2848 (7.58/57.920/207.82)	128.850±94.6994 (42.50/90.065/259.90)	294.297±123.0838 (95.08/291.850/478.60)
AUC_8 (h*pg/mL)	78.577±74.2848 (7.58/57.920/207.82)	128.608±94.6254 (42.50/90.065/259.90)	294.297±123.0838 (95.08/291.850/478.60)
C_{max} (pg/mL)	18.120±21.0008 (1.19/9.170/62.40)	24.390±15.2328 (8.65/24.100/42.20)	51.875±21.4319 (17.40/51.200/80.60)
T_{max} (h)	4.1±1.75 (1/4.0/7)	3.7±2.57 (0/4.0/7)	3.1±2.36 (1/3.0/8)
T_z (h)	8.00±0.000 (8.0/8.00/8.0)	8.01±0.031 (8.0/8.00/8.1)	8.00±0.000 (8.0/8.00/8.0)
Rac	8.618±6.8600 (1.61/9.694/16.99)	2.967±1.5688 (1.52/2.574/6.12)	3.593±2.6646 (0.69/3.820/7.48)

Mean±SD (min/median/max)

The plasma exposure generally increased with dose and some accumulation was observed between Day 1 and Day 14 exposure. However, the plasma concentrations of GPB creams were overall low, and after 14 days of treatment with the 1% GPB cream (Axhidrox), an AUC_{0-8h} of 0.129 ng.h/mL and a C_{max} of 0.024 ng/mL was observed. Between 168h and 312h there is no increase in C_{trough} indicating that steady state is reached and that no further accumulation is expected. The inter-individual variability was high on day 1 and day 14 for both AUC and C_{max} at all investigated strengths of GPB creams. There was insufficient data to characterize the elimination rate and half-life of the GPB creams. Providing some information regarding elimination, the plasma concentrations 7 days post dose are very low and shows that GP is almost completely eliminated.

Absorption of GP from other routes of administration (published data)

Comparative exposure of 1% GPB cream (Axhidrox) versus iv, oral and inhaled GPB formulations

The applicant has compared the exposure of 1% GPB cream versus i.v., i.m., oral and inhaled GPB formulations. The AUC_{0-8h} of 0.129 ng.h/mL and C_{max} of 0.024 ng/mL for the 1% GPB cream after 14 days of treatment is clearly lower compared to all systemically administered GP products presented by the applicant. The difference in exposure with the inhaled GPB product was clear but not as large. In general, the comparison of the area under the concentration time curve (AUC) is complicated by the fact that AUC was assessed in different studies and not over the same timeframe. However, as could

be expected with the 1% GPB cream being a locally applied, locally acting drug, both total and maximum exposure were low.

Comparative exposure of 1% GPB cream (Axhidrox) versus topically administered GP (Qbrexza)
The PK data of the 1% GPB cream was also compared to Qbrexa (approvd in the US, but not in EU), a topically applied GP (in form of glycopyrronium tosylate, GPT) product indicated for primary hyperhidrosis in adults and children (>9 years of age). When comparing the PK data of the 1% GPB cream (Axhidrox) with Qbrexza, the exposure was similar.

Elimination: Literature data show that renal elimination of unchanged drug appears to be the major elimination pathway of GP. After intravenous administration of radioactively labelled GP to adults, the GP was mainly excreted via the kidneys (85%) and to a lesser extent (< 5%) via the bile. Both in bile and in urine over 80% of the radioactivity corresponded to unchanged glycopyrrolate. Overall, the data suggest that metabolism appears to be a minor elimination route.

Special populations
No clinical studies of 1% GPB cream (Axhidrox) investigating PK in special populations have been conducted. The data on special populations is retrieved from literature.

In renally-impaired patients, the elimination of i.v. administered GP (4 μg/kg) is severely impaired. Compared to control patients, a significantly smaller plasma clearance, longer elimination $t_{1/2}$ and larger AUC were reported.
While the 24 h renal excretion was 65% in control patients, it was only 7% in uremic patients.

Glycopyrronium is predominantly cleared by renal excretion and therefore no major increase in exposure to the active substance is to be expected in patients with hepatic impairment.

The safety and efficacy in patients above 65 years has not been established for the 1% GPB cream (Axhidrox).

No clinical studies investigating PK have been made in children for the 1% GPB cream (Axhidrox). Published data indicate that the PK of GP is not dependent on age.

Interactions:
No clinical pharmacokinetic interaction studies have been performed.

Effects of GP on enzymes and transporters: GP has no or only slight properties to induce or inhibit CYP enzymes and ABC as well as OCT transporters. Given the low systemic exposure, no inhibition or induction is expected after topical 1% GPB exposure.

Effect of other drugs on GP pharmacokinetics: GP is mainly eliminated renally and therefore no effect of enzyme inhibitors or inducers is expected.

Discussion on pharmacokinetics
GP is a well-known active substance used in several indications and different routes of administration. The applicant has presented literature data exploring several of these. The comparison of the AUC is not optimal since it the data is retrieved from different studies and was not assessed over the same timeframe. However, comparing the data provides a general idea on the extent of exposure. The systemic exposure of topically administered 1% GPB cream (Axhidrox) was considerably lower compared to i.v., i.m. and orally administered formulations. In conclusion, the systemic uptake from the GPB cream has been shown to be lower or similar compared to the systemic GP exposure reported for the two examples of inhaled or topically applied GP products presented by the Applicant. Since these are products with relatively few reported systemic anticholinergic side effects this supports the observed benign safety profile of the product applied for observed in the phase 3 study.

Pharmacodynamics
Glycopyrronium is an anticholinergic agent that blocks the action of the neurotransmitter acetylcholine at the muscarinic acetylcholine receptors, mostly at the muscarinic subtype M3 receptor. Glycopyrronium can be formulated with various salts, in this case the bromide salt, however it is the glycopyrronium molecule in itself that is pharmacologically active.

The clinical experience with glycopyrronium is extensive, for systemic treatment of severe sialorrhea, and for pre-operative reduction of salivary tracheobronchial and pharyngeal secretions both indications approved in children and adults. Glycopyrronium formulated as inhalation powder is approved for maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease.

Topical glycopyrronium formulated with the tosylate salt (Qbrexza®) is approved in the US as cloth for treatment of primary axillary hyperhidrosis from the age of 9 years old. The cloth has been recently authorized in Japan (Rapifort® Wipes 2.5%). In 2020 another anticholinergic agent, sofpironium bromide containing gel (ECCLOCK® gel 5%), was approved for treatment of primary axillary hyperhidrosis in Japan. This product, Axhidrox, contains 1% GPB as a cream formulation.

Clinical efficacy
Design and conduct of clinical studies

The present application concerns a cream formulation of 1% glycopyrronium bromide (GPB) for topical administration to reduce axillary hyperhidrosis. Heavy axillary perspiration has been linked to dysregulation of the autonomous nervous system, it starts during puberty, and causes psychological distress in affected individuals.

The application is supported by one Phase 1b dose-response study (Hyp-02/2015), and one Phase 3 study (Hyp1-18/2016). Supportive evidence is provided by literature data.

Dose-finding Phase 1b study Hyp-02/2015
Study Hyp-02/2015 is a single-centre, randomized, placebo-controlled, double-blind, escalating dose study in patients with primary axillary hyperhidrosis investigating three different concentrations of GPB creams, 0.5%, 1% and 2 %.

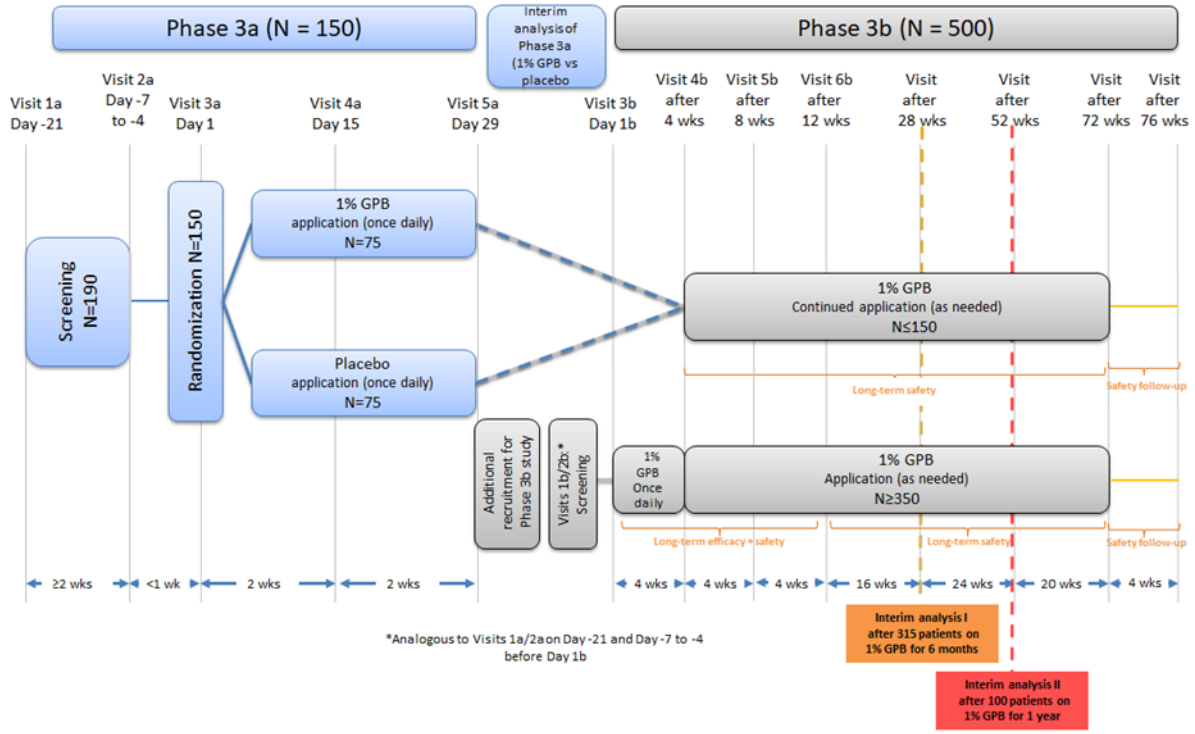
Subjects received topical doses of either GPB creams or placebo cream for 2 weeks once daily. In the first 8 days, the study drugs were administered in the Phase 1 unit by study personnel, while in the following 6 days, study drugs were self-administered by the patients at home.
The objectives of the study were to assess the safety, tolerability, PK, and efficacy of escalating concentrations of GPB in patients with axillary hyperhidrosis.

Eligible were adult patients, aged 18-65 years, with moderate to severe primary axillary hyperhidrosis. Efficacy assessments included gravimetry (GM) of sweat production (performed pre-dose, and at Day 2, 3, 4, 8, 14 and 21), assessment of the Hyperhidrosis Disease Severity Scale (HDSS) (performed pre-dose, and at Day 2, 3, 4, 5, 6, 8, 14 and 21), and the QoL questionnaires Dermatology Life Quality Index (DLQI) and Hyperhidrosis Quality of Life index (HidroQoL) performed pre-dose, and at Day 8, 14 and 21.

Phase 3 study Hyp1-18/2016

Study Hyp1-18/2016 is a multi-center, randomized, double-blind and placebo-controlled Phase 3 study that consists of two phases. The first part of the study, Phase 3a, evaluated efficacy and safety of 1% GPB 1% cream (Axhidrox) compared with placebo for 4 weeks and is completed. The long-term safety and efficacy part, Phase 3b, is presently ongoing, with interim parts of the results presented in this Assessment Report.
In Phase 3a, patients self-administered the study drug, 1% GPB cream (Axhidrox) or placebo cream, to both axillae once daily preferably in the evening for 4 weeks. In Phase 3b, newly enrolled patients (including placebo patients from Phase 3a) self-administered 1% GPB cream to both axillae once daily for 4 weeks. After 4 weeks initial daily dose administration, all patients, administered the 1% GPB cream as-needed (at least twice per week and not more than once daily) until Week 72 (see figure of the study design below).

Figure 1. Study Hyp1-18/2016



Note: The primary endpoint and 2 of the 3 key secondary endpoints were assessed at Week 12 in Phase 3b, with additional efficacy assessments for the remaining treatment period.
Source: Hyp1-18/2016_3b, Figure 1

Patients were instructed to press the pump head of the dispenser twice to release 0.54 g (2 x 0.27 g) of cream for each axilla, i.e. a total of 1.08 g of cream per application day. The subjects treated themselves with the test products at home, which is reasonable considering the disease to be treated and the nature of the product (topical cream formulation). Treatment compliance was verified through a combination of unused investigational product returned by the subject every 4 weeks, if possible, review of the dosing diary, and discussion with the subject.

The objectives of the study were the assessment of efficacy and safety of 1% GPB cream (Axhidrox) or placebo (Phase 3a part), and the assessment of long-term efficacy and safety of 1% GPB cream in patients with primary axillary hyperhidrosis (Phase 3b part).

Eligible were adult patients, aged 18-65 years (based on inclusion criteria), with a diagnosis of severe primary axillary hyperhidrosis according to the Hyperhidrosis Disease Severity Scale (HDSS) score of 3 or 4, with at least 50 mg of sweat production in each axilla measured gravimetrically at room temperature over a 5-minute period. Patients with secondary hyperhidrosis were excluded from the

studies. The inclusion and exclusion criteria are considered adequate to reflect the proposed therapeutic indication.

The primary efficacy endpoint in Phase 3a was the absolute change in sweat production assessed by gravimetry at day 29 in the 1% GPB cream (Axhidrox) group compared with the placebo group. The primary efficacy endpoint in Phase 3b was the absolute change in total sweat production at week 12 (Interim Analysis I and II). This primary efficacy endpoint is of clinical relevance if met.

The key secondary endpoints in Phase 3a were 1) the percent of responders assessed by the HDSS scale (≥2-point improvement from baseline) and 2) the absolute change in the Hyperhidrosis quality of life index (HidroQoL) from baseline to Day 29 in the 1% GPB (Axhidrox) group compared with the placebo group.

The key secondary efficacy endpoints in Phase 3b were 1) the percentage of responders assessed by the HDSS (≥2-point improvement from baseline) at week 12, 2) the percentage of responders assessed by the HDSS (≥2-point improvement from baseline) at week 28 and 3) the absolute change in the HidroQoL from baseline to Week 12. All key secondary endpoints have a clinical relevance if met. Moreover, several other secondary endpoints were investigated.

The study objectives and outcomes are considered adequate for clinical studies evaluating a new product with the proposed therapeutic indication axillary hyperhidrosis. The number of subjects included in the pivotal Phase 3 study and the duration of treatment are considered relevant. The study has a comparative design to placebo in Phase 3a, and an open label design in Phase 3b. Hence, there was an objective related to superiority and randomisation and blinding were necessary. The study design is overall accepted.

Clinical Safety
Topical glycopyrronium bromide (GPB), is a synthetic muscarinic anticholinergic agent. A number of glycopyrronium products, including parenteral, oral, or inhalational formulations are approved within EU and have been used for several years in various indications. The applied indication of 1% GPB cream (Axhidrox) is for the topical treatment of severe primary axillary hyperhidrosis in adults. The recommended dosing is two pump actuations per armpit (equivalent to 540 mg of cream per armpit) applied to each armpit evenly, once a day, preferably in the evening during the first 4 weeks of treatment. From the 5th week on, the frequency of application of GPB can be reduced to twice a week, depending on the response to treatment.

The treatment has been evaluated in adults 18-65 years of age in one Phase 1b study with GPB cream at 3 different concentrations (0.5%, 1% and 2%) and in a pivotal Phase 3 study with 1% GPB cream (Axhidrox). Uncertainties as to the study procedures and outcome of study Hyp-02/2015 including relatively few involved patients receiving the 1% GPB cream (Axhidrox), limits the value of this study from a safety perspective. The Phase 3 study consisted of two parts. In part 3a, patients were randomized and treated with 1% GPB cream (Axhidrox) or placebo with evaluation of primary endpoint (PEP) at Week 4. In Part 3b PEP was assessed at Week 12 in newly recruited patients and key secondary endpoints at different time points up to Week 72. Long-term exposure has been followed for a period of up to 12 months. See table below of Phase 3 study exposure.

Table 1. Overall summary of adverse events in study Hyp1-18/2016 Phase 3a (SAFa) and Phase 3b, Interim Analysis I and II (SAFb)

Study	Treatment	Dose and duration	Number of patients treated
Hyp1-18/2016 (Phase 3a part)	1% GPB	Once daily 0.54 g of cream to each axilla **Duration: 4 weeks**	87*
Hyp1-18/2016 (Phase 3b part)	1% GPB	Once daily 0.54 g of cream to each axilla for the first 4 weeks; thereafter 0.54 g of cream to each axilla as needed (at least twice per week and not exceeding once daily) **Duration: 6 months**	315** (Interim Analysis I)
	1% GPB	Once daily 0.54 g of cream to each axilla for the first 4 weeks; thereafter 0.54 g of cream to each axilla as needed (at least twice per week and not exceeding once daily) **Duration: 12 months**	100 (subset of the 315 patients treated for 6 months) (Interim Analysis II)
Hyp-02/2015 (Phase 1b)	0.5%, 1% or 2% GPB	Once daily 0.54 g of cream to each axilla **Duration: 14 days**	24 (of these, 8 patients treated with 1%)

The combined safety database of 351 patients exposed to the GPB creams, includes apart from the 315 patients of the Phase 3 study exposed to the 1 % GPB cream (Axhidrox) and the 24 patients exposed to 0.5%, 1% or 2% GPB cream respectively in the Phase 1b study, additionally 12 patients who were exposed to 1 % GPB cream (Axhidrox) in the initial part of Phase 3 study but did not continue the long-term study. To sum up, a total of 335 patients were exposed to the 1% GPB cream (Axhidrox) in clinical studies. Of these 335 patients, 327 patients were included in the Phase 3 study and 315 exposed for six months and a subset of 100 exposed for 1 year. The long-term study is still ongoing. The extent of exposure is considered satisfactory considering previous experience of glycopyrronium products including topical administration and the safety profile from that perspective is considered rather well characterised.

Adverse events

Table 2. Overall summary of adverse events in study Hyp1-18/2016 Phase 3a (SAFa) and Phase 3b, Interim Analysis I and II (SAFb)

	Number of patients (%)			
	Phase 3a		Phase 3b 6-month data Interim Analysis I	Phase 3b 12-month data Interim Analysis II
	1% GPB N=87	Placebo N=84	1% GPB N=315	1% GPB N=100
Any TEAE	43 (49.4)	37 (44.0)	210 (66.7)	79 (79.0)
Drug-related TEAE*	24 (27.6)	11 (13.1)	90 (28.6)	31 (31.0)
Severe TEAE	2 (2.3)	4 (4.8)	11 (3.5)	5 (5.0)
SAE	1 (1.1)	0 (0.0)	7 (2.2)	4 (4.0)
Fatal AE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)**	0 (0.0)**

In the placebo-controlled part of the pivotal Phase 3 study (Part a) any TEAEs overall were reported at similar frequencies in the 1% GPB cream (Axhidrox) and the placebo groups (49.4% versus 44.0%)

but then again a higher percentage of 1% GPB cream (Axhidrox) patients reported drug-related TEAEs compared to placebo patients (27.6% versus 13.1%). These differences are mainly due to gastrointestinal disorders such as dry mouth and eye disorders such as dry eye/ocular hyperemia, adverse reactions in line with anticholinergic influence.

Table 3. Common TEAEs in study Hyp1-18/2016 Phase 3a part. TEAEs occurring in 2 or more patients (corresponding to >2% of patients) in any treatment group, by SOC and PT (SAFa, N=171)

System organ class Preferred term	**Number of patients (%)**	
	1% GPB N=87	**Placebo N=84**
Any TEAE	43 (49.4)	37 (44.0)
Gastrointestinal disorders	**16 (18.4)**	**9 (10.7)**
Dry mouth	15 (17.2)	4 (4.8)
Gastritis	0 (0.0)	2 (2.4)
Infections and infestations	**15 (17.2)**	**15 (17.9)**
Nasopharyngitis	10 (11.5)	14 (16.7)
Urinary tract infection	2 (2.3)	0 (0.0)
Nervous system disorders	**11 (12.6)**	**9 (10.7)**
Headache	9 (10.3)	8 (9.5)
Dizziness	1 (1.1)	2 (2.4)
General disorders and administration site conditions	**11 (12.6)**	**6 (7.1)**
Application site erythema	5 (5.7)	4 (4.8)
Application site papules	2 (2.3)	0 (0.0)
Eye disorders	**4 (4.6)**	**1 (1.2)**
Ocular hyperaemia	2 (2.3)	0 (0.0)
Skin and subcutaneous tissue disorders	**4 (4.6)**	**5 (6.0)**
Rash papular	0 (0.0)	2 (2.4)
Injury, poisoning and procedural complications	**4 (4.6)**	**1 (1.2)**
Musculoskeletal and connective tissue disorders	**3 (3.4)**	**2 (2.4)**
Respiratory, thoracic and mediastinal disorders	**2 (2.3)**	**2 (2.4)**
Nasal dryness	2 (2.3)	0 (0.0)
Oropharyngeal pain	0 (0.0)	2 (2.4)
Ear and labyrinth disorders	**2 (2.3)**	**1 (1.2)**
Investigations	**2 (2.3)**	**0 (0.0)**
Vascular disorders	**1 (1.1)**	**2 (2.4)**
Hypertension	0 (0.0)	2 (2.4)

SAFa=Safety Analysis Set (Phase 3a), TEAE=treatment-emergent adverse event.
Sorted by descending frequency in the 1% GPB group.

Table 4. Study Hyp1-18/2016, phase 3 part b, Interim Analysis I. TEAEs occurring in ≥3% of patients in any group in Phase 3b (SAFb, N=315)

System organ class Preferred term	Number (%)[a] of patients		
	1% GPB Baseline to Week 4 N=247[b]	1% GPB After Week 4 N=315	1% GPB Baseline to Week 28 (Overall) N=315
Any TEAE	108 (43.7)	183 (58.1)	210 (66.7)
Infections and infestations	**36 (14.6)**	**102 (32.4)**	**118 (37.5)**
Nasopharyngitis	29 (11.7)	73 (23.2)	87 (27.6)
Gastrointestinal disorders	**34 (13.8)**	**41 (13.0)**	**63 (20.0)**
Dry mouth	26 (10.5)	12 (3.8)	36 (11.4)
Nervous system disorders	**24 (9.7)**	**44 (14.0)**	**60 (19.0)**
Headache	20 (8.1)	36 (11.4)	51 (16.2)
General disorders and administration site condition	**22 (8.9)**	**33 (10.5)**	**48 (15.2)**
Application site erythema	8 (3.2)	11 (3.5)	18 (5.7)
Skin and subcutaneous tissue disorders	**13 (5.3)**	**20 (6.3)**	**30 (9.5)**
Respiratory, thoracic and mediastinal disorders	**10 (4.0)**	**19 (6.0)**	**28 (8.9)**
Oropharyngeal pain	3 (1.2)	9 (2.9)	12 (3.8)
Musculoskeletal and connective tissue disorders	**5 (2.0)**	**19 (6.0)**	**23 (7.3)**
Eye disorders	**7 (2.8)**	**15 (4.8)**	**22 (7.0)**
Dry eye	3 (1.2)	10 (3.2)	13 (4.1)
Injury, poisoning and procedural complications	**8 (3.2)**	**14 (4.4)**	**22 (7.0)**
Investigations	**7 (2.8)**	**8 (2.5)**	**15 (4.8)**

[a] Percentages are based on the number of patients in each analysis group.

[b] Patients receiving placebo in Phase 3a are not included.

GPB=glycopyrronium bromide, SAFb=Safety Analysis Set (Phase 3b), TEAE=treatment-emergent adverse event. Sorted by descending frequency in the 1% GPB overall group.

Table 5. TEAEs occurring in ≥3% of patients in any group in study Hyp1-18/2016 Phase 3b, Interim Analysis II (SAFb, N=100)

System organ class Preferred term	Number (%)[a] of patients		
	1% GPB Baseline to Week 4 N=54[b]	1% GPB After Week 4 N=100	1% GPB Baseline to Week 52 (Overall) N=100
Any TEAE	30 (55.6)	73 (73.0)	79 (79.0)
Infections and infestations	**10 (18.5)**	**44 (44.0)**	**49 (49.0)**
Nasopharyngitis	7 (13.0)	33 (33.0)	38 (38.0)
Conjunctivitis	0 (0.0)	3 (3.0)	3 (3.0)
General disorders and administration site conditions	**10 (18.5)**	**16 (16.0)**	**24 (24.0)**
Application site erythema	6 (11.1)	8 (8.0)	13 (13.0)
Application site pruritus	1 (1.9)	3 (3.0)	4 (4.0)
Application site papules	2 (3.7)	1 (1.0)	3 (3.0)
Gastrointestinal disorders	**11 (20.4)**	**14 (14.0)**	**22 (22.0)**
Dry mouth	11 (20.4)	5 (5.0)	15 (15.0)
Abdominal pain upper	0 (0.0)	3 (3.0)	3 (3.0)
Nervous system disorders	**8 (14.8)**	**10 (10.0)**	**16 (16.0)**
Headache	6 (11.1)	9 (9.0)	14 (14.0)
Skin and subcutaneous tissue disorders	**3 (5.6)**	**14 (14.0)**	**15 (15.0)**
Eczema	1 (1.9)	4 (4.0)	5 (5.0)
Musculoskeletal and connective tissue disorders	**1 (1.9)**	**9 (9.0)**	**10 (10.0)**
Back pain	0 (0.0)	5 (5.0)	5 (5.0)
Injury, poisoning and procedural complications	**2 (3.7)**	**7 (7.0)**	**9 (9.0)**
Ligament sprain	1 (1.9)	2 (2.0)	3 (3.0)
Eye disorders	**2 (3.7)**	**5 (5.0)**	**7 (7.0)**
Dry eye	0 (0.0)	3 (3.0)	3 (3.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (1.9)**	**5 (5.0)**	**6 (6.0)**
Melanocytic naevus	1 (1.9)	2 (2.0)	3 (3.0)
Respiratory, thoracic and mediastinal disorders	**1 (1.9)**	**3 (3.0)**	**4 (4.0)**
Metabolism and nutrition disorders	**0 (0.0)**	**3 (3.0)**	**3 (3.0)**
Vascular disorders	**1 (1.9)**	**2 (2.0)**	**3 (3.0)**

[a] Percentages are based on the number of patients in each analysis group.
[b] Patients receiving placebo in Phase 3a are not included.
GPB=glycopyrronium bromide, SAFb=Safety Analysis Set (Phase 3b), TEAE=treatment-emergent adverse event.
Sorted by descending frequency in the 1% GPB overall group.

Dry mouth was the most frequent related TEAE, reported at an overall frequency of 17.2 % for 1% GPB cream (Axhidrox) treated vs 4.8 % for the placebo treated in the placebo-controlled part (Part a) of the pivotal Phase 3 study and for 1% GPB cream (Axhidrox) in Phase 3 Part b of six months follow up (Interim Analysis I) 11.4%, and 15.0% for 1 years follow-up (Interim Analysis II).

A questionnaire to assess anticholinergic effects was also used to in both studies with GPB cream. Most patients had no anticholinergic symptoms and only a few patients had mild anticholinergic symptoms throughout the placebo-controlled part of the pivotal Phase 3 study. The only 2 reports of severe symptoms were 1 patient with dry mouth in the 1% GPB cream (Axhidrox) group at Day 15 with no evidence of dry mouth at Day 29 without changing the treatment and 1 patient with dry eyes in the placebo group. In the 6 months follow-up part of the study there were 14 patients with mild or moderate (1 patient) dry mouth, 6 of whom also had mild or moderate (1 patient) dry eyes. One of these patients also had blurred vision in addition to dry mouth and dry eyes. Mild dry eyes and in one case mild red eyes and mild drowsiness were observed in a total of 15 patients. For 2 patients each with drowsiness and concentration difficulties at week 12, this condition was already present at

screening. During the 12 months follow-up a similar safety profile was shown.

The most common application site reaction was erythema. In the placebo-controlled part of the pivotal Phase 3 study application site reactions such as erythema was reported in 5.7 % on 1% GPB cream (Axhidrox) treated vs 4.8 % in placebo treated and application site papules in 2.3 % of GPB treated vs 0,0 in placebo treated. In Phase 3b, these reactions were more common during the initial 4 weeks with daily administration of 1% GPB cream (Axhidrox). Local tolerability at the application site was also assessed by the investigator using a skin reaction score. The vast majority of patients in both treatment groups (1% GPB cream and placebo) had a skin reaction score of 0 (i.e. no evidence of irritation) on both axillae at baseline, Day 15, and Day 29. In the Phase 3 Part b study, most patients (95 % - 97 %) showed no signs of irritation at the treated area between weeks 8 and 52.

Twelve SAEs in 11 patients were reported from the clinical studies. All were considered not drug-related except on case of unequal pupils with recovery. There were no deaths reported.Table 6. Comparison of drug-related TEAEs in study Hyp1-18/2016, Phase 3a (SAFa), Phase 3b Interim Analysis I (SAFb) and Interim Analysis II (SAFb)

	Number (%)[a] of patients, 1% GPB		
System organ class Preferred term	**Phase 3a** **N=87**	**Phase 3b** **Interim Analysis I** **N=315**	**Phase 3b** **Interim Analysis II** **N=100**
Any drug-related TEAE	24 (27.6)	90 (28.6)	31 (31.0)
Gastrointestinal disorders	**15 (17.2)**	**38 (12.1)**	**15 (15.0)**
Dry mouth	14 (16.1)	36 (11.4)	15 (15.0)
Constipation	1 (1.1)	3 (1.0)	1 (1.0)
Abdominal distension	0 (0.0)	1 (0.3)	0 (0.0)
Lip dry	0 (0.0)	1 (0.3)	0 (0.0)
General disorders and administration site conditions	**7 (8.0)**	**37 (11.7)**	**14 (14.0)**
Application site erythema	4 (4.6)	14 (4.4)	8 (8.0)
Application site pruritus	1 (1.1)	7 (2.2)	3 (3.0)
Application site pain	1 (1.1)	6 (1.9)	2 (2.0)
Application site irritation	0 (0.0)	5 (1.6)	1 (1.0)
Application site dermatitis	1 (1.1)	3 (1.0)	1 (1.0)
Application site dryness	0 (0.0)	3 (1.0)	0 (0.0)
Application site papules	1 (1.1)	3 (1.0)	1 (1.0)
Application site rash	0 (0.0)	3 (1.0)	0 (0.0)
Application site swelling	0 (0.0)	2 (0.6)	0 (0.0)
Application site acne	0 (0.0)	1 (0.3)	0 (0.0)
Application site eczema	0 (0.0)	1 (0.3)	1 (1.0)
Chest pain	0 (0.0)	1 (0.3)	0 (0.0)
Mucosal dryness	0 (0.0)	1 (0.3)	0 (0.0)
Eye disorders	**4 (4.6)**	**17 (5.4)**	**6 (6.0)**
Dry eye	1 (1.1)	9 (2.9)	2 (2.0)
Ocular hyperemia	2 (2.3)	2 (0.6)	1 (1.0)
Pupils unequal	0 (0.0)	2 (0.6)	1 (1.0)
Vision blurred	0 (0.0)	2 (0.6)	0 (0.0)
Eye irritation	1 (1.1)	1 (0.3)	1 (1.0)
Eye pruritus	0 (0.0)	1 (0.3)	0 (0.0)
Visual impairment	0 (0.0)	1 (0.3)	1 (1.0)
Skin and subcutaneous tissue disorders	**1 (1.1)**	**13 (4.1)**	**2 (2.0)**
Dry skin	1 (1.1)	4 (1.3)	0 (0.0)
Eczema	0 (0.0)	2 (0.6)	0 (0.0)
Dermatitis atopic	0 (0.0)	1 (0.3)	1 (1.0)
Erythema	0 (0.0)	1 (0.3)	0 (0.0)
Hyperhidrosis	0 (0.0)	1 (0.3)	0 (0.0)
Parapsoriasis	0 (0.0)	1 (0.3)	0 (0.0)
Pruritus	0 (0.0)	1 (0.3)	0 (0.0)
Rash	0 (0.0)	1 (0.3)	0 (0.0)
Skin irritation	0 (0.0)	1 (0.3)	0 (0.0)

In general, the safety profile seems comparable in the short term and long-term perspective although the number of any TEAEs is increasing by week 28 and through week 52. If considering TEAEs evaluated as drug related there is only a slight increase in the number over time (please refer to table above).

In summary, the safety profile is dominated by adverse events in line with anticholinergic effects and of application site reactions. There are few SAEs and no deaths reported. To conclude, no serious systemic adverse events were reported in the submitted data that would indicate a new serious safety concern in adults at the proposed clinical use. The extent of exposure in adults presented in submitted data is considered satisfactory.

Many of the adverse reactions were in line with anticholinergic effects. Based on the stated low systemic exposure to GPB when applying 1 % GPB cream (Axhidrox) it was considered that the ADR dry mouth -the most frequent ADR for oral administration of solution and tablets and for inhalative administration-may be partly due to contamination and partly due to systemic exposure. Dry mouth was also reported when GPB was used as powder for palmar or plantar treatment of hyperhidrosis. However, in comparison with i.v., i.m. and orally administered formulations of GPB, exposure of the GP cream was considerably lower. Furthermore, a systemic adverse event such as e g urinary retention, has not been reported for 1% GPB cream (Axhidrox) in Interim Analysis I and II. In conclusion, although the mechanism of suspected anticholinergic adverse effects has not been fully elucidated it is not unreasonable to assume that the facial including eye adverse events of suspected anticholinergic origin may at least partly be due to contamination. The instructions to minimise the risk of contamination and misuse have been satisfactorily described in the labelling. This includes also precautionary measures of careful dental hygiene and dental health checks due to the very common adverse reaction of dry mouth and the risk of dental caries due to reduced salivation.

Initially the suggested population to be treated would include children aged 12 years up to 18 years, However, the Applicant has in their response decided to exclude the paediatric population completely from the label until clinical data in the respective age group become available.
The safety profile including detailed frequencies of reported adverse reactions is adequately described in the labelling.

Conclusions on clinical safety
Axhidrox (1 % GPB cream) is applied topically to each armpit once a day the initial 4 weeks and thereafter twice a week, depending on the response to treatment. A number of GPB products, including parenteral, oral, or inhalational formulations are approved within EU and have been used for several years in various indications also in children and the safety profile is considered relatively well-known. The reported adverse events of Axhidrox are in line with expected anticholinergic effects such as e.g., dry mouth, dry eye and furthermore local skin reactions, mainly erythema, were reported. No serious systemic adverse events that would indicate a new serious safety concern in adults at the proposed clinical use were reported in the submitted data. The extent of exposure in adults presented in submitted data is considered satisfactory. From a safety perspective there are in the RMS opinion no major concerns related to the adult population.

Risk Management Plan
The MAH has submitted an updated risk management plan, version 0.3 with data lock point 29 July 2020 and final sign-off 13 January 2022 in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmaco-vigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to 1% GPB cream (Axhidrox).

Safety specification
Non-clinical
The Applicant has submitted a presentation of key findings of glycopyrronium from non-clinical studies/published literature concerning acute or repeat-dose toxicity studies, genotoxicity,

carcinogenicity, reproductive and developmental toxicity, local tolerance and other toxicity related information or data including safety pharmacology and discussed the relevance to human usage around these. Studies of genotoxicity, carcinogenicty, reproductive and developmental toxicit including separate safety pharmacology studies with GPB creams were not considered to add value and have not been performed.

Summary of conclusions by the applicant:

Single-and repeat dose toxicity
In the Phase 1b study (Hyp-02/2015), exposure with 1% GPB cream (Axhidrox) was lower than exposure known from systemic administration of mentioned glycopyrronium-containing products and also compared to Qbrexza®, which is licensed for the topical treatment of primary axillary hyperhidrosis in the US: 1% GPB cream (Axhidrox) as a topical formulation is expected to be well-tolerated in humans.

Genotoxicity
There is no evidence of any genotoxicity of glycopyrronium from approved products.
Relevance to human usage: No genotoxicity is expected for 1% GPB cream (Axhidrox).

Carcinogenicity
No indication for any systemic or local carcinogenic effect from glycopyrronium was observed. Thus, no carcinogenicity is expected for 1% GPB cream (Axhidrox).

Reproductive and developmental toxicity
Pregnancy
There are no or limited amount of data from the use of glycopyrronium in pregnant women. Studies in animals have shown reproductive toxicity. Based on the low systemic exposure following dermal application of 1% GPB cream (Axhidrox), these findings are not considered relevant for human dermal use at the approved dosing. The use of 1% GPB cream (Axhidrox) may be considered during pregnancy, if necessary (SmPC, Section 4.6).

Breast-feeding
Glycopyrronium and its metabolites distributed into milk from lactating rats and generally reached higher concentrations in milk when compared with those observed in plasma (up to 11.3 times). However, systemic exposure of glycopyrronium following dermal application in patients is low and consequently, enriched concentrations in the milk would also still be low with no pharmacologic or toxicologic concern (SmPC, Section 5.3).
The contact of the suckling child with the cream or 1% GPB cream (Axhidrox)-treated skin should be avoided, therefore a decision must be made whether to discontinue breast-feeding or to discontinue 1% GPB cream (Axhidrox) therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman (SmPC, Section 4.6).
Use in pregnancy and lactation is included as missing information in this RMP.

Local tolerance
Local tolerability of GPB creams at concentrations of 0.5%, 1%, and 2% and as a 4% gel was assessed as part of the 7-day dermal local tolerance and toxicity study in minipigs. All tested concentrations and formulations were well tolerated and there were no adverse findings at the application sites. GPB 1% cream (Axhidrox) is expected to be well-tolerated in humans.

Other toxicityrelated information or data
Inadvertent dosing into the eyes is not expected to result in ocular irritation. Based on the very low potential of sensitization in mice, a sensitizing effect in humans cannot be completely ruled out in very rare cases. However, no indication of any skin sensitizing effect was observed so far from approved drug products or in clinical studies with GPB creams. No phototoxicity is expected by topical application of 1% GPB cream (Axhidrox).

Safety pharmacology
Systemic exposure levels in dogs following inhaled administration of glycopyrronium doses that resulted in cardiovascular findings is expected to be 80- to 450-fold higher based on Cmax compared to systemic exposure levels detected in patients using the topically applied cream with 0.5%, 1% or 2% GPB. Thus, topical administration of 1% GPB cream (Axhidrox) is not expected to result in safety pharmacological effects in humans.

Clinical
The summary of safety concerns can be seen in the table below.

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy and lactation

Missing information 1: Use in pregnancy and lactation
There are no or limited amount of data from the use of GPB in pregnant women. Studies in animals have shown reproductive toxicity (see Module SII, Table SII.1). Based on the low systemic exposure following dermal application of 1% GPB cream (Axhidrox), these findings are not considered relevant for human dermal use at the approved dosing. With regard to lactation, contact of the suckling child with the cream or Axhidrox-treated skin should be avoided.
Risk-benefit impact: Based on the low systemic exposure following the dermal application of 1% GPB cream (Axhidrox), the use of Axhidrox may be considered during pregnancy, if necessary. The contact of the suckling child with the cream or Axhidrox-treated skin should be avoided, therefore a decision must be made whether to discontinue breast-feeding or to discontinue Axhidrox therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
Use in pregnancy and lactation will continue to be monitored through routine ongoing safety surveillance.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the Applicant.

Plans for post-authorisation efficacy studies

Not applicable. There are no planned or ongoing post-authorization efficacy studies.

The managing of the pharmacovigilance plan is by routine pharmacovigilance.

Risk minimisation measures (RMM)
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the Applicant.

Table Part V.3: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
Safety concern 1: Use in	Routine risk communication:	Routine pharmacovigilance

Safety concern	Risk minimization measures	Pharmacovigilance activities
pregnancy and lactation	SmPC, Sections 4.6, 5.3 PL, Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: medical prescription Additional risk minimization measures: none	activities are sufficient to monitor this risk

Routine risk minimisation with no additional risk minimisation activities will be performed.

Summary of activities in the risk management plan by medicinal product

The 1% GPB cream (Axhidrox) is authorized for the topical treatment of severe primary axillary hyperhidrosis in adults (see SmPC for the full indication).

It contains glycopyrronium bromide as the active substance and it is given by the topical route of administration.

Important risks of Axhidrox, together with measures to minimize such risks and the proposed studies for learning more about Axhidrox's risks, are outlined below.

Summary of important risks

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy and lactation

II.B Summary of important risks

Missing information: use in pregnancy and lactation	
Risk minimization measures	Routine risk communication: SmPC, Sections 4.6, 5.3 PL, Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: medical prescription Additional risk minimization measures: none

Summary of the RMP
The submitted Risk Management Plan, version 0.4 with data lock point 29 July 2020 and signed 24 February 2022 is acceptable.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was German.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Disease or condition and available therapies

Hyperhidrosis is a dysregulation of the autonomous nerve system characterized by disproportionate sweating, more than what is required to maintain regulation of normal body temperature in specific body locations (axillae, palms, feet). The exact cause of this dysfunction is not fully understood. Hyperhidrosis is classified as either primary or secondary in nature. Primary hyperhidrosis is idiopathic; it results from over-activity of the sympathetic nerves and involves a limited body area, most often the axillae (underarms), but also palms, soles, or craniofacial regions. Secondary hyperhidrosis results from an underlying medical condition or use of prescription medications and generally involves much larger body areas.

Axillary hyperhidrosis appears to be most common, affecting around half of individuals with hyperhidrosis, and starts earliest with entry into puberty.

Primary hyperhidrosis is a stigmatizing disease with physical and psychological symptoms affecting patients´ quality of life (QoL) such as limitations in daily activities, social relationships, study and work life and emotional wellbeing. Axillary sweating is in addition associated with an unpleasant odor, which is further complicating social contacts.

Current treatments for axillary hyperhidrosis are topical antiperspirants, Botulinum toxin A injections and systemic medications, e.g. oral anticholinergics. Further, surgical treatment options exist such as local sweat gland ablation.

In the US, a glycopyrronium tosylate cloth Qbrexza®, was approved in 2018 for treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years and older. Both the GP bromide (present product) and GP tosylate salts are soluble in water. In both topical products, 1% GPB cream (Axhidrox) and Qbrexza®, GP is dissociated from its anion in solution. Only the cationic GP portion is pharmacologically active. The targeted ACh receptor binds only the GP, while the salt is not relevant for receptor binding.

In Japan, a structural analogue to GP, sofpironium bromide containing gel (ECCLOCK® gel 5%), was approved in September 2020 for treatment of primary axillary hyperhidrosis, while just recently (January 2022), 2.5% GPT wipes (Rapifort®) have been approved.
.

There is a medical need for easy-to-use topical treatment of the more severe forms of axillary hyperhidrosis.

Product proposed for marketing

The 1% GPB cream (Axhidrox) containing glycopyrronium as the active drug substance, formulated with a bromide salt, has been developed for topical treatment of severe primary axillary hyperhidrosis in adults and adolescents aged 12 years and older. However, the inclusion of patients in the therapeutic indication between 12 and 17 years of age has been withdrawn by the applicant.

Glycopyrronium is a competitive antagonist of the muscarinic acetylcholine receptors. It inhibits acetylcholine-driven parasympathetic effects on smooth muscle and heart muscle cells and on various glands, including the sweat glands. In the sweat glands, this results in a reduction in perspiration.

The 1% GPB cream (Axhidrox) is a white, homogeneous, glossy cream. The cutaneous preparation is a hydrophilic cream in form of an oil-in-water emulsion.

The 1% GPB cream (Axhidrox) should be evenly applied once daily to each armpit, preferably in the evening for 4 weeks. From the 5th week on, the frequency of application can be reduced to twice a week, depending on the response to treatment. The recommended dosage of Axhidrox is two pump actuations per armpit (equivalent to 540 mg of cream per armpit).

Main clinical studies

The efficacy of Axhidrox is supported by one Phase 1b dose-response study (study Hyp-02/2015) performed in Germany, and one Phase 3 study (study Hyp1-18/2016) performed within the EU. Supportive evidence is provided by literature data.

The pivotal study Hyp1-18/2016 is a multi-center, randomized, double-blind and placebo-controlled Phase 3 study that consists of two phases. The first part of the study, Phase 3a, evaluated efficacy and safety of 1% GPB cream (Axhidrox) compared with placebo for 4 weeks and is completed. The long-term safety and efficacy part, Phase 3b, is presently ongoing, with interim parts of the results presented in this Assessment Report.

Favourable effects

In the pivotal study, a significant superior efficacy of the 1% GBP cream (Axhidrox) compared to vehicle cream was demonstrated for the primary endpoint; absolute change in sweat production assessed by gravimetry at Day 29. The absolute reduction in sweat production from baseline to Day 29 was -64% in the 1% GPB group (Axhidrox), compared with -29% in the placebo group, thus the primary effiacy endpoint of the study was met. The difference compared with placebo is assessed of clinical relevance and a favourable effect of the product.

The results for the key secondary endpoints assessing patient reported outcome scores using the HDSS score and the HidroQoL total score approached statistical significance ($p = 0.0542$) in favor of the 1% GPB cream (Axhidrox) in the HDSS score, or reached statistical significance in the HidroQoL total score ($p < 0.0001$).

The Interim analysis I performed after 12 weeks of treatment (four weeks daily product administration followed by 8 weeks with treatment as needed but not less than twice a week) demonstrated a relative change in total sweat production from baseline of 68.7% ($p<0.0001$).

The secondary endpoints were met for the first and second key efficacy endpoint (HDSS responders at Week 12 and 28). For the third key secondary endpoint assessing absolute changes in the HidroQoL total score and in the 2 domains thereof at Week 12 the results were statistically significant. The excessive perspiration experienced by patients with primary axillary hyperhidrosis is subjectively experienced. Therefore, the obtained efficacy in patient reported outcome is of favor of the product proposed for marketing.

The treatment regimen in Phase 3a was identical to the regimen in the first 4 weeks of Phase 3b i.e. once daily treatment with the 1% GPB cream (Axhidrox) which allowed a comparison of efficacy results for this time window. Overall, the results were very similar for Phase 3a and Phase 3b which confirms the reproducibility of the obtained results.

A post-hoc subgroup analyses were conducted based on data from Phase 3a and Phase 3b. Overall, the results indicate that 1% GPB cream (Axhidrox) is effective in both sexes and all age groups investigated (18-65 years of age).

Uncertainties and limitations about favourable effects

Although there are efficacy data available from the Interim analysis I and II, the Phase 3 study Hyp1-18/2016 is still ongoing. The results should be submitted when finalised, as a post approval commitment in the form of a Type II variation after completion of the MAA procedure. **(Commitment)**

After unblinding and analysis, it was noted that in 12 patients wrong or no values were entered for the pre- or post-procedure weight of glass vessel and filter papers and 1 patient was erroneously entered as not eligible. These errors were corrected, and the database was locked again. A sensitivity analysis using the original data base shows consistent results with the primary analysis presented.

Unfavourable effects

Available data suggests low systemic absorption of topical 1% GPB cream (Axhidrox). The safety profile of 1% GPB cream Axhidrox is dominated by adverse events in line with anticholinergic effects, mainly in the facial area such as e g dry mouth and dry eye/ocular hyperemia, and of local skin reactions. Dry mouth was the most frequent related TEAE, reported at an overall frequency of 17.2 % for 1% GPB cream (Axhidrox) treated vs 4.8 % for the placebo treated in the placebo-controlled part of the pivotal Phase 3 study. The most common application site reaction was erythema. However, in the Phase 3 study through 6-12 months, most patients (95 % - 97 %) showed no signs of irritation at the treated area between weeks 8 and 52. Twelve SAEs in 11 patients were reported from the clinical

studies. All were considered not drug-related except on case of unequal pupils with recovery. There were no deaths reported.

Long-term exposure of one year has been investigated in 100 patients. In general, the safety profile seems comparable in the short term and long-term perspective although the number of any TEAEs is increasing by week 28 and through week 52. If considering TEAEs evaluated as drug related there is only a slight increase in the number over time. The extent of exposure in adults is considered satisfactory. Furthermore, the safety profile of glycopyrronium is since previously rather well characterised, considering that a number of glycopyrronium products, including parenteral, oral, or inhalational formulations are approved within EU and have been used for several years in various indications in both adults and children.

Uncertainties and limitations about the unfavourable effects

The mechanism of suspected anticholinergic adverse effects has not been fully elucidated. Based on the stated low systemic exposure to GPB when applying 1 % GPB cream (Axhidrox), and that many of the adverse reactions in line with anticholinergic were observed in the facial area, the Applicant pointed out that the ADR dry mouth may be partly due to contamination and partly due to systemic exposure. Furthermore, a systemic adverse event such as e g urinary retention, has not been reported for 1% GPB cream (Axhidrox), in contrary to other GPB products with higher systemic exposure. It is therefore not unreasonable to assume that the facial (including eye) adverse events of suspected anticholinergic origin may at least partly be due to contamination. Furthermore, it cannot be excluded that there may be a risk of misuse by applying the 1 % GPB cream (Axhidrox) on other areas of the body where sweating may occur, and a risk of potential overdose. In addition, an increased risk of dental caries on a long-term basis cannot be excluded as a consequence of the very common adverse reaction of dry mouth and reduced salivation. The labelling with instructions and cautionary measures in order to minimise the risk of contamination, misuse and advice on careful dental hygiene and dental health checks are considered satisfactory.

Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects

A significantly superior efficacy for 1% GPB cream (Axhidrox) compared with vehicle cream was demonstrated for the primary endpoint in the pivotal Phase 3 study Hyp1-18/2016. The key secondary efficacy endpoints and other endpoints supported the efficacy of Axhidrox. The magnitude of efficacy demonstrated in the study is in the same range as for other topical products containing an anticholinergic agent approved for topical treatment of axillary hyperhidrosis and is considered of importance.

Axhidrox is applied topically to each armpit; once daily during the first 4 weeks and from the 5th week on, the frequency of application can be reduced to twice a week, depending on the response to treatment. Overall, adverse events are as could be expected and dominated by adverse events in line with anticholinergic effects, mainly in the facial area such as e g dry mouth and dry eye/ocular hyperemia, and of local skin reactions in the drug administration area. Twelve SAEs in 11 patients were reported from the clinical studies. All were considered not drug-related except on case of unequal pupils with recovery. There were no deaths reported.

Balance of benefit and risks

The efficacy results are considered robust and convincing and of clinical relevance to patients with axillary hyperhidrosis. There are some uncertainties regarding long-term efficacy since Phase 3b part of study Hyp1-18/2016 is ongoing.

The safety profile involves mainly adverse events in line with anticholinergic effects, such as dry mouth and dry eye/ocular hyperemia, and of local skin reactions in the drug administration area.

Overall, the efficacy and safety documentation presented for 1 % GPB cream (Axhidrox) is considered adequate.

Conclusions

The benefit/risk of this product is positive. Axhidrox (1% GPB cream) is recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

Post approval commitments

Description	Due date
The Phase 3b part of study Hyp1-18/2016 is still ongoing. It is anticipated that the final study report will be available in late April 2022. The results of the study should be submitted when finalised, as a post approval commitment in the form of a Type II variation after completion of the MAA procedure.	2022
Additional ERA studies will be performed and submitted as a Type II variation.	Q2 2024

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Axhidrox, 2.2 mg/pump actuation, cream was positively finalised on 2022-03-10.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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