19 September 2024
EMA/CHMP/498424/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

BUCCOLAM

International non-proprietary name: Midazolam

Procedure No. EMEA/H/C/002267/II/0061

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Neuraxpharm Pharmaceuticals S.L. submitted to the European Medicines Agency on 11 January 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include treatment of adults to Buccolam 10 mg, based on the results from study LESVIBUCCO/23/BQ-3. This is an Interventional Study, Relative Bioavailability to investigate the pharmacokinetics of a single dose of midazolam oromucosal solution (Buccolam) compared to midazolam solution for intramuscular injection (Hypnovel) in healthy volunteers under fasting conditions. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2, 6.5 and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 8.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 24/01/2022 on the clinical development program in adults (EMA/SA/0000080737).

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Mol Co-Rapporteur: Alexandre Moreau

Timetable	Actual dates
Submission date	11 January 2024
Start of procedure:	27 January 2024
CHMP Rapporteur Assessment Report	26 March 2024
PRAC Rapporteur Assessment Report	26 March 2024
CHMP Co-Rapporteur Assessment	8 April 2024
PRAC Outcome	11 April 2024
CHMP members comments	15 April 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 April 2024
Request for supplementary information (RSI)	25 April 2024
MAH responses to RSI	22 July 2024
CHMP Rapporteur Assessment Report	21 August 2024
PRAC Rapporteur Assessment Report	21 August 2024
PRAC Outcome	5 September 2024
CHMP members comments	9 September 2024
Updated CHMP Rapporteur Assessment Report	16 September 2024
Opinion	19 September 2024

2. Scientific discussion

2.1. Introduction

Buccolam (midazolam hydrochloride) is an oromucosal solution in a prefilled syringe that is indicated for the treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years). It was first approved on 5 September 2011 as a paediatric use marketing authorisation only (PUMA) under Article 30 of Regulation (EC) no. 1901/2006.

The scope of this variation is the extension of the indication to include the treatment of prolonged, acute, convulsive seizures in adults.

2.1.1. About the product

Midazolam is a derivative of the imidazobenzodiazepine group. Its mechanism of action is similar to other benzodiazepines. Midazolam has an anticonvulsant effect, a hypno-sedative effect, and an anxiolytic and muscle-relaxant effect. Midazolam's effects are mediated by enhancement of gamma-aminobutyric acid (GABA) neurotransmission in limbic, thalamic and hypothalamic regions of the central nervous system (CNS). The anticonvulsant activity of midazolam is mediated by inhibition of the spread of seizure activity. Effects of midazolam resolve rapidly due to fast metabolic transformation.

2.1.2. The development programme/compliance with CHMP guidance/scientific advice

The MAH received Scientific Advice from the CHMP on 24/01/2022 on the clinical development program in adults. The advice mainly concerned the acceptability of the extrapolation approach for the indication of prolonged acute convulsive seizures in adults, the validity of the underlying population PK model to define the optimal dose, the adequacy of the extrapolation approach for the indication of pre-hospital seizure cessation for adults in status epilepticus.

The CHMP considered that to support extrapolation of efficacy obtained with Buccolam in children to adults with prolonged, acute, convulsive seizures, the dose-exposure-response relationship of midazolam needs to be well-characterised before an extrapolation based on PK (exposure) can be accepted. In addition, several issues were identified with the M&S analysis as proposed by the Applicant that needed to be addressed before the proposal can be considered acceptable.

The strategy to support a claim of an adult indication for prehospital seizure cessation for subjects in status epilepticus was considered too simplistic and required further development and discussion before an extrapolation approach for a broad "pre-hospital treatment of SE" indication can be acceptable.

Based on the provided documentation, it appears that extrapolation of efficacy from children to adults based on PK is not used to support the extension of the indication.

2.1. Non-clinical aspects.

No new clinical data have been submitted in this application.

2.1.1. Ecotoxicity/environmental risk assessment

Based on the exclusive emergency use of Buccolam for prolonged, acute, convulsive seizures, the MAH provided a justification that no Environment Risk Assessment is needed. The CHMP is in agreement.

2.1.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2. Clinical aspects

2.2.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.2.2. Pharmacokinetics

2.2.3. Introduction

One new clinical study has been performed for this extension of indication. Study **LESVIBUCCO/23/BQ-3** is a comparative bioavailability, single-centre, single-dose, open-label, laboratory-blinded, randomised, two-sequence, two-treatment, two-period crossover study (n = 22) of Midazolam Oromucosal Solution 15 mg (Buccolam® 7.5 mg/1.5 mL) versus Midazolam Solution for Injection 10 mg (Hypnovel® 10 mg/2 mL) in healthy adult subjects under fasting conditions. In addition, the safety and tolerability of midazolam oromucosal solution compared to midazolam IM injection were assessed in healthy volunteers; and the effect of age and BMI on the PKs of midazolam were investigated.

2.2.4. Pharmacokinetics

The pharmacokinetic data presented in this procedure are limited to data that support the Extension of indication for Buccolam®, midazolam hydrochloride oromucosal solution (MHOS) formulation at the strengths of 2.5, 5, 7.5 and 10 mg (Applicant: Neuraxpharm Pharmaceuticals, S.L.)., to include treatment of prolonged, acute, convulsive seizures (PACS) in adults.

The paediatric indication was supported by a literature search and review investigating efficacy and safety of buccally administered midazolam in paediatric patients as well as through a single-dose PK and population pharmacokinetic (popPK) study (**MID001**), an *in silico* simulation study (**Simcyp Report 2009**), a phase 3 study in Japanese paediatric patients with convulsive SE (CSE) in the hospital and community setting (**SHP615-301** and **SHP615-302**), and a popPK analysis using data from studies **MID001** and **SHP615-301**.

For the adult indication, following EMA Scientific Advice, two studies were performed to support the application, a relative bioavailability (RBA) study of Buccolam® versus Hypnovel® in healthy adult volunteers (**LESVIBUCCO/23/BQ-3**) and a PopPK modelling study for midazolam and 1-hydroxymidaozlam using data from study **LESVIBUCCO/23/BQ-3**.

The proposed posology in adults is 10 mg as a single dose and is similar to the highest approved paediatric dose recommended in children aged 10 years < 18 years old.

Study **MID001** was an open-label, single-dose, sparse sampling PK modelling study (n = 53) in which oromucosal midazolam (0.2 mg/kg) was administered to children from 3 months to less than 18 years undergoing routine elective surgery to determine the single-dose PK profile of the proposed formulation and generate additional safety information to the current profile for buccal midazolam use in children. Since sparse PK sampling was applied, a popPK approach was applied to fit individual data simultaneously using a non-linear mixed effect modelling approach (NONMEM) and to calculate post hoc kinetic parameters.

Study **LESVIBUCCO/23/BQ-3** is a relative bioavailability (RBA), single-centre, single-dose, open-label, laboratory-blinded, randomised, two-sequence, two-treatment, two-period crossover study (n = 22) of Midazolam Oromucosal Solution 15 mg (Buccolam® 7.5 mg/1.5 mL) versus Midazolam Solution for Injection 10 mg (Hypnovel® 10 mg/2 mL) in healthy adult subjects under fasting conditions. In addition, the safety and tolerability of midazolam oromucosal solution compared to midazolam IM injection were assessed in healthy volunteers; and the effect of age and BMI on the PKs of midazolam were investigated.

The obtained PK data from study **LESVIBUCCO/23/BQ-3** were further analysed in a subsequent PopPK modelling and simulation exercise to support an adult posology for Buccolam® based on extrapolation from the efficacy demonstrated in children. The PK metrics (AUC and C_{max}) of the paediatric population were extracted from the simulations of the Buccolam® popPK model in paediatrics for the **MID001** clinical trial. This analysis is extensively discussed below.

2.2.4.1. Clinical Study LESVIBUCCO/23/BQ-3

Study population, treatment and design

23 adult subjects (16 women and 7 men, aged 18-68 years, BMI 23.2-31.8)) were admitted to randomization and received at least one dose of investigational product. Two subjects prematurely discontinued after first dosing (test n=1, reference n=1) due to treatment-emergent adverse event (TEAE). Hence, 21 subjects that received both test and reference products constitute the comparative bioavailability analysis population.

Test product (Buccolam® 15 mg (7.5 mg/1.5 mL) oromucosal solution) was administered directly in the buccal cavity (space between the gum and the cheek), using a 1.5 mL syringe. Reference product (Hypnovel® 10 mg (10mg/2mL) solution for injection) was administered as an intramuscular injection in the mid-outer thigh. Subjects received both investigational products following an overnight fasting of at least 10 hours.

In each study period, 19 venous blood samples (volume of 6 mL each) were scheduled at pre-dose (t=0h), and from 2 minutes to 24 hours post-dose, and were taken preferably via an indwelling cannula placed in a vein of an upper limb of the subject.

Bioanalytical methods

Samples were analysed at BioPharma Services Inc. (Toronto, Canada) to determine midazolam and 1-hydroxymidazolam in human plasma. The LC-MS/MS method was validated for midazolam and 1-hydroxymidazolam over a concentration range of 1 to 250ng/mL and 0.5 to 125ng/mL, respectively, using a sample aliquot volume of 100µL.

The mean intra-run precision for midazolam was between 1.8% and 6.3% and the mean intra-run accuracy was between 95% to 99.3%. The inter-run precision was between 2.6% and 7.4% and the inter-run accuracy was between 98.4% and 102.0%.

The mean intra-run precision for 1-hydroxymidazolam was between 1.3% to 5.3% and the mean intra-run accuracy was between 94.5% and 102.0% The inter-run precision was between 3.3% and 6.2% and the inter-run accuracy was between 96.1% to 104.0%.

Midazolam and 1-hydroxymidazolam and internal standards were stable in methanol for 99 days at -20°C $\pm$ 5°C.

A total of 836 midazolam study samples were analyzed in 7 runs, with no failed runs. Furthermore, a total of 3 samples were reanalyzed, two as they were above the upper limit of quantitation and one due to event investigation of an unusual value. 116 samples were used for incurred sample reanalysis where 93.97% of the samples in the evaluation demonstrated a percent difference within ±20.0%, thus meeting the acceptance criteria.

A total of 836 1-hydroxymidazolam study samples were analyzed in 6 runs, with no failed runs. Furthermore, a total of 1 sample was reanalyzed, due to event investigation of an unusual value. 116 samples were used for incurred sample reanalysis where 91.38% of the samples in the evaluation demonstrated a percent difference within ±20.0%, thus meeting the acceptance criteria.

Pharmacokinetic and statistical analysis

The pharmacokinetic endpoints were determined using non-compartmental analysis (NCA) with the use of Phoenix® WinNonlin ® software version 8.3 (Certara USA Inc., Princeton, NJ).

The pharmacokinetic parameters for both midazolam and 1-hydroxymidazolam were regular and dose-normalized C_{max}, AUC_{0-t}, AUC_{0-inf}, $\%AUC_{\%extrapol\_obs}$, apparent first-order elimination rate constant (λ_z), $t_{1/2}$, CL/F, and V_D/F. No values of λ_z, AUC_{0-inf}, $\%AUC_{\%extrapol\_obs}$, and $t_{1/2}$ were reported for cases where λ_z could not be reliably determined.

C_{max} and AUC_{0-t} were considered primary pharmacokinetic parameters for compartive bioavailability analysis. AUC_{0-inf} , and dose-normalized C_{max}, AUC_{0-t} and AUC_{0-inf} were secondary pharmacokinetic parameters.

In estimating the pharmacokinetic parameters, concentrations below the LLOQ, before t_{max}, were set to zero. After t_{max}, concentrations below the LLOQ were considered as missing. However, in case of two consecutive concentrations below the LLOQ, the first value was replaced by ½ of the LLOQ value, and the next values were considered as missing.

Estimation of the comparative bioavailability analysis was conducted on Phoenix® WinNonlin® 8.3 (Certara USA Inc., Princeton, NJ). All other statistical analyses were conducted on SAS® 9.4. For midazolam and 1-hydroxymidazolam an ANOVA was performed on the ln-transformed data of primary and secondary PK parameters obtained from 21 subjects. Proc GLM was applied, using Sequence, Subject nested within Sequence, Period and Formulation as fixed effects, assessed at a 5% significance level (α= 0.05).

For each comparison, the intrasubject coefficient of variation (ISCV%) was estimated for the primary and secondary pharmacokinetic parameters. With ISCV >30% to establish bioequivalence, the 90% Confidence Interval (CI) for the ratio (Test/Reference) of Least Square Means of the log transformed PK parameter (C_{max}) might be widened.

Results

Mean plasma concentration-time profiles obtained in study LESVIBUCCO/23/BQ-3 are shown in **Figure 1**. Pharmacokinetic parameters and summary statistics are presented in **Table 1** and **Table 2** for midazolam and **Table 3** and **Table 4** for 1-hydroxymidazolam.

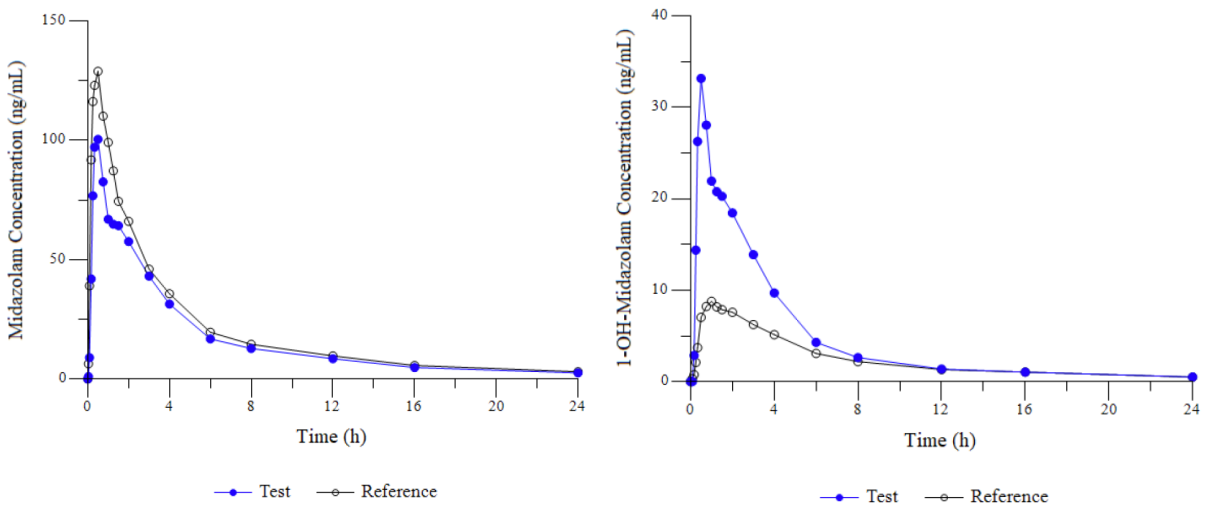

Figure 1 Arithmetic means of midazolam (left) and 1-hydroxymidazolam (right) plasma concentration versus time profiles following administration of Buccolam® (Test) and Hypnovel® (Reference) (n=22)

Table 1 Pharmacokinetic parameter data for midazolam (n=22) in study LESVIBUCCO/23/BQ-3

		Arithmetic means (±SD)	
Pharmacokinetic parameter		**Test product n[1] = 22**	**Reference product n[1] = 22**
$AUC_{(0-t)}$	**ng.h/ml**	392.50±87.08	474.27±104.82
$AUC_{(0-\infty)}$	**ng.h/ml**	420.76±103.76	509.40±122.87
C_{max}	**ng/ml**	130.85±53.19	142.95±38.32
t_{max}[2]	**h**	0.50 (0.25-3.00)	0.42 (0.08-1.50)

[1] "n" stands for number of subjects.
[2] t_{max} values presented correspond to the median values. Minimum and Maximum values are presented between brackets.

Table 2 Bioequivalence evaluation of midazolam (n=21) in study LESVIBUCCO/23/BQ-3

Pharmacokinetic parameter	**Test-to-Reference Geometric Mean Ratio (%)**	**90% Confidence Interval**	**Intra-Subject Coefficient of Variation (%)**
$AUC_{(0-t)}$	82.04	76.30 - 88.21	13.6
C_{max}	86.23	70.63 - 105.28	38.7

Table 3 Pharmacokinetic parameter data for 1-hydroxymidazolam (n=22) in study LESVIBUCCO/23/BQ-3

		Arithmetic means (±SD)	
Pharmacokinetic parameter		**Test product n[1] = 22**	**Reference product n[1] = 22**
$AUC_{(0-t)}$	**ng.h/ml**	106.61±37.84	55.28±16.98
$AUC_{(0-\infty)}$	**ng.h/ml**	117.03±38.53#	67.59±20.46#
C_{max}	**ng/ml**	45.78±27.08	9.81±4.18
t_{max}[2]	**h**	0.75 (0.33-3.00)	1.00 (0.25-3.00)

1 "n" stands for number of subjects.
2 tmax values presented correspond to the median values. Minimum and Maximum values are presented between brackets.
For AUC0-∞, n=21 for Test product and n=20 for Reference product.

Table 4 Bioequivalence evaluation of 1-hydroxymidazolam (n=21) in study LESVIBUCCO/23/BQ-3

Pharmacokinetic parameter	**Test-to-Reference Geometric Mean Ratio (%)**	**90% Confidence Interval**	**Intra-Subject Coefficient of Variation (%)**
$AUC_{(0-t)}$	189.77	174.28 - 206.64	16.0
C_{max}	420.17	334.32 - 528.08	44.8

In conclusion, comparable bioavailability between 15 mg Test product (Buccolam® 7.5 mg/1.5 ml oromucosal solution by Laboratorios Lesvi, S.L.) and 10 mg Reference product (Hypnovel® 10 mg/2 ml solution for injection from Cheplapharm Arzneimittel GmbH) cannot be concluded for the rate and extent of midazolam absorption, following a single dose administration under fasting conditions. However, the obtained PK data were further analysed in a subsequent PopPK modelling and simulation exercise performed by the Applicant in support of the current variation application.

The Applicant has updated the SmPC section 5.2. Pharmacokinetic properties with adult data from study **LESVIBUCCO/23/BQ-3** as follows:

Simulated pharmacokinetic parameters for the recommended posology in children aged 3 months to less than 18 years, based on a population pharmacokinetic study, as well as pharmacokinetic parameters for the recommended posology in adults, based on a bioavailability study in healthy adult subjects, are provided in tabulated format below.

Dose	Age	Parameter	Mean	SD
2.5 mg	3 m < 1 yr	$AUC_{0\text{-}inf}$ (ng.h/ml)	168	98
		C_{max} (ng/ml)	104	46
5 mg	1 yr < 5 yrs	$AUC_{0\text{-}inf}$ (ng.h/ml)	242	116
		C_{max} (ng/ml)	148	62
7.5 mg	5 yrs <10 yrs	$AUC_{0\text{-}inf}$ (ng.h/ml)	254	136
		C_{max} (ng/ml)	140	60
10 mg	10 yrs < 18 yrs	$AUC_{0\text{-}inf}$ (ng.h/ml)	189	96
		C_{max} (ng/ml)	87	44
10 mg	> 18 yrs	AUC0-inf (ng.h/ml) (n=22)	420.76	104
		Cmax (ng/ml) (n=22)	130.85	53

Simulated pharmacokinetic parameters for the recommended posology in adults, based on a pharmacokinetic study, suggested that the dose of 10 mg in all adults lead to similar exposure to that of all pediatrics age groups at their corresponding therapeutic doses.

2.2.4.2. Population pharmacokinetic analysis

Objective

The popPK modelling study for midazolam and 1-hydroxymidazolam using data from study **LESVIBUCCO/23/BQ-3** was performed for adult dose definition. The objectives of this Buccolam® PK model-based adult dose definition study were as follows:

I. To develop a popPK model for Buccolam® in adults with data from a Phase I study (**LESVIBUCCO/23/BQ-3**) after buccal administration of 15 mg.

II. To apply stochastic simulations to support the product posology in adult and elderly patients based on comparison of the effective exposures of midazolam in adults and children.

Data – Population pharmacokinetic model

Parent drug and metabolite data from study **LESVIBUCCO/23/BQ-3** of the test formulation (Buccolam®) were used to develop a pharmacokinetic model that explains the behaviour of midazolam and its metabolite 1-hydroxymidazolam in plasma after the administration of Buccolam® 15 mg in adults.

A total of 22 subjects from the pharmacokinetic analysis population have evaluable pharmacokinetic data in the test formulation period. Subjects were 72.2% female, had a median age of 32 years

(ranging from 18 to 68) and had a bodyweight range from 61 to 92.3 kg. 4 of these subjects were elderly ≥ 60 years of which 3 ≥ 65 years, and 7 obese (BMI>29) subjects. In these patients for both midazolam and 1-hdyroxymidazolam, 418 observations were eligible for inclusion in the population pharmacokinetic model. A total of 41 observations (9.8%) were reported as below the lower limit of quantification, including 22 pre-dose levels. Concentrations were expressed in nanomoles per Liter (nmol/L) for the joint modelling of midazolam and 1-hydroxymidazolam; molecular weights were 325.78 and 341.8 g/mol, respectively. The lower limit of quantification (LLOQ) were 1.0 ng/mL and 0.5 ng/mL, respectively.

Methods – Population pharmacokinetic model

NONMEM (version 7.4.4, Icon Plc, Dublin, Ireland) was used for PK model development using first-order conditional estimation with interaction (FOCE-INTER) to estimate the parameters. Other supportive software used for data management, graphics, metadata handling and plotting were R (version 4.3.0; www.r-project.org, running under Rstudio interface) and Perl-Speaks-NONMEM v5.3.1.

A joint popPK model was developed to explain the PK behaviour of midazolam (parent) and 1-hydroxymidazolam (metabolite) after administration of Buccolam® 15 mg in adults. A two-compartment PK model with two different absorption processes, buccal and gastrointestinal (GI), was developed in a first step for the parent drug. A one-compartment model was selected to determine a base model for the metabolite. In the joint model, the fraction metabolised was fixed to 0.7 to avoid identifiability issues and the volume of distribution of 1-hydroxymidazolam was estimated. During the development of the parent-metabolite model, the PK parameters for midazolam absorption and disposition were fixed for each subject to their individual post-hoc estimates derived using the best-fit midazolam covariate model. The general structure of the model is represented in **Figure 2**.

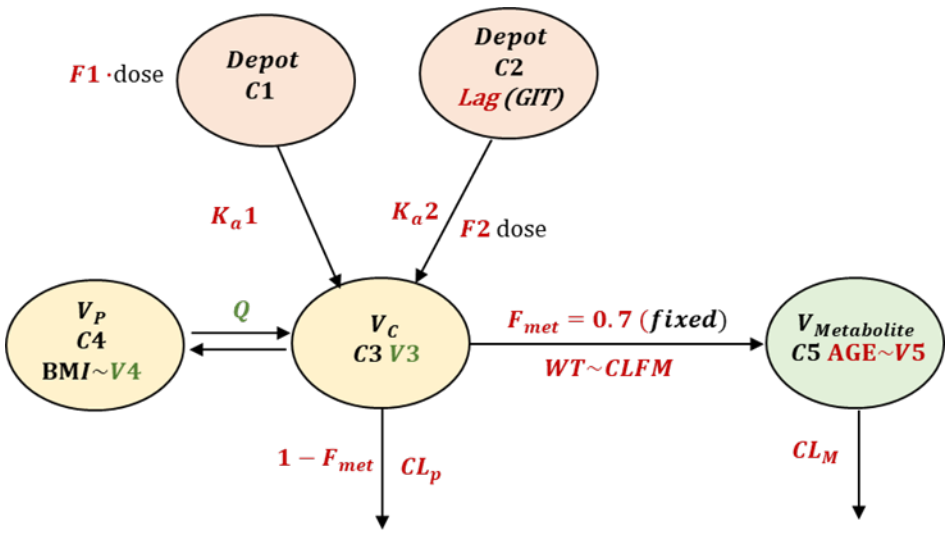

Figure 2 PK model structure for midazolam and alpha-1-hydroxymidazolam for Buccolam®.

Inter-individual variability on CL_P/F, V3, and Q were estimated for the parent, and V5 and CLFM/F for the metabolite and assumed to be log-normally distributed. The inclusion of first pass metabolite formation did not produce any improvement of the model. For the residual variability, a proportional error model was considered best for both parent and metabolite.

The relationship between patient specific covariates and PK model parameters was also incorporated into the model using a forward addition (P<0.05) and backward elimination (P<0.01) approach based on clinical relevance and plausibility. BMI was identified as significant covariate on the peripheral volume of distribution (V_P), body weight on the formation CL of the metabolite (CLFM/F) and age on

the metabolite volume of distribution (V_d). The metabolite model was included in the analysis with the objective of covariates evaluation. However, even when age was a significant covariate on the V_d of the metabolite, the impact on exposure was not significantly relevant and thus, no differences in the metabolite exposure of elderly subjects are expected with respect to younger adult subjects.

After qualification of the final joint popPK model, the robustness of the model and the accuracy of parameter estimates (SE computation) were assessed using a bootstrap method. From the original dataset, 500 bootstrap sets were drawn with replacement (re-sampling technique). For each of the 500 bootstrap sets, the population PK parameters were calculated. With the 500 estimates of each population PK parameter, the corresponding mean, median, standard deviation, 5th, 50th and 95th percentiles were calculated using PsN. The successful estimation accounted for 60% of 500 bootstrap replicates, and all results were used for summary statistics. Relative error of bootstrap mean to original mean of each parameter was acceptable. The centers of distribution are generally comparable to the original mean values of final model. These results suggest that the accuracy and robustness of the parameters estimated with the final parent and parent-metabolite model are generally acceptable.

Results – Population pharmacokinetic model

Table 5 summarizes the model parameters estimates of fixed effects with their corresponding relative standard error (RSE; %) for the final joint parent-metabolite model.

Table 5 Final joint popPK model parameters results.

Parameter	Estimate	RSE (%)	Parameter	Estimate	RSE (%)
KA1 (1/h)	0.51	15.0	-	-	-
KA2 (1/h)	8.80	5.1	-	-	-
CLP/F (L/h)	85.80	12.8	**ωCLP/F (L/h)**	0.10	68.0
FRAC	2.96	10.9	-	-	-
ALAG2 (h)	0.15	3.6	-	-	-
FMET	0.70 (FIX)	0.0	-	-	-
CLM/F (L/h)	43.80	5.5	-	-	-
V3 (L)	40.20	30.8	**ωV3 (L)**	0.37	68.8
V4 (L)	177.00	13.7	-	-	-
Q (L/h)	25.80	34.3	**ωQ (L/h)**	0.55	59.1
V5 (L)	6.38	18.5	**ωV5 (L)**	0.85	78.5
CLFM/F (L/h)	16.20	5.5	**ωCLFM/F (L/h)**	0.06	52.7
BMI ~ V4	2.45	60.0	-	-	-
AGE ~ V5	-0.84	53.6	-	-	-
WT ~ CLFM	-0.26	23.0	-	-	-
σ_parent	0.0805				
σ_metabolite	0.17				

The goodness-of-fit (GOF) plots (DV vs. (I)PRED, CWRES vs. PRED, CWRES vs. TIME, IWRES vs. IPRED) showed that the predicted concentrations correlated well with observed concentrations, and weighted-residual errors were distributed randomly around zero, suggesting that the final population pharmacokinetic model fitted concentration–time data well. No peculiarities were seen, hence no GOF plots are enclosed in this assessment report.

Visual predictive check was performed for the final model generated based on the dataset, simulating 500 subjects based on the structure of the original data and portrayed as mean and 90% CI (**Figure 3**). The data indicated the final model was effective to represent the disposition of parent and metabolite concentrations in plasma.

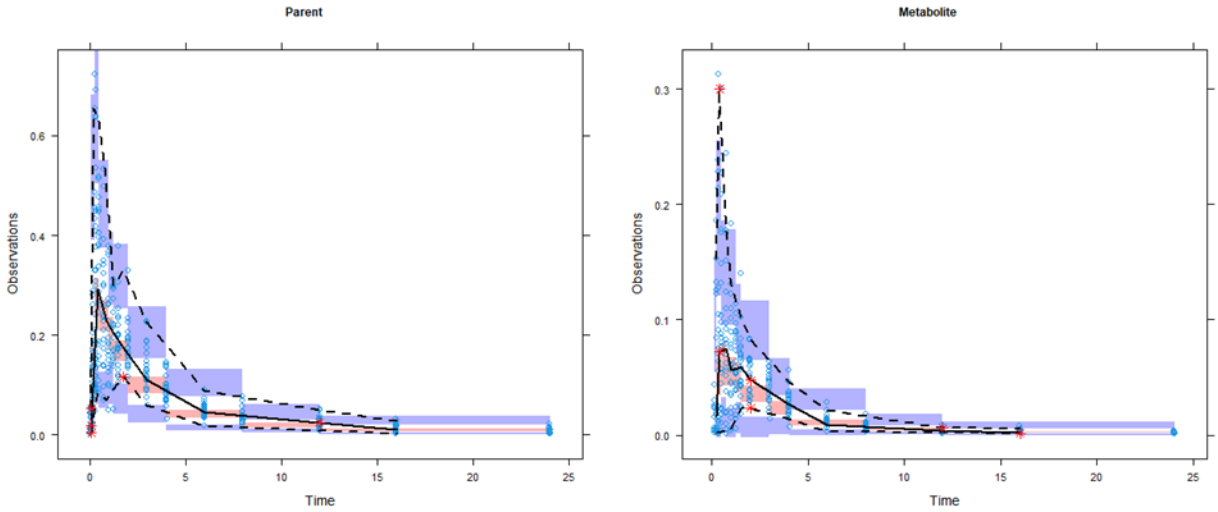

Figure 3 Visual predictive check from N=500 simulated data from the original dataset (n=22). Open circles, observed concentrations; solid black line, median; lower and upper dashed lines, 5th and 95th percentiles of the 500 simulated data, respectively; shaded areas, 95% confidence intervals for simulated predicted median (purple), 5th percentile (blue) and 95th percentile (blue) constructed from 500 simulated datasets of subjects from the original dataset.

In general, diagnostic plots did not reveal any model misspecification and estimated parameters were physiologically plausible. The model captured the central tendency of the data well and was deemed suitable to generate simulations.

Exposure comparison to paediatric data

The final popPK model was used to simulate midazolam exposure in adults after 10 and 15 mg and compared with midazolam exposures of Buccolam® in paediatrics. The pharmacokinetic metrics ($AUC_{0\text{-}inf}$ and C_{max}) of the paediatric population were extracted from the simulations of the Buccolam® popPK model in paediatrics for the study **MID001**.

Study **MID001** was conducted in 50 paediatric patients (3 months - <18 years; 37 males and 13 females) who were undergoing routine surgery and required premedication with midazolam. Blood samples were taken from time zero up to 8 hours post dose or just prior to the removal of the cannula (whichever was the latest). A maximum of 4 blood samples were taken in children under 2 years old and 6 samples in children over 2 years old. Patients were administered a single dose of 0.2mg/kg of Buccolam® (up to a maximum 10mg [2mL]) by the buccal route. Simulated pharmacokinetic metrics for the recommended posology in children aged 3 months to less than 18 years are provided in **Table 6**, as also reported in Section 5.2 of the approved SmPC.

Table 6 Simulated pharmacokinetic parameters for the recommended posology in children aged 3 months to less than 18 years (study MID001)

Dose (mg)	Age	Metric	Mean	SD
2.5	3 m < 1 yr	AUC_{0_inf} (ng.h/ml)	168	98
		C_{max} (ng/ml)	104	46
5	1 yr < 5 yrs	AUC_{0_inf} (ng. h/ml)	242	116
		C_{max} (ng/ml)	148	62
7.5	5 yrs <10 yrs	AUC_{0_inf} (ng.h/ml)	2.54	136
		C_{max} (ng/ml)	140	60
10	10 yrs < 18 yrs	AUC_{0_inf} (ng.h/ml)	189	96

	C_{max} (ng/ml)	87	44

The predictions in adults were separated into three population subgroups according to the demographic characteristics, namely: elderly (age>=65), obese (BMI>29) and normal adults (age 18<65, BMI<29). The curves of plasma concentrations as a function of time after the administration of Buccolam® 15 mg are presented for adults separated according to their BMI and age with varying number of samples from n=42 to n=458. In addition, predictions were made for one administration of Buccolam® 10 mg and Buccolam® 15 mg in adults, and Buccolam® 5 mg, 7.5 mg and 10 mg in paediatrics depending on age.

The curves of plasma concentrations as a function of time for adults after the administration of Buccolam® 15 mg are shown in **Figure 4** (classified by BMI, age controlled) and **Figure 5** (classified by age, WT controlled). The results of the simulation of area under the curve of plasma concentrations versus time from time zero to infinity ($AUC_{0\text{-}inf}$) and maximum plasma concentration (C_{max}) for one administration of 10 mg and 15 mg Buccolam® are presented in **Figure 6**.

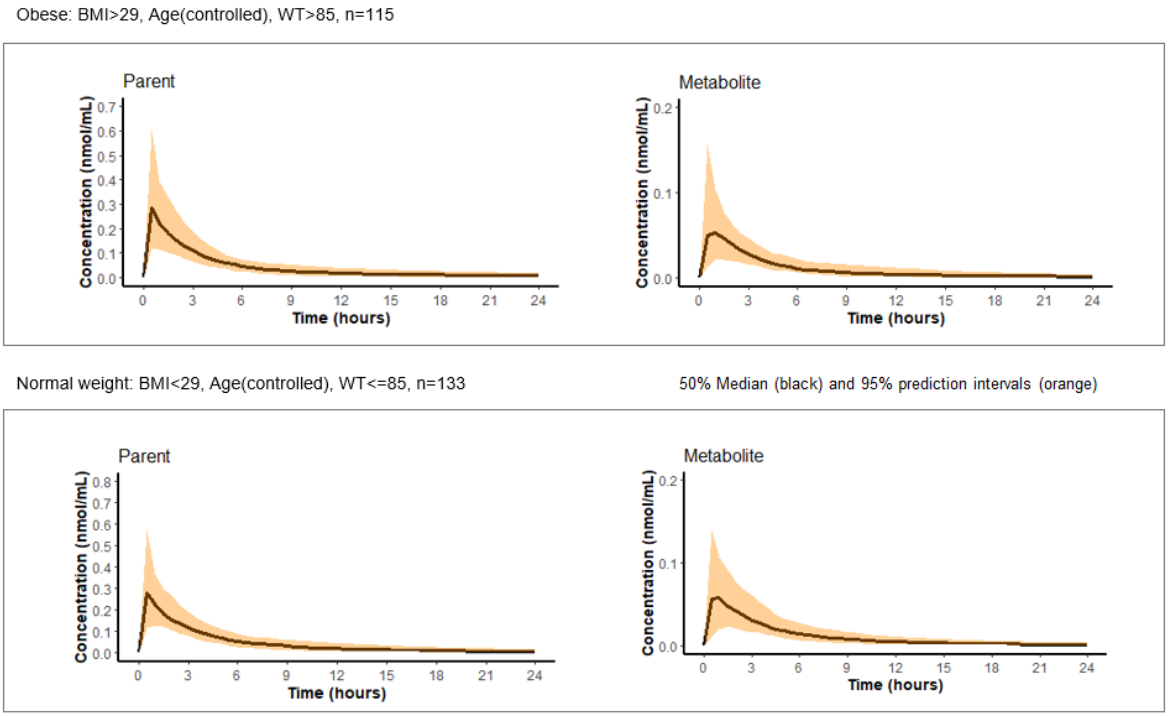

Figure 4 Buccolam® 15 mg simulations for adults separated according to their BMI (BMI<29 and BMI>29). No individual has a BMI=29.

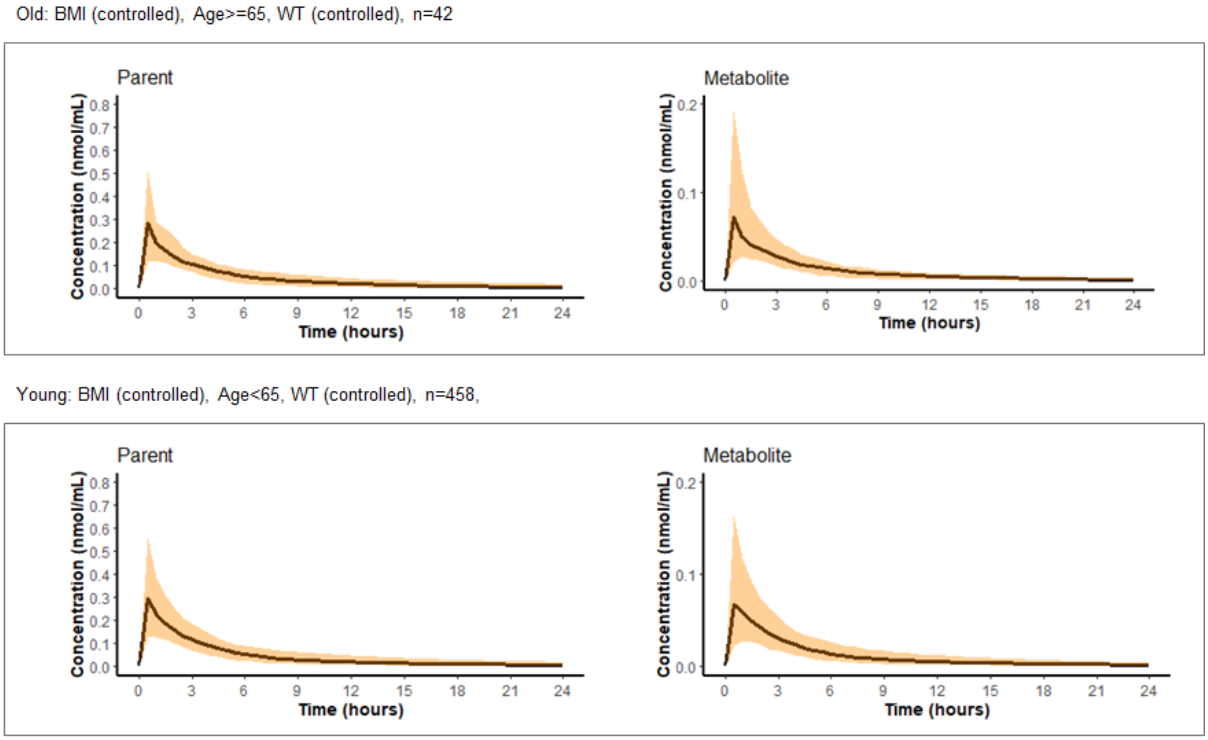

Figure 5 Buccolam® 15 mg simulations for adults separated according to their age (age<65 and age>=65).

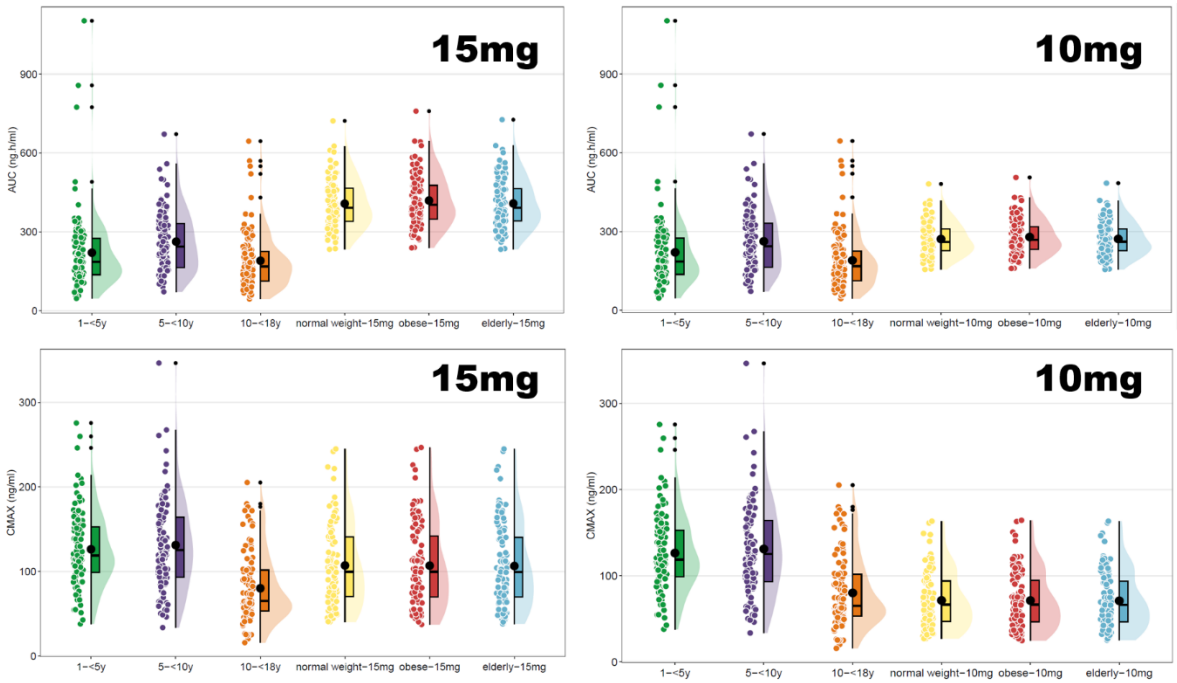

Figure 6 Buccolam® simulated AUC and C_{max} for adults and paediatric populations. Elderly (age>=65), obese (BMI>29) and normal adults (age 18<65, BMI<29).

Special populations

Obesity

According to the results of the popPK modelling study using data from study **LESVIBUCCO/23/BQ-3**, the PK following a 10 mg Buccolam® dose in adults is independent of body weight or BMI and also leads to similar $AUC_{0\text{-}inf}$ values compared to those in paediatrics when accounting for the different ages and doses, while the C_{max} was in line with that of the 10- to <18-year-olds. Hence, it can be indicated that increased weight and obesity is not expected to significantly affect buccal midazolam PKs in adults, leading to clinically significant alterations on the drug's well-known efficacy and safety profile.

Elderly

One of the objectives of the comparative bioavailability study **LESVIBUCCO/23/BQ-3** in adults conducted by the Applicant, was to characterize or confirm clearance differences in elderly subjects to support SmPC claims with respect to this population. The proposed SmPC describes elderly PK as follows: In adults over 60 years of age, the elimination half-life may be prolonged up to four times.

2.2.5. PK/PD modelling

No dedicated exposure-response modelling was performed.

The Applicant concludes in their popPK documentation (*Annex 1: Buccolam® PK model based adult dose definition)*: "The licensed dose of buccal midazolam in adolescents (10 mg) is equal to the unlicensed (off-label) adult buccal dose (10 mg), as recommended in many national clinical practice guidelines for the management of acute seizures and as reflected in the pivotal and supportive published clinical studies in adults (please refer to Module 2.5 Clinical Overview) describing the use and effectiveness of the 10-mg buccal midazolam dose to terminate seizures in adults (Nakken and Lossius, 2011; Kadel et al., 2018; Shankar et al., 2021). Overall, based on the above simulations and described considerations, the 10-mg dose is proposed as the optimal, efficacious and safe dose for Buccolam® to treat adults with PACS."

2.2.6. Extrapolation

The PK based-extrapolation approach for the indication of prolonged acute convulsive seizures in adults is acceptable. To support the extrapolation of efficacy obtained with Buccolam in children to adults with prolonged, acute, convulsive seizures, the dose-exposure-response relationship of midazolam has been characterised. The Applicant has shown that the updated popPK model is of relevance to the claimed indication (patients with prolonged seizures). New simulations have been provided in both paediatric and adult subjects. The target exposure range where efficacy and safety have been established in children 3m<10 years of age has been identified (0.431-1.714 nmol·h/mL for the total exposure of MDZ and 1-OH-MDZ (AUC0-inf)). To support the PK bridge, nine publications were discussed which compared buccal midazolam for the treatment of PACS versus rectal diazepam (6 studies), intravenous diazepam (2 studies) and intramuscular midazolam (1 study). The studies by McIntyre (2005), Mpimbaza (2008), Scott (1999), Baysun (2005) and Talukdar (2009) were considered pivotal to support the paediatric indication during the initial marketing authorisation application of Buccolam. Although these studies have several methodological flaws, it was concluded that the trials support the clinical efficacy of buccal midazolam in the treatment of acute seizures in children and adolescents irrespective of cause, with a magnitude of effect similar to standard treatments, a sufficiently rapid onset of effect and some evidence for efficacy in the prevention of recurrence of seizures up to 24 hours. The doses of buccal midazolam used in the trials align with the doses used in the PK analyses to support the target exposure in children.

Subsequently, the 10 mg dose was proposed as the optimal, efficacious, and safe dose for Buccolam to treat adults with prolonged acute convulsive seizures based on comparison with the paediatric

reference range. The modelling exercise is satisfactory to support a PK-bridge wherein the efficacy information can be extrapolated from children given buccal MDZ. Part of the extrapolation exercise is to also indicate if the disease is sufficiently similar between the age groups. Such a discussion was not provided. Although there are no indications that these types of acute seizures present differently between children and adults, a difference cannot be ruled out. However, various European guidelines recommend midazolam, albeit in various routes of administration, also for the treatment of PACS/initial status epilepticus in adults. Considering that this is an acute treatment in an emergency setting, combined with guideline recommendations, an extrapolation approach based solely on similarity in exposure can be accepted for the current product.

2.2.7. Discussion on clinical pharmacology

The Applicant has submitted a relative bioavailability (RBA) study, in which the bioavailability between 15 mg Buccolam and 10 mg Hypnovel was compared to define an adequate Buccolam posology in adults. Bioequivalence was also not to be expected upfront given the different types of formulation. The rational for this study is not clear. Presumably the Applicant anticipated the optimum dose in adults would be 15 mg, based on model-based simulations as submitted in the EMA SA. Another assumption is that the Applicant planned to bridge Buccolam in adults via Hypnovel.

Although the PK of the proposed dose of 10 mg Buccolam has not been acquired from the clinical setting, the exposure (AUC and C_{max}) can still be derived. Either from the NCA data from the clinical study by dose normalizing the mean and SD from this study (assuming dose linear PK), or alternatively based on the popPK analysis on the adult clinical data and model simulation, but then a full popPK report would be required (see EMA Guideline on reporting the results of population PK analyses, 2007). As in this case in the clinical RBA study full/dense PK sampling was performed, the NCA method and popPK method should produce similar PK exposure parameters.

Although the EMA SA stated the need for a well-characterised (or better justified) dose-exposure-response relationship of midazolam, extrapolation from children and adolescents to adults with PACS based on exposure matching was considered acceptable for an intranasal midazolam formulation (Nasolam, EMEA/H/A-29(4)/1511).

Following additional substantiation to support extrapolation of efficacy of Buccolam from children to adults with PACS, the CHMP agrees that the indication can be accepted.

2.2.8. Conclusions on clinical pharmacology

The PK-bridge for extrapolation of efficacy from children to adults based on exposure matching is considered acceptable to support the adult indication of Buccolam.

2.3. Clinical efficacy

The efficacy data to support the extension of the indication of Buccolam in adults with prolonged, acute, convulsive seizures is consists of the following data:

- Published pivotal and supportive clinical studies identified thorough a systematic review investigating the efficacy of buccal midazolam administration in the treatment of (status epilepticus (SE) and prolonged acute convulsive seizures (PACS) in adults.

2.3.1. Main study(ies)

Three bibliographic studies were identified by the MAH as pivotal. These are summarised in the following table provided by the MAH

Reference	Study design	Efficacy endpoint (s)	Patient group (sample size)/ Indication	Buccal midazolam dose	Comparator	Efficacy results/ trial conclusion	Comments
Meléndez et al. (2006)	Not stated (Spain)	Cessation of seizures within 2 min of administration	10 (aged 27-61 years; 5 men and 5 women) of the 73 adult epileptic patients who were residents in a centre for people with severe encephalopathy. Age bands, as follows: 18-30 years, n=3; 31-40 years, n=3; 41-60 years, n=3; and 61 years, n=1	5 mg (1 ml of the IV preparation)	NA	52 prolonged seizures (32 generalised tonic-clonic, 18 myoclonic and 2 atonic seizures) were treated in 10 patients enrolled in the study. The rest of the patients had seizures that lasted <1 min, thus, no emergency treatment being required and not included in the study. The treatment was effective with a single dose within 2 min in 80.7% of seizures (n=42) with 1 dose. In 19.3% of patients, a 2nd midazolam dose (n=8) or a 3rd midazolam and diazepam dose (n=2) was necessary. Conclusion: Buccal midazolam is effective in the treatment of prolonged seizures and has the advantage of being a convenient and socially acceptable dosage form.	Small sample size. No respiratory depression secondary to the treatment or bronchoaspiration were noted, given the small volume administered. None of the patients developed SE nor transferred to hospital due to complication.

Reference	Study design	Efficacy endpoint (s)	Patient group (sample size)/ Indication	Buccal midazolam dose	Comparator	Efficacy results/ trial conclusion	Comments
Nakken and Lossius (2011)	Prospective study (Norway)	Primary: cessation of seizure activity within 10 min without seizure relapse within 2 h (treatment access).	20 patients, aged 25-68 years, with CSE or non-CSE or prolonged/ serial seizures lasting >5 min, in a residential institution for adults with difficult-to-treat epilepsy, most often with additional neurological (n=5), cognitive (n=9) and/or psychiatric comorbidities (n=7)	Median (range) dose: 15.5 (10-20) mg (Epistatus®, Dales pharmaceuticals, buccal solution 10 mg/ml)	Rectal diazepam (Stesolid prefill 'Actavis', rectal solution, 5 mg/ml), when convulsive or non-convulsive seizures lasting >5 min arose	In the study period, 80 emergency situations (43 and 37 episodes in the midazolam [16 patients] and diazepam group [18 patients], respectively) occurred in 22 patients. Buccal midazolam: CSE was treated promptly, after a mean of 6.2 min, and terminated after a mean of 2.8 min. The seizure activity ceased after a mean of 7.6 min. The success rate was 74.4%. Rectal diazepam: CSE terminated after a mean of 5.0 min (n=0.012). The seizure activity ceased after a mean of 7.4 min (NS). The success rate was 83.3% (NS). The other subcategories of emergency situations were treated after a mean of 25.0 min. Conclusion: Buccal midazolam appeared to be at least as effective as rectal diazepam.	Small sample size. The difference in success rates was mostly due to slightly more seizure relapses during the first 2 h in the midazolam group. Both treatments were well-tolerated. All the nursing staff and 6/7 patients who gained experience with both treatments favoured the buccal route.

Reference	Study design	Efficacy endpoint (s)	Patient group (sample size)/ Indication	Buccal midazolam dose	Comparator	Efficacy results/ trial conclusion	Comments
Shankar et al. (2021)	Retrospective, observational, cross-sectional study (2016-2017 in 4 UK NHS secondary care outpatient clinics)	To describe the use, effectiveness and dosing of oromucosal midazolam maleate in emergency treatment of epileptic seizures in community settings.	146 adult people with epilepsy, mean ± SD age: 41.0± 15.2 years [49 subjects aged 18-30 years; 21 were 31-40 years old; 26 were 41-50; 10 were 61-70; 2 were 70+ years old] and mean ± SD weight: 64.8± 18.2 kg; 53% had intellectual disability; the majority of seizures occurred at home (n=92, 63%)	(as midazolam maleate; Epistatus®, Veriton Pharma Limited, UK) The most common initial dose was 10 mg (n=124, 84.9%), most often administered by family/ professional care givers (n=75, 48.4%) (please also see Table 1 within published article)		Generalised (tonic/clonic) seizures were recorded in most people (n=106, 72.6%). The mean ± SD times-to-seizure cessation after administration of an initial 10-mg and 5-mg dose were 5.5±4.5 min (median 5.0, IQR 2.1-5.0) and 17.9±11.8 min (19.8, 13.3-24.4), respectively. An initial dose was sufficient to achieve cessation of seizure in 82.9% (n=124) of participants, while 10 participants required additional doses (data not available for 12 remaining participants). An initial dose of 10 mg was administered in 65.5% (n=19/29) with body weights between 30 and 60 kg and in 83.3% (n=35/42) with body weights from 60 to 110 kg.	Time-to-cessation of seizure was not recorded for 71.2% (n=104) of participants. Only a minority of seizures led to ambulance callouts (n=18, 12.3%) or hospital admissions (n=13, 9%).

Abbreviations: CSE, convulsive status epilepticus; IQR, interquartile range; IV, intravenous; NA, not applicable; NHS, National Health Service; NS, not statistically significant; SD, standard deviation; SE, status epilepticus; UK, United Kingdom.

Study populations

The 3 pivotal literature studies involved a total of 196 adults with epilepsy, aged between 18 and ≥70 years, with prolonged acute seizures. The age range in the identified pivotal studies included adults within the age range from 18 to ≥70 years, with the majority of them being between 18 and 60 years old. All studies included also elderly patients, namely those aged ≥60 years. In the studies by Meléndez et al. (2006) and Shankar et al. (2021), in which specific data on the number of subjects per age band were available, 52 subjects were 18-30 years old, 24 subjects were 31-40 years old, 29 were 41-60 years old, 11 were 61-70 years old and 2 were >70 years of age. In one (Nakken and Lossius, 2011) of the 3 pivotal studies, detailed individual age data were not available and could not be retrievable, thus determining also the definition of the age bands discussed in the current review analysis.

Regarding the pathological conditions of the study participants, the clinic-residential subjects involved in the study by Meléndez et al. (2006) were epileptic adults with severe encephalopathy, occurred due to neonatal anoxia (n=3), Lennox-Gastaut (n=2) or Angelman (n=1) syndromes, postnatal meningitis (n=1), encephalitis (n=1) or unknown aetiology (n=2), also receiving antiepileptic treatment. Fifty-two prolonged seizures (32 generalised tonic-clonic, 18 myoclonic and 2 atonic seizures) were treated in 10 patients enrolled in this study. In the study by Nakken and Lossius (2011), the included clinic-residential subjects had focal epilepsy (n=20) or generalised epilepsy (n=2), with the following comorbidities: mild mental retardation (n=9), psychiatric or behavioural disorder (n=7) or cerebral palsy/other neurological deficit (n=5). In terms of the type of epileptic emergency situation, there were 23 episodes of convulsive serial seizures, 14 episodes of CSE, 23 episodes of non-convulsive serial seizures and 20 episodes of non-CSE. In the study by Shankar et al. (2021), among 146 epileptic adults, generalised tonic-clonic seizure was the most common type of seizure treatment with rescue medication (106 subjects, 72.6%). Also, 53% of the subjects had intellectual disability.

Effect on primary endpoint

The primary endpoint for 2 of the 3 pivotal studies incorporated a measure for cessation of visible signs of seizures (seizure termination) within 10 min (Nakken and Lossius, 2011) or 2 min (Meléndez et al., 2006) after administration of treatment, similar to that in the 4 identified pivotal paediatric clinical efficacy trials (Scott et al., 1999; Baysun et al., 2005; McIntyre et al., 2005; Mpimbaza et al., 2008) as well as in 6 of the identified supportive paediatric efficacy studies (Kutlu et al., 2003; Muchohi et al., 2008; Talukdar and Chakrabarty, 2009; Ashrafi et al., 2010; Tonekaboni et al., 2012; Alansari et al., 2020), in one (Nakken and Lossius, 2011) of these 2 studies, the primary endpoint further including the absence of seizure relapse within 2 h post-treatment. In the third study by Shankar et al. (2021), the objective was to describe the use, the effectiveness and dosing regimen of oromucosal midazolam in emergency treatment of epileptic seizures in commuting settings.

As summarised in the table above, overall, buccal midazolam was effective in the treatment of prolonged seizures, being a convenient and socially acceptable dosage form (Meléndez et al., 2006), as well as appearing to be at least as effective as rectal diazepam in adult patients with acute prolonged seizures (Nakken and Lossius, 2011), given at doses ranging from 5 to 20 mg. The products were also shown to be well-tolerated (Meléndez et al., 2006; Nakken and Lossius, 2011) with a similar safety profile but better acceptability than rectal diazepam (Nakken and Lossius, 2011). In addition to these results, in their study, Shankar and colleagues concluded that a 10-mg dose of oromucosal midazolam (maleate) is used most often as rescue medication for adults with epilepsy and is effective when administered in community settings (Shankar et al., 2021).

2.3.2. Supportive studies

Four bibliographic studies were marked as supportive by the MAH. These are summarised in the following table provided by the MAH

Reference	Study design	Efficacy endpoint (s)	Patient group (sample size)/ Indication	Buccal midazolam dose	Comparator	Efficacy results/ trial conclusion	Comments
Kadel et al. (2018)	Multicentre cohort study (questionnaire-based, retrospective survey conducted in Germany; real-world emergency treatment in epileptic adults)	Data accessed: emergency medication, its use, current antiepileptic drugs, healthcare resource utilisation, housing situation and quality of life.	481 adult [mean (range) age: 43.4 (18-94) years] epilepsy patients attending the epilepsy outpatient clinics of the university hospitals in Frankfurt and Marburg in 2015 (134 patients [27.9%] took prescription of an emergency medication during the last year)	Prescribed to 32 patients (23.9%); dose range of 2.5 to 10 mg (mean ± SD dose: 7.5±2.8 mg; mean dose: 10 mg)	Oral lorazepam tablets at a mean dose of 1.6±0.8 mg (65.7%; n=88 out of 134); rectal diazepam at a mean dose of 10.2±7.5 mg (17.9%, n=24), or others	The most common indications for administering the emergency medication were seizures continuing for several minutes (35.1%, n=47), but almost the same number of patients (33.6%, n=45) stated that the rescue medication was given during or after every seizure. Difficulties in administration were reported by 17 (13%) patients. Two-thirds assessed the efficacy of their emergency medication as good (50.7%, n=68) or as very good (15.7%, n=21).	Buccal midazolam was used off-label. For multivariate logistic regression analysis, aspects e.g., young age at onset, active epilepsy, structural aetiology, presence of generalised tonic-clonic seizures, past-medical history of SE and living with another person independently predicted prescription of emergency medication. Sedation was a major AE (18.7%, n=25) or moderate (29.1%; n=39) problem by a substantial number of patients.
Parenteral midazolam administration in SE							

Reference	Study design	Efficacy endpoint(s)	Patient group (sample size)/ Indication	Buccal midazolam dose	Comparator	Efficacy results/ trial conclusion	Comments
Silbergleit et al. (2012)	Double-blind, randomised, non-inferiority clinical trial: RAMPART (US)	Primary: absence of seizures at the time of arrival in the emergency department without the need for rescue therapy. Secondary: endotracheal intubation, recurrent seizures, and timing of treatment relative to the cessation of convulsive seizures.	448 subjects assigned to IM midazolam and 445 assigned to IV lorazepam, including children and adult patients with SE (total number of subjects=893, aged 0-102 years; more specifically: 0-5 years, n=61; 6-10 years, n=35; 11-20 years, n=49; 21-40 years, n=226; 41-60 years, n=338; ≥61 years, n=184	In adults and children with body weight of >40 kg: 10 mg of IM midazolam followed by IV placebo. In children with weight of 13-40 kg: 5 mg of IM midazolam	In adults and children with body weight of >40 kg: IM placebo followed by 4 mg of IV lorazepam. In children with weight of 13-40 kg: 2 mg of IV lorazepam.	At the time of arrival in the emergency department, seizures were absent without rescue therapy in 329/448 subjects (73.4%) in the IM midazolam and in 282 of 445 (63.4%) in the IV lorazepam group (absolute difference, 10 percentage points; 95% CI: 4.0-16.1; *P*<0.001 for both noninferiority and superiority). The two treatment groups were similar with respect to need for endotracheal intubation and recurrence of seizures. Among subjects whose seizures ceased before arrival in the emergency department, the median times to active treatment were 1.2 min in the IM-midazolam and 4.8 min in the IV lorazepam group, with corresponding median times from active treatment to cessation of convulsions of 3.3 minutes and 1.6 minutes.	IM route of administration; thus, supportive evidence. AE rates were similar in the two groups.

Reference	Study design	Efficacy endpoint (s)	Patient group (sample size)/ Indication	Buccal midazolam dose	Comparator	Efficacy results/ trial conclusion	Comments
						Conclusions: For subjects in SE, IM midazolam is at least as safe and effective as IV lorazepam for prehospital seizure cessation.	
Clemency et al. (2015)	Retrospective chart review of a single, large, commercial agency during a 29-month period (US)	Primary: cessation of seizure without repeat seizure during the prehospital encounter.	440 adults with epilepsy received 577 doses of diazepam or midazolam; 52% male, with a mean age of 48 (range: 18-94) years	**IM midazolam:** a total of 203 subjects received 248 doses of midazolam (2.5 mg IV/ 5 mg IM); 71 (35%) were treated with first-dose IM (5 mg).	A total of 237 subjects received 329 doses of diazepam (5 mg IV/IM), 64 (27%) were treated with first-dose IM.	Seizure stopped and did not recur in 49% of subjects after parenteral diazepam and 65% of subjects after IM midazolam (P=0.002). Diazepam and midazolam exhibited similar first dose success for IV dosing (58% vs 62%; P=0.294). Conclusion: For parenteral administration, midazolam showed superior first-dose seizure suppression.	IM route of administration; thus, supportive evidence. Age, gender, seizure history, hypoglycaemia, the presence of trauma, time-to-first administration, prehospital contact time, and frequency of IM administration were similar between groups.
Guterman et al. (2022)	Retrospective cohort study, using of the ESO Data Collaborative research dataset (US)	To examine the effectiveness of midazolam in a national out-of-hospital cohort.	7,634 out-of-hospital encounters from 657 EMS agencies; adult patients (aged ≥18 years) with an out-of-hospital diagnostic impression of	**IM midazolam** (5 or 10 mg) in 35% of the encounters	Intranasal or IV midazolam administration in 20% and 46% of the encounters	Compared with IM, intranasal midazolam increased (RD: 6.5%; 95% CI: 2.4% to 10.5%) and IV midazolam decreased (RD: -11.1%; 95% CI: -14.7% to -7.5%) the risk of rescue therapy. The differences in ventilatory support were not statistically significant (intranasal	IM route of administration; thus, supportive evidence. The instrumental variable analysis yielded similar results, except that dose was not associated with ventilatory support.

Reference	Study design	Efficacy endpoint (s)	Patient group (sample size)/ Indication	Buccal midazolam dose	Comparator	Efficacy results/ trial conclusion	Comments
			SE who received midazolam during the out-of-hospital encounter from January 1, 2019, to December 31, 2019			RD: -1.5%; 95% CI: -3.2% to 0.3%; IV RD: -0.3%; 95% CI: -1.9% to 1.2%). Higher doses were associated with a lower risk of rescue therapy (RD: -2.6%; 95% CI: -3.3% to -1.9%) and increased ventilatory support (RD: 0.4%; 95% CI: 0.1% to 0.7%). Conclusion: The route and dose of midazolam affect clinical outcomes. Compared with IM, intranasal midazolam may be less effective and IV more effective in terminating SE.	
Abbreviations: AE, adverse event; CI, confidence interval; IM, intramuscular; IV, intravenous; RAMPART, Rapid Anticonvulsant Medication Prior to Arrival Trial; RD, risk difference; SD, standard deviation; SE, status epilepticus; US, Unites States (of America).							

Study population

A total of 9,303 adult patients aged ≥18 years were involved in these studies, requiring pre-hospital administration of a BZD (including buccal or IM midazolam). A summary of the baseline characteristics of the study populations per study is presented in the table above

Effect on primary endpoint

The primary efficacy endpoint included absence of seizures at the time of arrival in the emergency department without the need for rescue therapy.

Based on the conclusions of the study by Kadel et al. (2018), the most common indications for administering the emergency medication were seizures continuing for several minutes (35.1%, n=47), but almost the same number of patients (33.6%, n=45) stated that the rescue medication was given during or after every seizure. Difficulties in administration were reported by 17 (13%) patients. Two-thirds assessed the efficacy of their emergency medication as good (50.7%, n=68) or as very good (15.7%, n=21).

In the IM midazolam supportive efficacy studies, for SE adult subjects, IM midazolam was demonstrated to be at least as effective as IV lorazepam (Silbergleit et al., 2012) and more effective than intranasal midazolam (Guterman et al., 2022) for prehospital seizure cessation, showing showed superior first-dose seizure suppression (Clemency et al., 2015).

2.3.3. Bridge to literature

Bridge to literature as provided by MAH

The qualitative and quantitative composition of the proposed formulation product is presented in Table 1. The 2.5, 5, 7.5 and 10 mg strengths are dose-proportional, in terms of the contained amounts of the active substance and the included excipients.

Table 1. Qualitative and quantitative composition of the currently applied MHOS 2.5, 5, 7.5 and 10 mg.

Component	**Quantity per syringe for MHOS**				**Function**	**Reference to Standard**
	2.5 mg	**5 mg**	**7.5 mg**	**10 mg**		
Midazolam HCl (prepared from midazolam base during formulation)	2.78 mg (2.50 mg as base)	5.56 mg (5.00 mg as base)	8.34 mg (7.50 mg as base)	11.12 mg (10.00 mg as base)	Active pharmaceutical ingredient	Ph. Eur.
Sodium Chloride*	4.018 mg	8.036 mg	12.054 mg	16.072 mg	Isotonic agent	Ph. Eur.
Hydrochloric Acid** (ml added to form midazolam salt *in situ*)	*qs* (approx. 0.0077 ml)	*qs* (approx. 0.0154 ml)	*qs* (approx. 0.0230 ml)	*qs* (approx. 0.0307 ml)	Solubilising agent and pH adjustment (to target pH 3.3)	Ph. Eur.
Sodium Hydroxide***	*qs* to target pH (3.3)				pH adjustment (when necessary)	Ph. Eur.

Component	Quantity per syringe for MHOS				Function	Reference to Standard
	2.5 mg	5 mg	7.5 mg	10 mg		
Water for Injections	to 0.5 ml	to 1.0 ml	to 1.5 ml	to 2.0 ml	Solvent	Ph. Eur.
Abbreviations: HCl, hydrochloride; Ph. Eur., European Pharmacopoeia; *qs*, quantity sufficient. * Input as Sodium chloride infusion 0.9% ** Maximum concentration ~0.2% w/w (resultant maximum molarity of 0.02 M) *** Maximum concentration ~0.02% w/w (resultant maximum molarity of 0.005 M)						

As previously indicated, the existing MHOS product consisted of a novel buccal formulation of midazolam. The product development was initially based on the composition of another originator midazolam injectable formulation, i.e. Hypnovel® ampules 10 mg/2 ml (Roche), which has been authorised worldwide for more than 20 years, and has been clinically used since then, in an off-label basis through the buccal route, for the management of paediatric PACS in both community and hospital settings. Tables 2 and 3 list the identified midazolam formulations administered buccally in published clinical efficacy and PK studies, along with the respective qualitative compositions, where available. Indeed, in the majority of the identified published clinical studies with buccal midazolam, the IV Hypnovel® (10 mg/2 ml) or the equivalent Dormicum® (5mg/ml) formulations were used. Importantly, in the 4 paediatric and 1 adult pivotal identified efficacy/safety studies with buccal midazolam, Hypnovel® 10 mg/2 ml IV formulation was the used formulation given buccally for seizure management *(Scott et al., 1999; Baysun et al., 2005; McIntyre et al., 2005; Mpimbaza et al., 2005; Meléndez et al., 2006)*, rendering Hypnovel® as the most appropriate comparator product for bridging the currently applied formulation with the scientific literature.

Table 2. Published clinical efficacy studies with buccal administration of midazolam for the management of status epilepticus in paediatric and adult patients (pivotal literature studies are indicated in bold).

References	Product used (brand name/MAH)	Composition	Comments
Baysun et al. (2005); Muchohi et al. (2008) *__Scott et al. (1999);__ Kutlu et al. (2003); **McIntyre et al. (2005); Meléndez et al. (2006); Mpimbaza et al. (2008);** Talukdar and Chakrabarty (2009);	Dormicum® 5 mg/ml solution for injection (Roche)-given through buccal route / Equivalent to Hypnovel® 10mg/2ml) solution for injection (Roche)	Sodium chloride Hydrochloric acid Sodium hydroxide Water for injections	Dormicum® seems to be the same product to Hypnovel® solution for injection (Roche); although today MAH(s) have changed in the different Member States *(EMA list of midazolam authorised products, 2023)*, it may be concluded that this product, i.e., Dormicum®/Hypnovel® in different strengths/ presentations is the initial parenteral midazolam innovator product authorised by Roche.

Alansari et al. (2020)			
Ashrafi et al. (2010); **Nakken and Lossius (2011)**; Tonekaboni et al. (2012); **Shankar et al. (2021)**	Epistatus® (midazolam maleate) buccal solution 10 mg/ml (Veriton Pharma Limited or Dales pharmaceuticals)	Ethanol Saccharin sodium Glycerol Purified water Sodium hydroxide Liquid maltitol	Epistatus® is approved as Hybrid vs Hypnovel® and has been declared bioequivalent (*in vivo*) with Hypnovel® when both are administered via the oromucosal route *(PAR Epistatus)*.
Abbreviations: BE, bioequivalence; EU, European Union; IV, intravenous; MAH, Marketing Authorisation Holder; MHOS, midazolam hydrochloride oromucosal solution; N/A, Not Applicable. *In those studies, even though brand was not clearly stated, descriptions of the formulation provided pointed the Dormicum®/ Hypnovel® formulation.			

Table 3. Published PK studies with buccal midazolam administration**.**

References	**Product used (brand name/ MAH)**	**Composition**
Alfonzo-Echeverri et al. (1990)	Versed® solution for injection (Hoffmann-La Roche) (US Brand)	
Schwagmeier et al. (1998); Kiene et al. (2019); Grass et al. (2021)	Dormicum® 5 mg/5 ml solution for injection (Roche Pharma AG, Grenzach-Wyhlen, Germany) / Equivalent to Hypnovel® 10mg/2ml) solution for injection (Roche)	Sodium chloride Hydrochloric acid Sodium hydroxide Water for injections
Muchohi et al. (2008)	Dormicum® 15 mg/3 ml solution for injection (F. Hoffmann–La Roche Ltd, Basel, Switzerland) / Equivalent to Hypnovel® 10mg/2ml) solution for injection (Roche)	
Abbreviations: MAH, Marketing Authorisation Holder.		

Overall, the formulation was developed to be essentially similar in terms of composition to the reference injectable product Hypnovel® 10mg/2ml ampoules; the originator product that was most commonly identified in the scientific literature and used in the retrieved published clinical studies. Therefore, an *in vivo* bridging PK study to demonstrate relative bioavailability or bioequivalence to the formulation used in the pivotal studies and delivered oromucosally was not required since the proposed buccal formulation is identical to the Hypnovel® 10mg/2ml formulation. Also, as the current variation is an extension of indication of the already approved paediatric oromucosal formulation into adults, there is no need for additional *in vitro* bridging studies versus Hypnovel® and none are performed.

Another buccally applied formulation of midazolam with a different formulation has been also identified in the published literature. More specifically, in some published clinical studies (Table 2), the EU authorised Epistatus® midazolam maleate 10 mg oromucosal solution was used, which demonstrates a

completely different qualitative and quantitative composition compared to Hypnovel®. Epistatus® was approved by the European Medicines Agency (EMA) as a hybrid application (Article 10.3 of Directive 2001/83/EC, as amended) to the reference product Hypnovel® 10 mg/2 ml solution for injection (ex-Roche), for the treatment of PACS in children and adolescents aged 10 to less than 18 years. In support of that application, two bioequivalence studies, according to the standards of Good Manufacturing Practice [GMP], and one *in silico* simulation study were conducted. The PK profiles obtained for Epistatus® and Hypnovel® were quite similar and the observed differences were not deemed to be of clinical significance in terms of overall efficacy and safety. Based on the overall assessment by the EMA, Epistatus® has been declared as bioequivalent to Hypnovel®, despite the substantial differences in their excipient compositions. Indeed, Epistatus® contains several critical excipients from a biopharmaceutical point of view such as ethanol, glycerol and liquid maltitol *(PAR Epistatus Oromucosal solution, 2020 and 2021)*, however, these excipient differences do not seem to significantly affect buccal absorption of midazolam, its overall kinetics and *in vivo* drug performance, as demonstrated by the *in vivo* bioequivalence results obtained for the two products.

It should be finally noted at this point that, midazolam is a Biopharmaceutics Classification System (BCS) and Biopharmaceutics Drug Disposition Classification System (BDDCS) Class I drug *(Wu and Benet, 2005; Bocci et al., 2022)*, demonstrating high solubility and membrane permeability and rather simple and straightforward absorption kinetics following the oral (gastrointestinal [GI] route). Thus, even though, the drug's oral systemic bioavailability is limited due to a present first-pass metabolism, midazolam displays very fast and reasonably good systemic absorption after buccal administration, in line its well-acknowledged biopharmaceutical properties. It can be, therefore, derived from the above that the currently applied formulation, having a qualitative and close quantitative composition similarity, along with a demonstrated *in vitro* quality comparability with the reference originator product Hypnovel®, is not expected to significantly deviate from the well-established clinical efficacy and safety record of the already marketed midazolam formulations, administered buccally in the published clinical studies.

In terms of pharmacokinetics, midazolam has been shown to exhibit PK linearity by both the IV and oral routes of administration over the range of therapeutic doses (0.25 to 1.0 mg/kg) *(FDA Clinical Pharmacology and Biopharmaceutics Review Versed; van Groen et al., 2019)*. Dose linearity of buccal midazolam PKs in the dose range of 0.05-1 mg/kg across paediatric age range 0-18 years has been also demonstrated, based on data derived by a dedicated *in silico* modeling and simulation study, initially performed by the Applicant in order to predict exposure and PK linearity of buccal midazolam in children of different age groups *(Simcyp Report 2009)*. This *in silico* modeling study, in line with the data obtained from the other routes, also predicted PK linearity for midazolam given by the buccal route of administration over the proposed therapeutic dose range for both paediatric and adult populations.

Ancillary analyses

Substantiation of midazolam for the treatment of PACS in adults as provided by MAH

Oromucosal midazolam has been recognised as the first-line choice to treat prolonged, acute, convulsive seizures in children, in order to mitigate the development of SE in both hospital and non-hospital community settings. Several studies have evaluated the effectiveness of buccal midazolam in children as the incidence of epilepsy and SE is much more common in this population than in adults. Indeed, it has been early recognised that the number of cases of SE peaks in early childhood and gradually declines until early adulthood. Thereafter, the number of cases increases as the population ages, with individuals aged >60 years being particularly susceptible *(Hanley and Kross, 1998)*.

The types and aetiologies of epileptic seizures may also vary between the paediatric and adult populations. By far the most common cause of SE in children is systemic, non-CNS infection or fever. Other major causes include changes in medication (e.g., decrease in antiepileptic drugs), metabolic disorders, and congenital malformations of the brain or nervous system. Infections of the CNS, anoxia, trauma, and idiopathic causes also account for a considerable number of cases of SE in children. On the other hand, seizures in older children and adolescents begin to manifest the causes seen in adults, such as withdrawal from anticonvulsant medication, metabolic diseases, trauma, and complications of alcohol and drug abuse. Thus, from an age onward, older children, adolescents and adults seem to present more similarities in pathophysiology and causes of epilepsy compared to those in early childhood *(Hanley and Kross, 1998)*.

As already discussed, beyond two years of age, brain neurophysiology tends to approach the adults in several characteristics, and EEG patterns of epilepsy become comparable. Despite acknowledged developmental and pathophysiological differences between the age extremes of adult and lower age groups of the paediatric populations, adults and children above 2 years of age share several common types of epileptic seizures, with similar clinical manifestations and therapeutic management, as already discussed in a previous section.

In a relatively recent evidence-based Guideline published by the Guideline Committee of the American Epilepsy Society *(Glauser et al., 2016)*, no differentiation relevant to paediatric or adult groups also exists in the proposed treatment algorithm. According to the Committee, this lack of age-specificity in treatment recommendations is based on the fact that the disease pathophysiology of prolonged seizures and SE and the anticonvulsant drug effects on neuronal receptors are the same from infants through adults, permitting a unified approach for all patients older than neonates.

It can be acknowledged, therefore that, though certain types of seizures and epilepsy syndromes are specific to the paediatric population (such as infantile spasms or other epileptic forms preferentially occur in childhood and wane in adolescence, such as rolandic or absence seizures) and thus require clinical studies in age-appropriate groups, other seizure types (including partial and generalised) are common in both adults and older children/adolescents, and the antiepileptic drugs used to treat them have typically similar effects. Therefore, extrapolation of efficacy data between the two populations has been proposed as a predictive tool for assessing efficacy in either group and suggested as an alternative to additional randomised, double-blind, placebo-controlled phase III trials *(Pellock et al., 2012)*.

It has been also well-recognised that, prolonged seizures in both children and adults with epilepsy may progress to SE and the longer an episode of epileptic seizure is allowed to persist, the more therapy resistant it will be, and the greater is the risk for a bad outcome *(Nakken and Lossius, 2011)*. Earlier non-clinical studies have shown that prolongation of SE induces $GABA_AR$ trafficking resulting in loss of inhibition and resistance to pharmacological treatment *(Naylor et al., 2005)*; this pharmacological mechanism. Indeed, the rapid evolution of seizure activity and time-dependent loss of pharmacological response have been well-recognized in clinical practice, with the transition from single seizures to pharmaco-resistant self-sustaining SE, in cases where initial seizure activity is left untreated or significant delays in early intervention occur. Time to treatment, the interval of time that elapses between the onset of a prolonged seizure and the initiation of seizure-abortive measures, are, therefore, important variables in seizure care and are likely to affect the outcome of seizure emergencies *(Sánchez Fernández et al., 2015)*.

Prompt intervention in seizure emergencies is, therefore, considered critical in both paediatric and adult patients, for reducing morbidity and mortality risks associated with SE and delays in the treatment of PACS need to be shortened markedly in all patients *(Pellock et al., 2004; Kämppi et al., 2013)*. All clinical evidence, therefore, argue strongly for the use of an easily applicable first-stage

medication in a non-hospital community setting for both children and adult patients. It is acknowledged that adult patients at risk of SE (e.g., frequent epileptic seizures, epileptic syndromes, cumulative risk factors, drug abstinence) tend to develop SE in an unobserved setting, and when they are found with SE, they have likely been convulsing for several minutes before being discovered. Children are usually not left alone too long and are supervised by adults, and it is easier for these latter to administer medication as soon as they identify something is going on.

However, even though children are considered to commonly develop SE in observed settings, it has been shown that time to treatment does not significantly differ between adults and paediatric patients. In a retrospective review of hospital patients during a 5-year period (1989-1994), it was found that the time to treatment ranged between 40-263 min in both population age groups *(Pellock et al., 2004)*. Records were available for 889 patients, who were divided into two subgroups: children (age <16 years, 29.7% of the cohort) and adults. Time to seizure treatment varied broadly: 369 patients (41.5%) received their first acute seizure treatment within 30 min of seizure onset, 261 (29.4%) within 30-60 min and 98 (11.0%) within 60-90 min. A total of 161 (18.1%) patients were treated after 90 min, and, of those, 57 patients (6.4%) received their first acute seizure treatment >240 min (4 h) after seizure onset. In this data set, children were slightly more likely than adults to be treated within 60 min, but less likely to be treated within the first 30 min of seizure onset; however, these differences were not statistically significant between the two groups.

Similar to adult patients, children with epileptic seizures have also commonly experienced prolonged seizure duration before hospital presentation that does not seem to influence subsequent management *(Lewena et al., 2009)*. In any case, because data suggest that earlier treatment of seizure emergencies results in better patient outcomes than delayed treatment, the seizure emergency plan should be designed to terminate the seizure or cluster as quickly as possible in both adults and children. Therefore, equipping epilepsy patients with an at-home seizure-abortive treatment option, such as buccal midazolam, may be an effective way to shorten the time it takes to initiate treatment.

As previously reported, oromucosal midazolam solution has been well recognized as the first-line choice to treat PACS in children, having already received a Marketing Authorization, under the brand name Buccolam®, within the European market for over a decade now. The adult indication was not initially included in the registration of Buccolam®, because the product was registered via a PUMA, i.e. exclusive use in paediatric patients. Indeed, given the higher prevalence of epileptic seizures in the paediatric population, a large number of dedicated paediatric clinical studies has been conducted evaluating the usage of buccal midazolam, demonstrating a well-established favourable efficacy and safety profile of this treatment option in the specific patient population *(Ülgey et al., 2012)*. However, there is extensive data also supporting the use of buccal midazolam in adults. The pharmacology is known to be similar for adolescents and adults, and consequently the efficacy and safety is also similar. This is further confirmed by bibliographical data *(Scott et al., 1998; Nakken and Lossius, 2011; Kadel et al., 2018; Shankar et al., 2021)* and by the recommendation for use of buccal midazolam in adults in national treatment guidelines of different European countries. Indeed, many of the most recently published European national guidelines, recommend the unlicensed use of buccal midazolam for the management of acute seizures in adults.

Therefore, it is evident that clinical practice recommendation is consistent with the bibliographic data demonstrating the safety and effectiveness of buccal midazolam in the management of different types of seizures in adults. As discussed, a few clinical studies using buccally administered midazolam in adults have been identified in the literature *(Meléndez et al., 2006; Nakken and Lossius, 2011; Kadel et al., 2018; Shankar et al., 2021)*. All these studies were performed in the targeted adult population (including young adults, adults, elderly) aged between 18 and ≥70 years. Study settings included both residential centres for adults as well as commuting settings, all within the European territory.

Regarding the pathological conditions of the study participants, these included different epilepsy presentations and aetiologies. Prolonged seizures also included generalised tonic-clonic, myoclonic and atonic seizures, focal epilepsy, convulsive and non-convulsive serial seizures, episodes of CSE and non-CSE. In terms of the administered dose, a 10-mg dose of oromucosal midazolam was most often used as rescue medication in adults with epilepsy and was effective when administered in either hospital or community settings. Overall, the identified studies via the buccal route, clearly demonstrated that buccal midazolam is effective in the treatment of acute prolonged seizures of different aetiologies in the adult population, being a safe, convenient and socially acceptable dosage form, especially when used in pre-hospital settings.

It should be noted at this point that the IM preparation of midazolam has been also used for the treatment of SE in adults. Indeed, midazolam given by IM injection was shown to be rapidly effective for the control of generalised convulsive seizures, focal seizures and status epilepticus in both adults and children *(Hirsch, 2012; McDonagh et al., 1992; Silbergleit et al., 2012)*. Studies have demonstrated that IM midazolam was able to control focal and generalised seizure activity and to rapidly terminate prolonged seizures, being an effective and safe first-line treatment for all types of epileptic seizures *(Towne and DeLorenzo., 1999; Riva et al., 2021)*.

Additional studies have also shown that nasally administered midazolam is able to stop seizures faster than rectal or IV diazepam *(De Haan et al., 2010)* and is absorbed faster than IM midazolam *(Knoester et al., 2002; De Haan et al., 2010)*. The positive clinical outcomes with nasal midazolam led to the approval of the nasal formulation Nayzilam® in May 2019 by the FDA *(Nayzilam FDA Review)* for the acute treatment of seizures in patients 12 years of age and older who require control of intermittent episodes of increased seizure activity (e.g., seizure clusters, acute repetitive seizures). More recently and following a Referral procedure under Article 29(4) of Directive 2001/83/EC as amended, nasal midazolam has also received Marketing Authorisation within several European Member States, under the brand name Nasolam® also for the treatment of prolonged, acute, convulsive seizures, both in adults and children from 2 years and over *(Nasolam EMA Referral, 2022)*. The application was filed under the hybrid legal basis (versus Dormicum® 5mg/ml solution for injection) and the antiepileptic indication in adults and children was supported by literature data demonstrating midazolam use in this population, as well as by PopPK-pharmacodynamic modeling and simulation analyses, comparing the nasal and the buccal routes. Administration of midazolam via the buccal and nasal routes, do not present identical PK profiles, with the nasal formulation reaching peak levels earlier and presenting a higher value for this parameter. Nevertheless, the Committee for Medicinal Products for Human Use finally accepted treatment of PACS in adults for Nasolam®, in view of PK comparison to intrabuccal administration (which is not yet approved for this indication in adults).

Another point of confirmation of dose-response similarity between adults and children is the acknowledged minimum efficacy threshold for midazolam, being necessary for seizure cessation. This efficacy threshold has been justified based on literature data from *Silbergleit et al. (2012)* who conducted a double-blind, randomised, noninferiority trial wherein the efficacy of IM midazolam was compared to that of IV lorazepam for children and adults in SE treated by paramedics. The median time for seizure cessation in both adults and children treated with 10 mg IM midazolam was 3.3 min. The concentration of midazolam at this timepoint was 17 ng/ml, which was derived from a quantitative PK study of IM midazolam by *Reichard et al. (2010)*. Therefore, this threshold for an efficacious concentration of midazolam may be considered appropriately justified and valid for both adults and children and this was indeed accepted also by the CHMP during Nasolam® Referral procedure. With respect to safety, taking into account that the adults finally proposed Buccolam® posology is the current adolescent single dose of 10 mg, no safety issues are anticipated, taking also into account that doses up to 20 mg have been used in the published clinical trials without any safety concern. Safety

observations from market use of buccal midazolam also support the safety of this route of administration.

In addition to the above, similarity of the efficacy and pharmacology of midazolam between adolescents and adults is also endorsed by the appreciation that the dosing recommendation of the injection formulation Hypnovel® is the same in adults as in adolescents aged 12 to 18 years. Similarly, the licensed dose of buccal midazolam in adolescents (10 mg) is equal to the unlicensed (off-label) adult buccal dose (10 mg), as recommended in national guidelines for the management of acute seizures and as reflected in several publications describing the use and effectiveness of 10 mg buccal midazolam to stop seizures in adults *(Nakken and Lossius, 2011; Kadel et al., 2018; Shankar et al., 2021)*. This implies treatment specialists also endorse equivalence in exposure response relationships between adolescent and adults and among the different dosage forms for the indication of PACS. As Guidelines recommend the same dose for adults and adolescents and the PK profile of midazolam in adults and adolescents do not differ, the posology in adults is considered substantiated.

From all the above, the Applicant considers that the efficacy demonstrated by buccal midazolam for the treatment of prolonged, acute, convulsive seizures in the paediatric population can be extrapolated to adults based on PK exposure matching as well as published clinical data considerations. The proposed route of buccal administration is not expected to introduce difference in safety and efficacy, provided pharmacokinetic similarity with respect to exposure and time to onset of effect is met also in adults. Overall, based on the consistency of the overall submitted data package, i.e. literature data on adults and children/adolescents, the performed PK studies and PopPK simulations in adults and children, as well as the same dose recommendation in adults and adolescents in clinical practice, it can be derived that the use of oromucosal midazolam formulation in adults can be considered clinically justified.

2.3.4. Discussion on clinical efficacy

To support the efficacy of buccally administered midazolam for the treatment of PACS in adults, the MAH submitted limited discussion of 3 pivotal studies (Mendelez 2006, Nakken & Lossius 2011 and Shankar 2021) and 4 supportive studies. No randomized, double-blind, placebo/active controlled (non-inferiority) studies were submitted.

Two formulations of buccal midazolam were evaluated in the studies with a dose ranging from 5 mg to 20 mg. Bioequivalence between the formulations used in the bibliographic data and Buccolam is considered established.

All submitted bibliographic studies have methodologic flaws which hamper the interpretation of efficacy of buccal midazolam for the treatment of PACS in adults.

In the Mendelez study, prolonged seizures were defined as lasting > 1 minute. Using benzodiazepines in seizures with a duration < 5 minutes may be too early, i.e. treatment is associated with more harmful effects than benefit (Hussein, 2019). In addition it cannot be excluded that the seizures could not have resolved by itself without need for treatment.

Although rectal diazepam was used as active comparator in the Nakken & Lossius study, treatment allocation was not randomized. The authors' conclusions that "buccal midazolam seems to be at least as effective as rectal diazepam in alleviating serial seizures or SE", is not supported as a statistical nonsignificant difference between groups on the seizure cessation success rate is not an indication that the two treatments are equal in terms of efficacy. Numerically, the success rate was higher in the diazepam group and was associated with a lower number of treatment failures and fewer relapses when

compared to midazolam. Conclusive evidence that indicates comparative efficacy between buccal midazolam and rectal diazepam should come from a well-designed non-inferiority study.

The Shankar study was primarily designed to evaluate how buccal midazolam was used in the community setting. Bias cannot be excluded due to the observational design of the study. Although seizure cessation after midazolam administration was reported for a large percentage of patients, it is unclear for what kind of seizures the drug was administered and seizure re-occurrence was not recorded.

Overall, the provided bibliographic studies differ greatly in terms of study design, presence of an adequate comparator arm, midazolam dose used, definition of prolonged seizures (or lack of definition) and endpoints. No conclusions can be drawn with respect to efficacy of buccal midazolam for the treatment of PACS in adults. It is acknowledged that the emergency setting of PACS complicates a blinded placebo-controlled approach. Nevertheless, in absence of such studies, randomized studies with an established comparator such as diazepam can provide confirmative evidence of efficacy. This was the case for the majority of pivotal bibliographic studies support the initial MAA of Buccolam. Of the 3 pivotal studies submitted to support the adult indication, only one (Nakken and Lossius) included a comparator arm, but in absence of randomisation and proper non-inferiority assessment, interpretation of efficacy is hampered.

A discussion of the extrapolation of efficacy from children to adults with PACS has been provided, with sufficient substantiation for the efficacy of buccal midazolam in children with PACS to be extrapolated to adults based on similarity of exposure only.

2.3.5. Conclusions on the clinical efficacy

Based on exposure matching, extrapolation of efficacy from children to adults is considered acceptable to support the adult indication of Buccolam

2.4. Clinical safety

Introduction

In the extension of the indication, the clinical safety data is provided from the following sources:

- Study LESVIBUCCO/23/BQ-3, a comparative bioavailability, single-dose, open-label, randomised, two-sequence, two-treatment, two-period crossover study in healthy adult subjects under fasting conditions.
- Published literature studies in adults with PACS treated with buccal midazolam and other midazolam routes of administration (intranasal, intramuscular).

Patient exposure

Study LESVIBUCCO/23/BQ-3

Study LESVIBUCCO/23/BQ-3 was comparative bioavailability, single-dose, open-label, randomised, two-sequence, two-treatment, two-period crossover study in healthy adult subjects under fasting conditions.

Twenty-three healthy adult volunteers, aged 18-59 years, were enrolled in the study and were administered at least one dose of IPs, namely a single buccal 15-mg dose of Buccolam® (orally,

directly in the buccal cavity using 2×7.5 mg pre-filled oral syringes) and an IM injected 10-mg dose of Hypnovel®.

Published literature

All pivotal efficacy adult studies, retrieved from the scientific literature search, were performed in the targeted adult population (including young adults, adults, elderly), in the claimed indication, one of them (Nakken and Lossius, 2011) using rectal diazepam as an active comparator. They cover a chronological period from 2006 to 2021, involving a total of 196 adults with epilepsy, aged between 18 and ≥70 years, with prolonged acute seizures, being treated with of buccal midazolam at a median dose range of 15.5 mg. The studies by Meléndez et al. (2006) and Nakken and Lossius (2011) were conducted in residential centres for adults with encephalopathy and difficult-to-treat epilepsy, respectively, and the study by Shankar et al. (2021) in commuting settings, all within the European territory.

All these studies have been performed before the EU marketing authorisation of the developed midazolam oromucosal solution. Hence, one of them (Meléndez et al., 2006) used the injectable formulation of midazolam hydrochloride, Hypnovel® 10 mg/2 ml (or else Dormicum®) ampoules administered via the oromucosal route, while in the remaining two studies (Nakken and Lossius, 2011; Shankar et al., 2021), the authorised midazolam maleate-containing buccal solution Epistatus® 10 mg/ml was administered oromucosally. In the study by Nakken and Lossius (2011), rectal diazepam was administered as an active comparator, to treat convulsive or non-convulsive seizures lasting more than 5 min.

In the most recent study by Shankar et al. (2021), an initial dose of 10 mg was administered in 65.5% (n=19/29) of the subjects with body weights between 30 and 60 kg and in 83.3% (n=35/42) of the subjects with body weights of 60-110 kg. It has to be mentioned here that the most common location for administration of oromucosal midazolam in this study was recorded as home (92 cases, 63.0%), the drug being most often administered by a professional caregiver (75 cases, 48.4%). In one study (Meléndez et al., 2006), a single dose of 5 mg was administered, being effective as one dose in 80.7% of the seizure episodes, while in 19.3% of the subjects, a second midazolam dose (n=8) or a third midazolam dose and diazepam dose (n=2) was required.

The four supportive studies included a total of 9,303 adult patients aged ≥18 years were involved in these studies, requiring pre-hospital administration of a BZD (including buccal or IM midazolam). One was conducted in Germany (Kadel et al., 2018) and the other 3 studies were conducted in the US (Silbergleit et al., 2012; Clemency et al., 2015; Guterman et al., 2022).

In the study by Kadel et al. (2018), midazolam was prescribed for buccal administration at a dose range of 2.5 to 10 mg (mean ± SD dose: 7.5±2.8 mg; mean dose: 10 mg), whereas in the 3 remaining studies (Clemency et al., 2015; Silbergleit et al., 2012; Guterman et al., 2022), midazolam was administered IM at doses of 5 mg or 10 mg, as per the current national clinical practice guidelines followed by various countries within the European territory. Although investigating the effective of midazolam given via parenteral rather than the buccal route, these 3 studies were included in the supportive studies as in the comparative bioavailability Study LESVIBUCCO/23/BQ-3, also Hypnovel® solution for injection was administered at a single dose of 10 mg via IM injection in the mid-outer thigh vs buccal administration of Buccolam® in healthy adult volunteers.

In all studies, active comparators were used, namely oral (Kadel et al., 2018) or IV (Silbergleit et al., 2012) lorazepam, diazepam (Clemency et al., 2015) or intranasal/IV midazolam (Guterman et al., 2022), at doses recommended by the clinical practice guidelines on the management of SE.

Adverse events

Study LESVIBUCCO/23/BQ-3

All subjects (N=23) who received the IPs reported a total of 61 TEAEs. Among the 22 subjects who received Test product, namely Buccolam® 7.5 mg/1.5 ml oromucosal solution, a total of 30 TEAEs were reported, of which 27 TEAEs were considered drug-related. The most common TEAE was "Somnolence", reported by all subjects.

Among the 22 subjects who received buccally Hypnovel® 10 mg/2 ml solution for injection, i.e., the Reference product, a total of 31 TEAEs were reported, of which 30 TEAEs were considered drug-related (see Table 7). The most common TEAE was "Somnolence", reported by all subjects.

Table 7 Summary of Treatment-Emergent Adverse Events (TEAEs)

	Test (n=22)		**Reference (n=22)**		**Total (N=23)**	
	All TEAEs	**Drug-related TEAEs**	**All TEAEs**	**Drug-related TEAEs**	**All TEAEs**	**Drug-related TEAEs**
Number of Subjects {Nr. of TEAEs} (% of Subjects)	**22 {30} (100%)**	**22 {27} (100%)**	**22 {31} (100%)**	**22 {30} (100%)**	**23 {61} (100%)**	**23 {57} (100%)**
MedDRA System Organ Class (SOC) Preferred Term (PT)						
General disorders and administration site conditions	**1 {1} (5%)**	**1 {1} (5%)**	**3 {3} (14%)**	**3 {3} (14%)**	**4 {4} (17%)**	**4 {4} (17%)**
Influenza like illness	1 {1} (5%)	1 {1} (5%)	0	0	1 {1} (4%)	1 {1} (4%)
Injection site pain	0	0	3 {3} (14%)	3 {3} (14%)	3 {3} (13%)	3 {3} (13%)
Infections and infestations	**1 {1} (5%)**	**0**	**0**	**0**	**1 {1} (4%)**	**0**
COVID-19	1 {1} (5%)	0	0	0	1 {1} (4%)	0
Investigations	**0**	**0**	**1 {1} (5%)**	**1 {1} (5%)**	**1 {1} (4%)**	**1 {1} (4%)**
Oxygen saturation decreased	0	0	1 {1} (5%)	1 {1} (5%)	1 {1} (4%)	1 {1} (4%)
Musculoskeletal and connective tissue disorders	**1 {1} (5%)**	**0**	**1 {1} (5%)**	**0**	**2 {2} (9%)**	**0**
Back pain	1 {1} (5%)	0	1 {1} (5%)	0	2 {2} (9%)	0
Nervous system disorders	**22 {26} (100%)**	**22 {26} (100%)**	**22 {24} (100%)**	**22 {24} (100%)**	**23 {50} (100%)**	**23 {50} (100%)**
Headache	4 {4} (18%)	4 {4} (18%)	2 {2} (9%)	2 {2} (9%)	5 {6} (22%)	5 {6} (22%)
Somnolence	22 {22} (100%)	22 {22} (100%)	22 {22} (100%)	22 {22} (100%)	23 {44} (100%)	23 {44} (100%)
Respiratory, thoracic and mediastinal disorders	**1 {1} (5%)**	**0**	**2 {2} (9%)**	**2 {2} (9%)**	**3 {3} (13%)**	**2 {2} (9%)**
Epistaxis	1 {1} (5%)	0	0	0	1 {1} (4%)	0
Hyperventilation	0	0	1 {1} (5%)	1 {1} (5%)	1 {1} (4%)	1 {1} (4%)
Hypoxia	0	0	1 {1} (5%)	1 {1} (5%)	1 {1} (4%)	1 {1} (4%)

All TEAEs were of mild (19 TEAEs) or moderate (42 TEAEs) intensity.

Subject #LESVIBUCCO/23/BQ-3_05 was discontinued from the study due to TEAE "COVID-19" and subject #LESVIBUCCO/23/BQ-3_06 was discontinued from the study due to TEAE "Back pain". These TEAEs were considered not drug-related.

Four subjects reported pre-treatment AEs, namely "Cough", "Anxiety" and "Flu-Like Syndrome", before randomisation, 1 of which was not admitted to randomisation. There were no TEAEs with associated vomiting and/or diarrhoea.

Overall, both Test and Reference products were similarly well-tolerated in this study.

Published literature

Buccal midazolam was generally demonstrated to be safe and well-tolerated in the studied population groups. In the vast majority of the studies, no significant difference in AEs between the treatments and no adverse cardiorespiratory events were observed in either group. No respiratory depression secondary to the treatment or bronchoaspiration were noted in any of the studies. None of the patients developed SE nor transferred to hospital due to complication. In one study (Kadel et al., 2018), sedation was reported as a major (18.7%, n=25) or moderate (29.1%; n=39) problem by a substantial number of patients. Reported major or moderate sedation did not differ among treatments. No clinically important AEs were reported and there were no AEs recorded leading to withdrawal of patients across all studies evaluating the use of midazolam for treatment of seizures. This reduced record of AEs with buccal midazolam, identified in the published literature, may be actually expected given the single, one-off administration of the drug in the intended emergency indication. The safety results of buccal midazolam from these studies are summarised in **Table 8**.

Table 8 Safety data from studies with buccal midazolam administered in adults with acute convulsive seizures. (provided by MAH)

Reference	Study design	Patient group (sample size)/ Indication	Buccal midazolam dose	Comparator	Safety results
Meléndez et al. (2006)	Not stated (Spain)	10 (aged 27-61 years; 5 men and 5 women) of the 73 adult epileptic patients who were residents in a centre for people with severe encephalopathy. Age bands, as follows: 18-30 years, n=3; 31-40 years, n=3; 41-60 years, n=3; and 61 years, n=1	5 mg (1 ml of the IV preparation)	NA	No respiratory depression secondary to the treatment or bronchoaspiration were noted, given the small volume administered. None of the patients developed SE nor transferred to hospital due to complication.
Nakken and Lossius (2011)	Prospective study (Norway)	20 patients, aged 25-68 years, with CSE or non-CSE or prolonged/ serial seizures lasting >5 min, in a residential institution for adults with difficult-to-treat epilepsy, most often with additional neurological (n=5), cognitive (n=9) and/or psychiatric comorbidities (n=7)	Median (range) dose: 15.5 (10-20) mg (Epistatus®, Dales pharmaceuticals, buccal solution 10 mg/ml)	Rectal diazepam (Stesolid prefill 'Actavis', rectal solution, 5 mg/ml), when convulsive or non-convulsive seizures lasting >5 min arose	The AEs were modest, tiredness being most frequently reported. Tiredness lasting more than 2 h occurred more frequently in the diazepam than in the midazolam group.
Kadel et al. (2018)	Multicentre cohort study (questionnaire-based, retrospective	481 adult [mean (range) age: 43.4 (18-94) years] epilepsy patients attending the epilepsy outpatient clinics of the university	Prescribed to 32 patients (23.9%); dose range of 2.5 to 10 mg (mean ± SD dose:	Oral lorazepam tablets at a mean dose of 1.6±0.8 mg (65.7%; n=88 out of 134); rectal	Sedation was named as a major (18.7%, n=25) or moderate (29.1%; n=39) problem by a substantial number of patients. Reported major or moderate sedation did not differ between oral

Reference	Study design	Patient group (sample size)/ Indication	Buccal midazolam dose	Comparator	Safety results
	survey; Germany)	hospitals in Frankfurt and Marburg in 2015	7.5±2.8 mg; mean dose: 10 mg)	diazepam at a mean dose of 10.2±7.5 mg (17.9%, n=24), or others	lorazepam (n=45/68; 66.2%, *P*=0.065), buccal midazolam (n=8/20; 40%) and rectal diazepam (n=14/19; 73.7%, *P*=0.07). Dizziness, anxiety and pain were reported less frequently.
Shankar et al. (2021)	Retrospective, observational, cross-sectional study (2016-2017 in 4 UK NHS secondary care outpatient clinics)	146 adult people with epilepsy, mean ± SD age: 41.0± 15.2 years [49 subjects aged 18-30 years; 21 were 31-40 years old; 26 were 41-50; 10 were 61-70; 2 were 70+ years old] and mean ± SD weight: 64.8± 18.2 kg; 53% had intellectual disability; the majority of seizures occurred at home (n=92, 63%)	(as midazolam maleate; Epistatus®, Veriton Pharma Limited, UK). The most common initial dose was 10 mg (n=124, 84.9%), most often administered by family/ professional care givers (n=75, 48.4%) (please also see Table 1 within published article)		Not available data

Abbreviations: AE, adverse event; CSE, convulsive status epilepticus; IV, intravenous; NA, not applicable; NHS, National Health Service; SD, standard deviation; SE, status epilepticus; UK, United Kingdom.

Serious adverse event/deaths/other significant events

Serious adverse events

There were no serious adverse events reported in Study LESVIBUCCO/23/BQ-3.

Deaths

No deaths were reported during the Study LESVIBUCCO/23/BQ-3 or in the published literature.

Safety in special populations

Tolerability of midazolam in elderly patients has been investigated in several clinical studies and relevant systematic reviews, assessing different midazolam posologies and routes of administration (Trinka et al., 2015; Berg et al., 2017; Bloch et al., 2019; Zaporowska-Stachowiak et al., 2019; Willems et al., 2022). The most commonly recorded adverse events for this population concerned cardiac and pulmonary complications, hypotension, tachycardia, bradycardia, desaturation below 90%, airway obstruction, pulmonary infection, excessive sedation, hyperactivity, delirium and vomiting. Desaturation below 90% was significantly more frequent in the patient group with a mean age >70 years, when midazolam was not used orally or when it was used in association with other drugs. No significant difference was found in the nature of reported adverse events between the elderly and younger adult populations, but occasionally the frequency and severity were augmented in geriatric patients (Willems et al., 2022).

Indeed, altered physiology in elderly patients is known to cause altered clinical response to sedative-anxiolytic drugs, such as benzodiazepines. Literature findings indicate that an increase in age may potentially lead to variations in pharmacokinetics (PK) or an increased intrinsic sensitivity to some benzodiazepines, compared to younger individuals (Greenblatt et al., 1991). More specifically, previous studies have shown that the observed enhanced pharmacodynamic (PD) responses in elderly with this drug class may be attributed to age-related changes in the subunit makeup of the $GABA_A$ receptor (Li et al., 2007). GABA is the primary inhibitory neurotransmitter in the brain, and it plays an important role in reducing neuronal excitability throughout the nervous system and in producing a calming effect on the brain. Studies examining ion flux in membrane vesicles have revealed functional changes in $GABA_A$ receptors during aging (Griffin et al., 2013). Age-related increases of α1 and γ2 subunits of the $GABA_A$ receptors have been reported in the hippocampus. As a result, age-related pharmacological alterations in $GABA_A$ receptors may occur, which could produce a greater inhibitory effect of midazolam in some geriatric patients making them more susceptible to adverse effects (Mihic et al., 1994; Gutiérrez et al., 1996; Griffin et al., 2013).

Previous studies compared the PK and PD of midazolam in older versus younger participants for different routes of administration (intravenous, intramuscular, intranasal, buccal, oral) and formulations of midazolam (Greenblatt et al., 1984; Smith et al., 1984; Berg et al., 2017; Bow et al., 2021; Wheless, 2021; Barends et al., 2023). While some studies showed PK or PD differences between elderly and younger adults (Greenblatt et al., 1984; Jacobs et al., 1995; Platten et al., 1998; Sun et al., 2008; Ko et al., 2020), others showed no differences (Avram et al., 1983; Smith et al., 1984; Castleden et al., 1987; Albrecht et al., 1999; Berg et al., 2017). In fact, for midazolam, the only PK process that may change with aging is total clearance, which may be lower in elderly patients of advanced age. Impaired clearance might decrease maintenance dose requirements but would not be expected to affect acute, single-dose requirements used in the management of seizures. Importantly, midazolam's initial distribution volume and plasma protein binding, factors that could influence the

induction dose requirement, are not affected by aging (Jacobs et al., 1995; Platten et al., 1998; Albrecht et al., 1999; Fujisawa et al., 2002; Zaporowska-Stachowiak et al., 2019).

Based on the above, a potential increased susceptibility in elderly patients, mainly those of advanced age, cannot be excluded and, therefore, dose reductions may be indicated. Recommendations for dose reductions of midazolam in elderly patients (commonly over 70 years of age) compared to the younger adult population have been included in several Clinical Practice Guidelines for the different formulations and routes of administration of midazolam (Chauhan et al., 2014; NHS, 2014; Trinka et al., 2015; Scottish Ambulance Service; Emergency Care Institute NSW; GGC guideline; Scottish Palliative Care Guidelines).

Contrary to the general therapeutic recommendation "start low, go slow" in geriatric patients, an adequate, sufficiently high dosage of first-line therapy should always be considered in the treatment of SE, since a dosage that is too low can promote a refractory course (Willems et al., 2022). In any case, medical problems in older people should also be considered when treatment with midazolam is indicated, since clinical conditions such as cardiovascular, respiratory and endocrine issues, hypertension, heart failure, dysrhythmias and diabetes are frequently seen in these patients. Apart, from the underlying pathology of these conditions, concomitant medications should also be accounted for their possible impact on midazolam activity, as many drugs can affect the sedative and hypotensive effect of the drug, including very commonly prescribed drugs such as statins, calcium channel blockers, dopaminergic medicinal products, muscle relaxants and some antifungal, antiviral and antibiotic drugs (Chauhan et al., 2014).

The above literature findings, but most importantly, the proprietary data obtained from the dedicated modeling and simulation exercise supporting the use of buccal midazolam in adults (popPK report MID-Neurax-24-BUCCO-popPK-01, 06JUN2024 included in Module 5.33.5), indicate that, the exposure to and elimination half-life of midazolam after oromucosal administration in adults between 60 and 70 years of age is similar to younger adults. Very elderly may have prolonged elimination half-life as stated in the Hypnovel SmPC for intravenous administration, and very elderly maybe more sensitive to the effects of benzodiazepines. In these "high risk'' patients, the dose should be decided on a patient basis by the clinical practitioner, and a lower dose may be required. Based on the above, and to align with precautions in related midazolam products (e.g. Hypnovel SmPC), respective amendments are now proposed in Sections 4.2, 4.4 and 5.2 of the SmPC.

The review of fatal cases retrieved for midazolam in the post-marketing data showed that 12 out of the 25 cases referred to elderly patients, who presented with underlying conditions contributing to the fatal outcome, including physiological decline caused by age, or COVID-19. Overall, no new or relevant information that may change the safety profile for Buccolam® have been identified from the reviewed post-marketing data. The use of the product in patients aged 18 and over is clearly identified, and no clear differences has been observed when comparing the safety profile between different age groups. Since elderly patients are considered to be more sensitive to the effects of benzodiazepines, and drug exposure alterations may occur in patients over 70 years of age, such high-risk patients may require lower doses.

Safety related to other midazolam routes of administration

Table 9 below presents an overview of the most important identified studies evaluating the safety of midazolam in adult patients with epileptic seizures, administered by different routes of administration, i.e. buccal, intranasal and intramuscular routes of administration. Indeed, given the fact that systemic exposure of buccal midazolam falls within the observed exposure levels following intranasal and intramuscular midazolam, respectively, in adults, for the same doses, it is expected that its systemic

safety profile will be comparable and the reported safety profile of the other two routes of administration (Schwagmeier et al., 1998; Brigo et al., 2015; Almohaish et al., 2021) will be relevant. Previous studies have, indeed, shown that an IM midazolam dose of 10 mg presents a bioavailability of >90%, whereas buccal midazolam of the same dose has a bioavailability lying within the range of 75-87%. On the other hand, intranasal midazolam (maximum dose 15 mg) presents a somewhat lower bioavailability compared to buccal midazolam, providing a variable drug exposure of 44-83% (Almohaish et al., 2021). However, because the nasal mucosa is located near the brain, it is easier for drugs to directly enter the brain and obtain a higher concentration in the cerebrospinal fluid than in plasma, therefore, such differentiations in systemic exposure may not be clinically significant in the overall pharmacodynamic response (Kälviäinen, 2015).

An overall summary of the doses administered and reported adverse event profiles of the three different routes of midazolam administration for the same indication and intended patient population is provided in Table 9.

Table 9 Safety data from individual studies with buccal, intranasal and intramuscular midazolam administered in adults with acute convulsive seizures.

Reference	Study design	Patient group (sample size)/ Indication	Dose/ Formulation	Safety results
Buccal Route				
Meléndez et al. (2006)	Not stated (Spain)	10 (aged 27-61 years; 5 men and 5 women) of the 73 adult epileptic patients who were residents in a centre for people with severe encephalopathy. Age bands, as follows: 18-30 years, n=3; 31-40 years, n=3; 41-60 years, n=3; and 61 years, n=1	5 mg (1 ml of the IV preparation)	No respiratory depression secondary to the treatment or bronchoaspiration were noted, given the small volume administered.
Nakken and Lossius (2011)	Prospective study (Norway)	20 patients, aged 25-68 years, with CSE or non-CSE or prolonged/ serial seizures lasting >5 min, in a residential institution for adults with difficult-to-treat epilepsy, most often with additional neurological (n=5), cognitive (n=9) and/or psychiatric comorbidities (n=7)	Mean (range) dose: 15.5 (10-20) mg (Epistatus®), buccal solution 10 mg/ml)	The adverse events were modest, tiredness being most frequently reported. Tiredness lasting more than 2 h occurred more frequently in the diazepam than in the midazolam group. Other adverse events recorded in the midazolam group included ataxia, a prolonged bitter taste in mouth, numbness in mouth, whereas 34 patients reported no adverse effects.
Kadel et al. (2018)	Multicentre cohort study (questionnaire-based, retrospective survey; Germany)	481 adult [mean (range) age: 43.4 (18-94) years] epilepsy patients attending the epilepsy outpatient clinics of the university hospitals in Frankfurt and Marburg in 2015	Prescribed to 32 patients (23.9%); dose range of 2.5 to 10 mg (mean ± SD dose: 7.5±2.8 mg; mean dose: 10 mg)	Sedation was named as a major (18.7%, n=25) or moderate (29.1%; n=39) problem by a substantial number of patients. Reported major or moderate sedation did not differ between oral lorazepam (n=45/68; 66.2%, *P*=0.065), buccal midazolam (n=8/20; 40%) and rectal diazepam (n=14/19; 73.7%, *P*=0.07). Dizziness, anxiety and pain were reported less frequently.

Shankar et al. (2021)	Retrospective, observational, cross-sectional study (2016-2017 in 4 UK NHS secondary care outpatient clinics)	146 adult people with epilepsy, mean ± SD age: 41.0± 15.2 years [49 subjects aged 18-30 years; 21 were 31-40 years old; 26 were 41-50; 10 were 61-70; 2 were 70+ years old] and mean ± SD weight: 64.8± 18.2 kg; 53% had intellectual disability; the majority of seizures occurred at home (n=92, 63%)	(as midazolam maleate; Epistatus®, Veriton Pharma Limited, UK). The most common initial dose was 10 mg (n=124, 84.9%), most often administered by family/ professional care givers (n=75, 48.4%)	A 10-mg dose of oromucosal midazolam was well tolerated.
Intranasal Route				
Scheepers et al. (2000)	Prospective cohort study	22 adolescent and adult patients (age from 12–72, median 26 years) with severe epilepsy	Intranasal midazolam 5 mg (< 50 kg), 10 mg (> 50 kg)	None of the patients complained of debilitating effects on questioning
Detyniecki et al. (2019)	Double-blind, randomized controlled study	174 epileptic adults	Intranasal midazolam 5 mg (first dose) 5 mg (second [optional] dose)	*First dose:* Nasal discomfort: 9% Somnolence: 10% Lacrimation: 1% Product taste abnormal: 3% Throat irritation: 4% Headache: 5% *Second dose:* Nasal discomfort: 16% Somnolence: 10% Lacrimation: 7% Product taste abnormal: 6% Throat irritation: 5% Headache: < 1%
Spencer et al. (2020)	Double-blind, randomized controlled study	31 epileptic adults	Intranasal midazolam 5 mg (single dose)	Nasal discomfort: 16.1% Nausea: 9.7% Throat irritation: 9.7% Product taste abnormal: 6.5% Somnolence: 6.5% Headache: 3.2% Rhinitis: 0% Suicidal ideation: 3.6%

				Blood pressure: no reported differences (compared to Placebo group) that were considered clinically meaningful
Wheless et al. (2019)	Prospective cohort study	161 patients ≥ 12 years with epilepsy and history of seizure clusters	Intranasal midazolam 5 mg (first dose) 5 mg (second dose; 10 min after first dose)	Nasal discomfort: 12.4% Somnolence: 9.3% Headache: 6.2% (8.7%h) Fatigue: 4.3% (6.8%) Rinorrhea: 4.3% Sneezing: 3.7% Convulsion: 2.5% (5.6%) Dizziness: 2.5% (4.3%) Nausea: 2.5% (4.3%) Throat irritation: 2.5% Rhinalgia: 2.5% Product taste abnormal: 2.5% Lacrimation increased: 2.5%
Kyrkou et al. (2006)	Cohort study	80 epileptic adults	Intranasal midazolam (not stated if single or multiple doses): 10 mg (recommended dosage)	Not systematically reported ("There were no instances of respiratory arrest, and only one report of apparent shallow breathing. Some individuals complained of discomfort or a burning sensation in the nasal passages, but this was only when they were awake for the test dose.")
De Haan et al. (2010)	Retrospective cohort study	21 epileptic adults	Intranasal midazolam (single dose): 10 mg (each)	Drowsiness: 68% Local irritation (sneezing, coughing, dry mouth, lacrimation): 29% Sedation: 8% Restlessness: 2% Headache: 0%
Kay et al. (2019)	Retrospective cohort study	42 epileptic adults	Intranasal midazolam (single dose): 5 mg (in 90.5%) or 2.5 mg (in 9.5%)	Nasal irritation: 12% Prolonged sedation: 3%

Li et al. (2022)	Retrospective cohort study	38 epileptic adults	Intranasal midazolam 5 mg (first dose) 5 mg (second dose; 10 min after first dose)	Fatigue: 24% Nasal discomfort: 10% Headache: 0% Dizziness: 0%
Theusinger et al. (2019)	Retrospective cohort study	44 epileptic adults	Intranasal midazolam 0.2 mg/kg (first dose) Second dose: repetition after first dose allowed (20 mg as largest dose) or IV midazolam: 5–15 mg IM midazolam: 10 mg	Nasal irritation: 8.1% Headache: 0.9% Cough: 2.0% Prolonged sedation: 5.7% Nausea and vomiting: 2.6% Nosebleed: 1 patient Decline in oxygen saturation (< 90%): 17%
Von Blomberg et al. (2020)	Retrospective cohort study	224 epileptic adults	Intranasal midazolam (median dose): 5 mg	Nasal irritation: 8.1% Headache: 0.9% Cough: 2.0% Prolonged sedation: 5.7% Nausea and vomiting: 2.6% Nosebleed: 1 patient Decline in oxygen saturation (< 90%): 17%
Kay et al. (2015)	Retrospective cohort study	75 epileptic patients ≥ 12 years	Intranasal midazolam (median dose): 5 mg	Nasal irritation: 4% Respiratory or circulation difficulties: 0%
Intramuscular Route				

Silbergleit et al. (2012)	Double-blind, randomized noninferiority trial	893 adult, elderly and paediatric subjects weighing >13 kg, requiring treatment with benzodiazepines for status epilepticus	IM midazolam (13–40 kg = 5mg; >40 Kg = 10 mg) vs. IV lorazepam (13–40 kg = 2mg; >40 Kg = 4 mg)	In total 137 (26.7%) serious adverse events were recorded for IM midazolam. The majority of adverse events included depressed level of consciousness, respiratory depression, convulsion, mental status changes, sepsis, myocardial infarction, hypotension, rhabdomyolysis, cerebral haemorrhage and acute renal failure.
Wroblewski and Joseph (1992)	Case reports	10 case reports	IM midazolam 5-15mg, more commonly 10 mg	No adverse events or slight sedation, drowsiness, minimal cognitive slowing, lethargy
Mayhue (1988)	Case report	A 71-year-old male patient	IM midazolam 10 mg	No adverse effects were noted
McDonagh et al. (1992)	Observational study	38 patients with seizures	IM midazolam at an average dose of 0.12mg/kg (range 0.07-0.2Img/kg), meaning an average dose of 9mg for a 75kg adult	No adverse effects were reported in any patients. In particular no cases of cardiovascular or respiratory depression requiring treatment occurred.
Galdames-Contreras et al. (2006)	Prospective open clinical trial	38 adult patients with status epilepticus	An initial dose of 15 mg IM of midazolam, with 2 repeated doses of 15 mg every 8 if needed.	No patient had neither cardiovascular, respiratory or local complications. The only adverse effect was drowsiness in a variable grade.

As seen from the Table 9, buccal midazolam was generally demonstrated to be safe and well-tolerated in the studied population groups. In the vast majority of the studies, no significant difference in adverse events were observed between the treatments. Further, no adverse cardiorespiratory events and no respiratory depression secondary to the treatment or bronchoaspiration were noted in any of the studies.

Further to the safety data obtained for buccal midazolam, a wider overall critical discussion on the safety profile of midazolam in adult epilepsy, as recorded also for other authorized routes of administration (e.g. intranasal, intramuscular) is provided in the following.

Previous experience with the intranasal midazolam formulation in 243 patients with epilepsy (mean age 35.5 years; age range 5–76 years) during the treatment of 459 seizures has indicated that following a median dose of intranasal midazolam 5 mg (i.e., two puffs; range 2.5–15 mg), the treatment was well tolerated without major adverse events being recorded. The most common side effects were irritation of the nasal mucosa [37 cases (8.1%)], prolonged sedation [26 cases (5.7%)], nausea and vomiting [12 cases (2.6%)]. A decline in oxygen saturation was measured in relation to 78 seizures (17%). One patient had respiratory depression, but recovered quickly after oxygen was applied and no intubation was necessary. Oxygen levels of all other patients recovered within seconds after seizure cessation. No other major cardiocirculatory or respiratory adverse events were observed at doses providing similar systemic drug exposure as those obtained after buccal midazolam administration and no major adverse events were detected that required additional medical assistance (von Blomberg et al., 2020).

Previous studies have also suggested a well-defined and favorable safety profile of intranasal midazolam in adults. Detyniecki et al. (2019) detected TEAEs in 57.1% of patients (n = 161), mainly nasal irritation (12.4%) and somnolence (9.3%) following nasal administration of 5 mg midazolam. Kay et al. (2015) (n = 75) also observed some side effects in four patients (5.3%) treated with a mean dose of 5.1 mg (up to 10 mg in selected patients) of intranasal midazolam, with three showing nasal irritation and one patient delaying use of the study drug due to peri-ictal movement of the head. In a similar study of 21 patients receiving a total of 10 mg midazolam, De Haan et al. (2010) reported 68% of in-midazolam administrations (n = 59) to have caused drowsiness, while 29% led to nasal irritation. None of these studies reported a high incidence of serious respiratory depression effects by midazolam treatment or related serious adverse events.

As has been particularly discussed in the scientific literature, the number of patients with postictally reduced oxygen saturation reported in studies with intranasally or buccally administered midazolam is similar or rather low when compared with results of dedicated studies on the effect of seizures on breathing (von Blomberg et al., 2020). Bateman et al. (2008) demonstrated that pulse oximetry will show oxygen desaturations below 90% in 33.2% of all seizures, and such data was confirmed in several recent studies, pointing especially at generalized tonic–clonic seizures that lead to a temporary decline in breathing efforts and reduced peripheral oxygenation (Devinsky, 2004; Lacuey et al., 2018; Vilella et al., 2019). Overall, as has been indicated, postictal respiratory depression may be caused by multiple reasons not limited to anticonvulsive treatment (McIntyre et al., 2005; von Blomberg et al., 2020). Indeed, in adults, 22.5% of patients who received placebo therapy experienced either hypotension, cardiac dysrhythmia, or a respiratory problem that required an intervention compared to 10.6% in the IV lorazepam group and 10.3% in the IV diazepam group (Alldredge et al., 2001).

Accordingly, several studies evaluating the efficacy and safety of intramuscular midazolam in the management of seizures in patients (including adults) have demonstrated an overall acceptable safety profile. A list of adverse events associated with IM midazolam along with their reported frequency is listed in Table 10. As can be seen, common adverse reactions (>1% of cases) concern the inhibitory

effect of IM midazolam on the central nervous system (CNS), including reduced consciousness and mental status changes (Riva et al., 2020).

Table 10 Adverse events reported for IM midazolam. Table adopted from Riva et al. (2020).

	Common (> 1%)	Uncommon (0.1% to 1%)
Blood and lymphatic syste		-Anemia -Transfusion reaction
Cardiovascular system		-Myocardial infarction -Hypotension -Bradycardia -Cardiac arrest -Ventricular tachycardia -Deep vein thrombosis
Endocrine system		-Hypoglycemia -Hyperglycemic hyperosmolar nonketotic syndrome
Gastrointestinal system	-Vomiting/Nausea	-Pancreatitis, acute
CNS	-Depressed level of consciousness -Seizures -Mental status changes	-Cerebral hemorrhage -Ischemic stroke -Encephalopathy -Delirium -Subarachnoid hemorrhage -Suicidal ideation
Musculoskeletal disorders		-Rhabdomyolysis
Genitourinary system		-Renal failure, acute -Hematuria
Respiratory system	-Respiratory depression	-Apnea -Pneumothorax -Pulmonary embolism - Pneumonia/Aspiration pneumonia
General disorders	-Pyrexia -Sepsis/SIRS/organ failure	-Drug withdrawal syndrome -Chest pain -Hematoma -Cellulitis

CNS = Central Nervous System; SIRS = Systemic Inflammatory Response Syndrome.

IM midazolam has been found at least as safe as other benzodiazepines in all age groups (including adult patients) (Riva et al., 2020). The major clinical study of IM midazolam which involved adult patients and children with status epilepticus (SE) under a double-blind, randomised, non-inferiority design was RAMPART (Silbergleit et al., 2012). In this study, 448 subjects were assigned to IM midazolam and 445 were assigned to IV lorazepam, (total number of subjects=893, aged 0-102 years; more specifically: 0-5 years, n=61; 6-10 years, n=35; 11-20 years, n=49; 21-40 years, n=226; 41-60 years, n=338; ≥61 years, n=184). This study showed that IM midazolam was at least as safe and effective as the well-established active comparator, IV lorazepam, for prehospital seizure cessation, presenting also a similar adverse event rate. In another study in 38 patients, aged 15 months to 89 years, being treated with IM midazolam at an average dose of 0.12 mg/kg (range 0.07-0.21 mg/kg), corresponding to an average dose of 9 mg for a 75 kg adult, seizures terminated in all but two cases in an average time of 1 minute 53 seconds overall, with no adverse side effects being reported in any patient. In particular, no cases of cardiovascular or respiratory depression requiring treatment occurred (McDonagh et al., 1992). For subjects with SE, IM midazolam was at least as safe and effective as IV lorazepam for prehospital seizure cessation.

Safety data in adults have been also obtained from midazolam pharmacokinetic studies investigating the buccal route (Schwagmeier et al., 1998; Scott et al., 1998). No respiratory or cardiovascular depression have been observed in either of these trials. Safety data obtained from the proprietary comparative bioavailability study performed in adults (Study LESVIBUCCO/23/BQ-3), receiving 15 mg of midazolam buccally, indicated that all treatment-related adverse events were of mild to moderate intensity, with the most common adverse event being somnolence reported by all subjects. Other recorded adverse events among subjects who received the currently applied buccal midazolam formulation included influenza-like illness, COVID-19 infection, back pain, headache and epistaxis, with only somnolence, headache and influenza-like symptoms being considered related to drug treatment.

Overall, given the well-acknowledged acceptable safety profile of midazolam in all age groups as derived from literature data, it may be safely concluded that buccally administered midazolam in adults is not expected to present any additional, unexpected serious adverse events that could potentially alter the already recorded positive benefit/risk balance of midazolam administered by any route in the identified published clinical studies involving adult patients.

Safety related to drug-drug interactions and other interactions

Not applicable.

Discontinuation due to adverse events

Not applicable.

Post marketing experience

The clinical safety profile of buccal midazolam can be considered as well-established based also on the extensive exposure of patients during the licensed clinical use of the EU/UK authorised product Buccolam® over the last decade. In this respect, relevant postmarketing safety data of Buccolam® clinical use, since its first authorisation in 2011 till present, are presented and discussed.

Table 11 Postmarketing information obtained from the PSURs over the chronological period of 2011-2022.

Reference	Reported period	Exposures based on data from PSURs	Comments
PSUR (May 2012)	05/09/2011 to 05/09/2012	During the reporting period of this PSUR in the marketed environment, there were approximately 6,770 boxes of Buccolam® distributed worldwide with each box containing 4 pre-filled oral syringes. Given the difficulty in estimating how many seizures a child will have over a given period, it is very challenging to link the number of boxes distributed to the number of patients treated since seizures in severe patients can happen several times per week.	During the reporting period of this PSUR, 2 spontaneous ICSRs were received including those received from literature and regulatory agencies. Of these 2 ICSRs, both were medically confirmed and non-serious. During the reporting period of this PSUR, there were no reports from clinical studies. The SmPC for Buccolam® that was current as of 05-Mar-2012 was the initial SmPC for the product which was approved on 05-Sep-2011. During the reporting period of this PSUR, there were no safety related updates to the SmPC. Examination of the data contained within this PSUR supports the conclusion that the overall benefit-risk balance for Buccolam® continues to be positive. As with all MAH products, the safety profile of Buccolam® is monitored on a continuing basis.

Reference	Reported period	Exposures based on data from PSURs	Comments
PSUR (November 2012)	06/03/2012 to 05/09/2012	During the reporting period of this PSUR from 06-Mar-2012 through 05-Sep-2012, there were approximately 20,990 boxes of Buccolam® distributed worldwide with each box containing 4 pre-filled oral syringes. This total number is representative of exposure data from 3 distribution routes. Given the difficulty in estimating how many seizures a child will have over a given period, it is very challenging to link the number of boxes distributed to the number of patients treated since seizures in severe patients can happen several times per week.	During the reporting period of this PSUR, there were no reports from clinical studies. During the reporting period of this PSUR, 7 spontaneous ICSRs were received including those received from literature and regulatory agencies. Of these 7 ICSRs, 6 were medically confirmed and the remaining 1 was not medically confirmed. Of the 6 medically confirmed ICSRs, 1 was serious and the remaining 5 were non-serious. The SmPC for Buccolam® that was current as of 05-Sep-2012 is the initial SmPC for the product which was approved on 05-Sep-2011. During the reporting period of this PSUR, there were no safety related updates to the SmPC. Examination of the data contained within this PSUR supports the conclusion that the overall benefit-risk balance for Buccolam® continues to be positive. As with all MAH products, the safety profile of Buccolam® is monitored on a continuing basis.
PSUR (November 2013)	06/09/2012 to 09/09/2013	During the interval of 06-Sep-2012 to 09-Sep-2013, 94,206 boxes of Buccolam® were distributed. Cumulatively, from 05-Sep-2011 to 09-Sep-2013, 120,144 boxes of Buccolam® were distributed worldwide, with each box containing 4 pre-filled oral syringes. During the reporting interval in the named patient programme, there were approximately 1,831 boxes of Buccolam® distributed with each	During the reporting period of this PSUR, there were no MAH-sponsored interventional clinical studies in which subjects were exposed to investigational product (Buccolam®, placebo or comparator). During this reporting period, a non-interventional cross-sectional observational survey to identify quality of life and burden of disease issues was initiated: European Survey of Children Living with Prolonged, Acute, Convulsive Seizures: Patient and Parent Experience of Current Practice in the Community Setting; Part of the PERFECT Initiative. During the reporting interval of this PSUR, there were no reports from clinical studies. In total 23 postmarketing ICSRs were received, including those from literature and regulatory agencies. In addition, there was

Reference	Reported period	Exposures based on data from PSURs	Comments
		box containing 4 pre-filled oral syringes. Given the difficulty in estimating how many seizures a child will have over a given period, it is very challenging to link the number of boxes distributed to the number of patients treated since seizures in some patients with severe manifestations of their disease can happen several times per week.	1 ICSR received through the named patient programme. There were no safety related updates to the CCDS for Buccolam®. Overall, the previously established favorable benefit-risk profile for Buccolam® has not changed with information received during this reporting interval.
PSUR (November 2014)	10/09/2013 to 09/09/2014	During the interval, 158,932 boxes (635,728 doses) of midazolam were distributed. Cumulatively as of 09 Sep 2014, there were 428,015 boxes (1,712,060 doses) of midazolam distributed worldwide with each box containing 4 pre-filled oral syringes. Given the difficulty in estimating how many seizures a child will have over a given period, it is very challenging to link the number of boxes distributed to the number of patients treated since seizures in some patients with severe manifestations of their disease can happen several times per week.	During the reporting period, no new safety signals/ risks were identified. Ongoing risks: Previously identified and ongoing safety risks with midazolam, as delineated in the EU Risk Management Plan for Buccolam®, are as follows: Identified Risks: • Respiratory/Cardiac insufficiency • Anterograde amnesia • Paradoxical reactions • Nausea/Vomiting • Pruritus Potential Risks: • Abuse/Diversion • Accidental exposure • Asphyxiation/Aspiration • Buccal irritation • Choking on syringe cap • Misuse/Attaching lines to syringe • Overdose

Reference	Reported period	Exposures based on data from PSURs	Comments
			• Interaction with CNS acting substances • Underdosing in adolescents • Medication error • Off-label use No significant new information was received during the reporting period on any of the open important risks for midazolam. No risks were closed during the reporting period.
PSUR (October 2015)	10/09/2014 to 09/09/2015	During the interval approximately 220,973 boxes (883,892 doses) of midazolam were distributed. Cumulatively as of 09 September 2015, there were approximately 482,368 boxes (1,929,472 doses) of midazolam distributed worldwide with each box containing 4 pre-filled oral syringes. Given the difficulty in estimating how many seizures a child will have over a given period, it is very challenging to link the number of boxes distributed to the number of patients treated since seizures in some patients with severe manifestations of their disease can happen several times per week.	The identified and potential risks for midazolam remain in accordance with previous experience and as delineated in the EU Risk Management Plan (version 5, effective at the start of the reporting period): Identified Risks: • Respiratory/Cardiac insufficiency • Anterograde amnesia • Paradoxical reactions • Nausea/Vomiting • Pruritus Note: The EU-RMP is being updated to version 6.0 during the reporting period and no changes have been made to the identified and potential risks at this time. Identified risks Nausea/Vomiting and Pruritus are listed ADRs in the CCDS for midazolam. Based on a comprehensive cumulative review of available worldwide safety data (from clinical trial/non-clinical/literature and post-marketing cases), nausea/vomiting and pruritus are considered well-characterised risks and no significant changes in frequency/severity/ specificity were identified for these events over the last 5 years. The MAH therefore proposes the closure of identified risks of nausea/ vomiting and pruritus and their removal from the list of ongoing identified risks, upon positive opinion received via

Reference	Reported period	Exposures based on data from PSURs	Comments
			Final PSUR Assessment Report. Potential Risks: • Abuse/Diversion • Accidental exposure • Asphyxiation/Aspiration • Buccal irritation • Choking on syringe cap • Misuse/Attaching lines to syringe • Overdose • Interaction with CNS acting substances • Underdosing in adolescents • Medication error • Off-label use No significant new information was received during the reporting period on any of the ongoing important risks for midazolam. No risks were closed during the reporting period.
PSUR (October 2016)	10/09/2015 to 09/09/2016	During the reporting interval, there were approximately 1,114,356 doses of midazolam distributed worldwide. Given the difficulty in estimating how many seizures a child will have over a given period, it is very challenging to link the number of doses distributed to the number of patients treated since seizures in some patients with severe manifestations of	During the reporting period under review, there was no action taken for safety reasons that resulted in Marketing Authorisation withdrawal or suspension, failure to obtain marketing authorisation renewal, clinical trial suspension, dosage modification, change in target population or pharmaceutical changes due to identified safety reasons. Also, no new safety signals/risks were identified. The identified and potential risks for midazolam remain in accordance with previous experience and as delineated in the EU Risk Management Plan (version 6.1, effective at the start of the reporting period): Identified Risks: • Respiratory/Cardiac insufficiency • Anterograde amnesia • Paradoxical reactions

Reference	Reported period	Exposures based on data from PSURs	Comments
		their disease can happen several times per week. Approximately 496 children have been exposed in clinical trials to single doses of buccal midazolam ranging from 0.2 to 0.6 mg/kg, and up to a 10-mg dose.	Note: Upon positive opinion received from PRAC for the Final PSUR Assessment Report for PSUR 005/PBRER 003 (10 Sep 2014 to 09 Sep 2015) dated 17 Mar 2016, identified risk: Nausea/Vomiting and Pruritus which are listed ADRs in the CCDS for MDZ have been closed. Potential Risks: • Abuse/Diversion • Accidental exposure • Asphyxiation/Aspiration • Buccal irritation • Choking on syringe cap • Misuse/Attaching lines to syringe • Overdose • Interaction with CNS acting substances • Underdosing in adolescents • Medication error • Off-label use No significant new information was received during the reporting period on any of the ongoing important risks for midazolam. The following important identified risks were closed during reporting period: nausea, vomiting, pruritus.
PSUR (November 2019)	10/09/2016 to 39/09/2019	During the reporting period interval, approximately 1,094,734 boxes (4,378,936 doses) of midazolam were distributed. Cumulatively as of 09 September 2019, there were approximately 1,956,817 boxes (7,827,268 doses) of	During the reporting period, no new risks were identified. However, 2 safety signals were identified and evaluated, i.e.: • Coma and death with concomitant use of opioids and midazolam. • Choking on syringe cap. Previously important identified and potential risks for midazolam remain in accordance with previous experience and as delineated in the EU Risk Management Plan. New information was received during

Reference	Reported period	Exposures based on data from PSURs	Comments
		midazolam distributed worldwide with each box containing 4 pre-filled oral syringes. Given the difficulty in estimating how many seizures a child will have over a given period, it is very challenging to link the number of boxes distributed to the number of patients treated since seizures in some patients with severe manifestations of their disease can happen several times per week. A total of 707 subjects (approximately 663 children and 44 adults) have been exposed to buccal midazolam in clinical studies based on literature findings and information included the Investigator's Brochure.	the reporting period regarding the important potential risk of "Choking on syringe cap." No risks were closed during the reporting period. However, the MAH has proposed some important risks to be reworded (Respiratory and cardiac insufficiency; Asphyxiation/Aspiration; Choking on syringe cap) and some to be closed (Paradoxical reactions; Buccal irritation; Accidental exposure and Misuse by attaching lines to the syringe).
PSUR (November 2022)	10/09/2019 to 09/09/2022	It has been estimated that approximately 1,318,413 units of midazolam were distributed during the period covered by this safety report (at least equivalent to 1,318,413 patients exposed). Cumulatively, 3,275,230 units of the product have been sold (at least equivalent to 3,275,230 patients exposed).	In total, 649 case reports involving 1,922 AEs (1,044 serious and 878 non-serious) associated with midazolam-containing products were received from spontaneous sources. 13 cases reports, involving 67 AEs (11 serious and 56 non-serious) were received from non-interventional post marketing studies and reports from other solicited sources. Cumulatively, 1,393 case reports have been collected from spontaneous sources; these cases involved 3,820 coded adverse reactions; 2,029 of them were regarded as serious. Sixty-three (63) cases reports, involving 148 AEs (68 serious and 80 non-serious) were received from non-

Reference	Reported period	Exposures based on data from PSURs	Comments
		Post-marketing patient exposure to midazolam in the reporting period was estimated to be approximately 1,318,413 patients exposed and cumulatively 3,275,230 patients exposed.	interventional post-marketing studies and reports from other solicited sources. Updated safety concerns: • The important identified risks "Respiratory/Cardiac insufficiency", "Anterograde amnesia" and "Paradoxical reactions" have been removed from the list of safety concerns. • The important potential risks "Abuse/Diversion", "Accidental exposure", "Buccal irritation", "Misuse by attaching lines to syringe", "Overdose", "Interaction with CNS acting substances", "Under dosing in adolescents" and "Off-label use" have been removed from the list of safety concerns. • The important missing information "Use in patients with chronic renal failure", "Use in patients with impaired hepatic function", "Use in patients with myasthenia gravis", "Use in patients with history of drug or alcohol abuse" and "Use in pregnancy" have been removed from the list of safety concerns. • The important potential risk "Asphyxiation/aspiration" has been reworded as "Aspiration/Aspiration pneumonia" and "Asphyxiation" has been encompassed in the important potential risk of "Choking on syringe cap" so that it has been reworded as "Choking on syringe cap" to address and prevent the risk of inhalation or ingestion of the pre-filled syringes. No other relevant information affecting the known safety profile of midazolam has been identified. Based on the evaluation of the cumulative safety data and the benefit-risk analysis,

Reference	Reported period	Exposures based on data from PSURs	Comments
			no new safety trends or signals have arisen during the reporting interval. No changes to the Reference Safety Information (RSI) or other safety actions beyond routine pharmacovigilance are necessary. The benefit-risk balance for midazolam remains favourable.
Abbreviations: ADR, adverse drug reaction; AE, adverse event; CCDS, Company Core Data Sheet; CNS, central nervous system; EU, European Union; ICSRs, individual case safety reports; MAH, Marketing Authorisation Holder; PRAC, Pharmacovigilance Risk Assessment Committee; PSUR, Periodic Safety Update Report; RSI, Reference Safety Information; SmPC, Summary of Product Characteristics.			

In the last updated PSUR *(PSUR November 2022)*, no other relevant information affecting the known safety profile of midazolam has been identified in the overall risk/benefit assessment performed. In addition, based on the evaluation of the cumulative safety data and the benefit-risk analysis, no new safety trends or signals have arisen during the reporting interval. The benefit-to-risk balance for midazolam remains, thus, favourable.

Discussion on Important Safety Concerns (postmarketing)

Medication errors

According to the data reported within the updated PSUR Report (10 September 2019 to 9 September 2022) published in 2022, cumulatively, 537 cases related to midazolam involving a total of 613 AEs (71 serious and 542 non-serious) associated with medication errors were received. The most frequently reported events were product use issues (188), product use in unapproved indications (49), incorrect dose administered (37), product administered to patients of inappropriate age (37). Based on this information, the reporting rate for these events when calculated per 1,000,000 patients exposed was 18.72 [95% confidence interval (CI): 17.26-20.26]. The review of the cases related to medication errors showed that most often reported events concerned product use issues which appeared to be actually use in non-paediatric patients or product administered to patients of inappropriate age. Similar medication error cases (i.e., reporting the event of administration of product to patients above the age range) were included in the PSUR for Epistatus®. Intended administration and use outside the registered age and/or indication is concerned to be off-label use of the products, and the Marketing Authorisation Holders (MAHs) should classify such cases accordingly.

The potential risk of medication errors can be serious. Patients or caregivers of patients who are misinformed about the correct dosing and administration of the medication are risk groups. Hence, medical attention should be immediately sought for patients who have been exposed to other than the recommended dose.

For the prevention of occurrence of medication errors, pre-filled syringes are coloured differently for the different strengths and the intended patient age population groups. In addition, the product information of the licensed oromucosal midazolam provides information on dosing, method of administration and precautions to be taken before administering the product. Furthermore, additional risk minimisation measures (RMMs) have been implemented in some countries ('Patient booklet' and 'Buccolam administration guide') to address and prevent the risk of inhalation or ingestion of the pre-

filled syringes, thus, minimising to the minimum the potential risks of "Choking/asphyxiation on the syringe cap" and "Medication error".

Overall, based on the cumulative case reports collected in the Applicant's safety database and the cumulative exposure, no specific trend on patterns of medication errors and potential medication errors have been identified. Therefore, the Applicant considers that the safety profile presented is adequate and the potential impact on public health is expected to be low, with additional measures being not warranted.

Underdosing in adolescents

Underdosing has not been observed in subjects during clinical trials of midazolam and has not been described in post marketing surveillance reports or scientific literature. Underdosing in adolescents could result in a subtherapeutic effect; it potentially could occur in adolescent patients aged >12-years with weight above 40 kg, namely due to variations of patient's weight *(PSUR November 2019)*.

Detailed and specific administration instructions under the Posology and Method of Administration section are presented. During the reporting interval of the PSUR (November 2019), there were no events of underdosing in adolescents. Also, routine pharmacovigilance during the reporting period did not identify any new significant safety information impacting the cumulative knowledge in relation to the potential risk of underdosing adolescents whilst administering midazolam. Events of underdosing in adolescents associated with midazolam therapy, however, needs to be monitored through routine pharmacovigilance.

Off-label use

Off-label use of buccal midazolam is a potential risk which has been added to the Risk Management Plan of the authorised Buccolam® product, based on the obtained PSUR Assessment Reports. During post-marketing surveillance, 91 reports involving off-label use or product use issue were retrieved, describing a total of 93 events which coded to the following MedDRA Preferred Terms: 'Off label use' (n=48), 'Product use issue' (n=25), 'Product administered to patient of inappropriate age' (n=16) and 'Intentional product use issue' (n=4). Among the 91 reports, the majority (63%; 57/91) were non serious and reported no associated AEs and these reports are not discussed further. Of the remaining 34 reports that reported associated AEs, 5 reported drug ineffective (including 3 involving adult patients). Of the remaining 29 reports, 18 were serious *(PSUR November 2019)*.

Off-label use in adult patients

Of the 18 reports, 11 were from regulatory authorities and involved the use of midazolam in adult patients. Nine of these 11 reports did not specify the dose or route of administration and had multiple cos-suspects such as fentanyl, bromazepam, clonazepam, etomidate, methadone, mirtazapin, heparin, ketamine, nimodipine, propofol, sufentanil and enoxaparin. The reported indication was other than seizure or epilepsy in 2 of the reports (anaesthesia and anxiety). Midazolam with the trade name Buccolam® was the only suspect in 2 of the 11 reports, including a report of asphyxia and a consumer report involving a 34-year-old female patient (patient of inappropriate age) and reporting seizure, however, this report provided insufficient information such as dosage, duration of treatment, time to onset and patient's medical history for a complete assessment. Of the remaining 7 serious reports, 4 reports with unknown age and midazolam being the only suspect included the following: 1 report with seizure as the associated AE and the report was poorly documented and it was not clear what the reporter meant by 'the patient wants to continue despite having seizures' as the indication for the drug is seizure. It is likely that the patient was using it as a prophylactic rather than treatment for attacks, against the pharmacist's recommendation. The other 3 reports described the occurrence of mouth ulcer, drug diversion and respiratory arrest, respectively *(PSUR November 2019)*.

Off-label use in paediatric patients

Of the 18 reports, 3 involved paediatric patients. Based on the available safety information provided in these reports describing the off-label use, there is no new safety signal noted that changes the safety profile of midazolam. The review of interval and cumulative cases reporting off-label use, reported within the PSUR (November 2019), did not reveal any significant safety findings impacting the cumulative knowledge in relation to this potential risk or the safety profile of midazolam.

Hence, taking into account the cumulative review and analysis of safety data from clinical trials and postmarketing exposure, it can be indicated that the frequency, pattern and characteristics of reports of off-label use have not changed since initial marketing approval. By taking the appropriate measures and precautions related to the proposed medicinal product distribution, it can be suggested that off-label use can be restricted within rational and acceptable limits.

Overall, the general safety profile of buccal midazolam can be considered as well-established by the extensive safety data, including those derived from the published clinical studies conducted in adult and paediatric patient populations, the proprietary efficacy and PK studies (in both adults and children) and the postmarketing data record available for Buccolam®. An overall acceptable benefit-risk profile has been demonstrated for the use of buccal midazolam as a single, fixed-dose product, banded by age, for the treatment of individual acute seizures in children (aged 3 months to <18 years) and adults known to have epileptic seizures.

2.4.1. Discussion on clinical safety

The safety data provided to support the safety profile of Buccolam for the treatment of PACS in adults is based on two sources: Study LESVIBUCCO/23/BQ-3 (a comparative bioavailability study in healthy volunteers) and published literature studies of buccal, intranasal and intramuscular midazolam for prolonged seizures.

Although the safety profile of midazolam can be considered well-characterised, the safety data provided of buccal administration in the acute setting of PACS in adults is considered too limited to establish a safety profile for this specific formulation. The safety information that can be derived from these publications are limited, as these were not clinical trials designed to support registration and thus detailed information about adverse events and causality are not included. Thus, these studies are insufficient to support a safety profile of buccal midazolam in adults with PACS

Additional safety information has been provided derived from studies that evaluated different routes of midazolam for the treatment of PACS in adults, i.e. intranasally and intramuscular. Most of these studies evaluated 10 mg of midazolam in adults, a lower dose of 5 mg was used in several studies. Although the level of detail differs per study, depending on the study design and objectives, the overall safety profile appears consistent with what is described for Buccolam in children (Buccolam SmPC). Most commonly reported events are somnolence, sedation and drowsiness. Several adverse events such as nasal irritation are specifically related to the route of administration. No cardiorespiratory events were reported in the literature.

Considering that the PK profiles cross the routes of administration for midazolam are similar, there is no reason to expect a different safety profile for buccal administration in adults. Thus, the safety data from the studies that evaluated intranasal and intramuscular midazolam can be considered supportive for the safety profile of buccal midazolam in adults. Overall, the safety profile in adults appear consistent with that what has been observed in children. No additional risks have been identified for a single dose of Buccolam in adults.

Additional data have also been provided with respect to safety of (buccal) midazolam in elderly patients. The provided literature mainly consists of review articles that evaluate treatment options for status epilepticus in adult or geriatric patients, which do not include a thorough evaluation of the safety profile of midazolam at the target dose of 10 mg. Other articles reviewed midazolam in a different treatment setting (i.e. agitation or palliative care) and cannot be readily applied to the setting of PACS in geriatric patients. The referenced study by Berg et al. (2019) concerned a PK/PD study of intranasal midazolam (NASOLAM nasal spray) in healthy geriatric and non-geriatric adults. Doses of 2.5 and 5 mg were evaluated and the safety outcomes indicated similar adverse events between the two patient populations. Vital signs, including oxygen saturation levels remained acceptable. Overall the study indicated intransal midazolam was well tolerated in the older patient population.

As discussed previously, the PK profiles of different routes of midazolam administration are considered similar, thus the safety profile of intransal midazolam can be applied to buccal midazolam. The study by Berg et al (2019) did indicate that overall and maximum plasma midazolam exposure were higher in geriatric versus non-geriatric patients (including the metabolite) for the product evaluated. A lower dose of Nasolam is recommended for elderly patients compared to adults. This is likely due to the intranasal route providing a faster uptake of midazolam, therefore increasing a risk of respiratory depression for this vulnerable patient population. No such effect has been observed for buccal midazolam. Moreover, for Buccolam, the Applicant has provided updated PK analyses (see clinical pharmacology) that includes 4 elderly subjects to evaluate the impact of age on exposure. Based on these analyses, no clinically meaningful differences in the metabolite exposure of elderly subjects (≥65 years) are expected. It is agreed that in elderly patients, caution should be applied in elderly patients as elimination of midazolam may be delayed and the clinical effects of midazolam prolonged.

Limited information has been provided for other at-risk patient populations. Considering that this is a single dose in an emergency setting, it can be reasonable assumed that caution should be applied with use of Buccolam in this patient population. A similar PK profile is expected in patients with renal or hepatic impairment. A dose adjustment may be warranted but this will depend on the individual patient and thus should be up to the prescriber's clinical judgement as adequately reflected in the Buccolam SmPC.

2.4.2. Conclusions on clinical safety

No new safety risks are identified for buccal midazolam for the treatment of PACS in adults.

2.4.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.5. Risk management plan

The MAH submitted an updated RMP with this application.

The PRAC considered that the risk management plan version 8.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 8.2 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	None.
Important potential risks	Aspiration/aspiration pneumonia. Choking/asphyxiation on syringe cap. Medication errors.
Missing information	Use in children < 6 months of age.

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Aspiration/aspiration pneumonia	Routine risk minimisation measures: *SmPC section 4.2.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*
Choking on a syringe cap / Asphyxiation	Routine risk communication: *SmPC Section 4.2.* *SmPC Section 6.6.* *PIL: Section 5.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*
Medication Errors	Routine risk communication: *SmPC Section 4.2.* *SmPC Section 4.9.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*
Use in children < 6 months of age	Routine risk communication: *SmPC Section 4.4.* *SmPC Section 5.1.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: *None.*	Additional pharmacovigilance activities: *None.*

2.6. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.5 of the SmPC are being updated to include information on the use in adults. The Package Leaflet (PL) is updated accordingly. In addition, the MAH took the opportunity to update the local representative in the PL.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.6.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

A bridging report making reference to the currently approved PIL for Buccolam has been submitted and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The MAH is seeking extension of the indication of Buccolam (oromucosal/buccal midazolam) to the treatment of prolonged acute convulsive seizures (PACS) in adults.

3.1.1. Disease or condition

Epilepsy is a chronic neurologic condition characterised by recurrent episodes of seizures, namely brief episodes resulting from an excessive and hypersynchronous electrical discharge of neurons in the brain.

Of the patients being at risk for breakthrough seizures, a given number will experience PACS, which, if uncontrolled, may lead to SE. Apart from possible secondary injuries (e.g. head trauma, drowning and burning), prolonged seizures can induce significant medical emergencies, such as cardiac arrhythmias, lung congestion, liver failure, severe cerebral damage or rhabdomyolysis. Increased seizure duration is associated with increased morbidity and mortality. Therefore, early treatment may prevent such consequences.

3.1.2. Available therapies and unmet medical need

Initial treatment of the acute prolonged seizure is often carried out by emergency room physicians, paediatricians and in some communities, paramedical personnel, family or carers before arrival at an emergency facility. Benzodiazepines are first line treatment for the control of PACS. PACS were historically managed by the rectal administration of diazepam. However, the rectal route has now

largely fallen out of favour due to practical and social concerns. Alternative treatment options are the use of midazolam, either intranasal or buccal as it is seen as quicker and easier to access and as it avoids the social stigma of rectal administration.

3.1.3. Main clinical studies

To support the extension of the indication, the MAH provided the following data:

- A relative bioavailability (RBA) study of Buccolam® versus Hypnovel® in healthy adult volunteers (LESVIBUCCO/23/BQ-3)
- An updated population PK model for midazolam and 1-hydroxymidaozlam using paediatric data from study MID001 and study SHP615-301.
- A population PK modelling study for midazolam and 1-hydroxymidaozlam using adult data from study LESVIBUCCO/23/BQ-3.
- 7 bibliographic studies evaluating the efficacy/safety of midazolam for the treatment of PACS in adults (3 are "pivotal", 4 "supportive")

3.2. Favourable effects

The 3 bibliographic studies marked as pivotal by the MAH suggest a potential beneficial effect of midazolam in the treatment of PACS in adults with epilepsy.

3.3. Uncertainties and limitations about favourable effects

The provided bibliographic studies differ greatly in terms of study design, presence of an adequate comparator arm, midazolam dose used, definition of prolonged seizures (or lack of definition) and endpoints. All submitted bibliographic studies have methodologic flaws which hamper the interpretation of efficacy, i.e. lack of randomisation, lack of comparator, bias, lack of proper non-inferiority assessment etc.

It is acknowledged that the emergency setting of PACS complicates a blinded placebo-controlled approach. Nevertheless, in absence of such studies, randomized studies with an established comparator such as diazepam can provide confirmative evidence of efficacy. Of the 3 pivotal studies submitted to support the adult indication, only one (Nakken and Lossius) included a comparator arm, but in absence of randomisation and proper non-inferiority assessment, the interpretation of efficacy is hampered.

Based on the provided literature, conclusions with respect to efficacy of buccal midazolam for the treatment of PACS in adults cannot be drawn.

Alternatively, to support the extrapolation of efficacy obtained with Buccolam in children to adults with PACS, the dose-exposure-response relationship of midazolam has been characterised. The Applicant has shown that the updated popPK model is of relevance to the claimed indication (patients with prolonged seizures). New simulations have been provided in both paediatric and adult subjects. The target exposure range where efficacy and safety have been established in children 3m<10 years of age has been identified (0.431-1.714 nmol·h/mL for the total exposure of MDZ and 1-OH-MDZ (AUC0-inf)). To support the PK bridge, 9 publications were discussed which compared buccal midazolam for the treatment of PACS versus rectal diazepam (6 studies), intravenous diazepam (2 studies) and intramuscular midazolam (1 study).

The studies by McIntyre (2005), Mpimbaza (2008), Scott (1999), Baysun (2005) and Talukdar (2009) were considered pivotal to support the paediatric indication during the initial marketing authorisation application of Buccolam. Although these studies have several methodological flaws, it was concluded that the trials support the clinical efficacy of buccal midazolam in the treatment of acute seizures in children and adolescents irrespective of cause, with a magnitude of effect similar to standard treatments, a sufficiently rapid onset of effect and some evidence for efficacy in the prevention of recurrence of seizures up to 24 hours. The doses of buccal midazolam used in the trials align with the doses used in the PK analyses to support the target exposure in children.

Subsequently, the 10 mg dose was proposed as the optimal, efficacious, and safe dose for Buccolam to treat adults with prolonged acute convulsive seizures based on comparison with the paediatric reference range. The modelling exercise is satisfactory to support a PK-bridge wherein the efficacy information can be extrapolated from children given buccal MDZ. Part of the extrapolation exercise is to also indicate if the disease is sufficiently similar between the age groups. Such a discussion was not provided. Although there are no indications that these types of acute seizures present differently between children and adults, a difference cannot be ruled out. However, various European guidelines recommend midazolam, albeit in various routes of administration, also for the treatment of PACS/initial status epilepticus in adults.

Considering that this is an acute treatment in an emergency setting, combined with guideline recommendations, an extrapolation approach based solely on similarity in exposure can be accepted for the current Buccolam extension of indication to the adult population.

3.4. Unfavourable effects

Limited safety data is discussed from study LESVIBUCCO/23/BQ-3 and the bibliographic studies provided to support the extension of the indication to adults.

3.5. Uncertainties and limitations about unfavourable effects

Although the safety profile of midazolam can be considered well-characterised, the safety data provided of buccal administration in the acute setting of PACS in adults is considered too limited to establish a safety profile for this specific formulation. Most of the bibliographic studies lacked detail with respect to the occurrence of adverse events and other safety aspects. The safety information that can be derived from these publications are limited, as these were not clinical trials designed to support registration and thus detailed information about adverse events and causality are not included. Thus, these studies are insufficient to support a safety profile of buccal midazolam in adults with PACS

Additional safety information derived from studies that evaluated different routes of midazolam for the treatment of PACS in adults, i.e. intranasally and intramuscular has been provided. Considering that the PK profiles cross the routes of administration for midazolam are similar, there is no reason to expect a different safety profile for buccal administration in adults. Thus, the safety data from the studies that evaluated intranasal and intramuscular midazolam can be considered supportive for the safety profile of buccal midazolam in adults. Overall, the safety profile in adults appear consistent with that what has been observed in children. No additional risks have been identified for a single dose of Buccolam in adults.

Additional data have also been provided with respect to safety of (buccal) midazolam in elderly patients. Based on the updated PK analyses which included 4 elderly subjects, no clinically meaningful differences in the metabolite exposure of elderly subjects (≥65 years) are expected. It is agreed that in elderly patients, caution should be applied in elderly patients as elimination of midazolam may be

delayed and the clinical effects of midazolam prolonged. This is adequately reflected in the Buccolam SmPC.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The bibliographic data initially provided was insufficient to establish efficacy of buccal midazolam for the treatment of PACS in adults.

Considering this has been accepted previously for intranasal midazolam, the extrapolation of efficacy from children to adults with PACS as an alternative route to substantiate the adult indication may be based on exposure matching.

The updated popPK model provided by the MAH during the assessment is considered of relevance to the claimed indication (patients with prolonged seizures). New simulations have been provided in both paediatric and adult subjects. The target exposure range where efficacy and safety have been established in children 3m<10 years of age has been identified (0.431-1.714 nmol·h/mL for the total exposure of MDZ and 1-OH-MDZ ($AUC_{0\text{-}inf}$)). The PK bridge is supported by literature of buccal midazolam for the treatment of PACS in children. Subsequently, the 10 mg dose was proposed as the optimal, efficacious, and safe dose for Buccolam to treat adults with prolonged acute convulsive seizures based on comparison with the paediatric reference range. The modelling exercise is satisfactory to support a PK-bridge wherein the efficacy information can be extrapolated from children given buccal MDZ.

Disease similarity was not discussed as part of the extrapolation exercise. Although there is no indication that these types of acute seizures may present differently between children and adults, a difference cannot be ruled out. Considering that this is an acute treatment in an emergency setting, combined with clinical guideline recommendations, an extrapolation approach based solely on similarity in exposure can be accepted for the current product.

Safety data in derived from intranasal and intramuscular midazolam in adults with PACS has indicated that no differences are to be expected in adults when compared to children.

3.6.2. Balance of benefits and risks

Overall, based on exposure matching, the efficacy of Buccolam in children can be extrapolated to adults with PACS.

3.7. Conclusions

The overall B/R of Buccolam in adults is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the

following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include treatment of adults to Buccolam 10 mg, based on the results from study LESVIBUCCO/23/BQ-3. This is an Interventional Study, Relative Bioavailability to investigate the pharmacokinetics of a single dose of midazolam oromucosal solution (Buccolam) compared to midazolam solution for intramuscular injection (Hypnovel) in healthy volunteers under fasting conditions. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, 6.5 and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. In addition, the MAH took the opportunity to update the local representative in the PL. The RMP Version 8.2 has been agreed.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, IIIA and IIIB and to the Risk Management Plan are recommended.