EU Risk Management Plan for Buccolam (Midazolam)

RMP version to be assessed as part of this application:

RMP version number: 8.2

Data lock point for this RMP: 30 November 2023

Date of final sign-off: 04 June 2024

Rationale for submitting an updated RMP: *compliance with the Committee for Medicinal Products for Human Use (CHMP)/ Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur's preliminary assessment report (EMEA/H/C/002267/II/0061) for Buccolam.*

Summary of significant changes in this RMP:

Part Module/annex	**Date last updated for submission (sign off date)**	**Version**	**Significant changes**
Part I Product Overview	10 January 2024	8.1	Updated with the latest information and the new indication.
Part II Safety Specification			
SI Epidemiology of the indication and target population(s)	10 January 2024	8.1	Updated with the latest information and the new indication.
SII Non-clinical part of the safety specification	26 August 2020	7.1	No changes.
SIII Clinical trial exposure	26 August 2020	7.1	No changes.
SIV Populations not studied in clinical trials	26 August 2020	7.1	No changes.
SV Post-authorisation experience	10 January 2024	8.1	Updated with the latest information.
SVI Additional EU requirements for the safety specification	10 January 2024	8.1	Updated with the latest information.
SVII Identified and potential risks	04 June 2024	8.2	No relevant changes. Updated with the latest information regarding Risk Minimisation Measures (RMMs).
SVIII Summary of the safety concerns	26 August 2020	7.1	No changes.

Part Module/annex	**Date last updated for submission (sign off date)**	**Version**	**Significant changes**
Part III Pharmacovigilance Plan	04 June 2024	8.2	Updated as per CHMP/PRAC Rapporteur's preliminary assessment report.
Part IV Plan for post-authorisation efficacy studies	10 January 2024	8.1	Updated with the latest information.
Part V Risk Minimisation Measures	04 June 2024	8.2	Updated as per CHMP/PRAC Rapporteur's preliminary assessment report.
Part VI Summary of RMP	04 June 2024	8.2	Updated with the latest information and the new indication.
Part VII Annexes			
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	26 August 2020	7.1	No changes.
ANNEX 3 Protocols for proposed, on-going and completed studies in the pharmacovigilance plan	26 August 2020	7.1	No changes.
ANNEX 4 Specific adverse drug reaction follow-up forms	26 August 2020	7.1	No changes.
ANNEX 5 Protocols for proposed and on-going studies in RMP part IV	26 August 2020	7.1	No changes.
ANNEX 6 Details of proposed additional risk minimisation activities (if applicable)	04 June 2024	8.2	Updated as per CHMP/PRAC Rapporteur's preliminary assessment report.
ANNEX 7 Other supporting data (including referenced material)	10 January 2024	8.1	Updated with the latest information.
ANNEX 8 Summary of changes to the risk management plan over time	04 June 2024	8.2	Updated with the latest information.

Other RMP versions under evaluation:

RMP version number: 8.1.

Submitted on: 10 01 2024.

Procedure number: EMEA/H/C/002267/II/0061.

Details of the currently approved RMP:

Version number: 7.1.

Approved with procedure: EMEA/H/C/002267.

Date of approval (opinion date): 21 January 2021.

QPPV name: Lucía Castrillo Soto

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List of Abbreviations

ANSM	French Competent Authorities *(Agence nationale de sécurité du médicament et des produits de santé)*
Approx.	Approximately
aRMM	additional Risk Minimisation Measure
ATC	Anatomical Therapeutic Chemical classification
BM	Bone Marrow
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CNS	Central Nervous System
CSE	Convulsive Status Epilepticus
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug administration
GVP	Good Pharmacovigilance Practices
ICSR	Individual Case Safety Report
IM	Intramuscular
INN	International Non-proprietary Name
IV	Intravenous
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MDZ	Midazolam
MedDRA	Medical Dictionary for Regulatory Activities
NICE	National Institute for health and Care Excellence
NLSTEPSS	North London Status Epilepticus in Childhood Surveillance Study
NS	Not Specified

PAC	Post Authorisation Commitment
PIL	Patient Information Leaflet
PK	Pharmacokinetics
PSUR	Periodic Safety Updated Report
PT	Preferred Term
PUMA	Paediatric Use Marketing Authorisation
QPPV	Qualified Person for Pharmacovigilance
RD	Randomised
RMP	Risk Management Plan
RTC	Randomised Controlled Trial
SE	Status Epilepticus
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SUDEP	Sudden, Unexpected Death In Epilepsy
Tmax	Time to peak drug concentration
UK	United Kingdom

Additional clarification

The report follows the general format and content described in the Guideline on Good Pharmacovigilance Practices (GVP) Module V – Risk management systems Rev. 2 (28 March 2017) and the Guidance on the format of the Risk Management Plan (RMP) in the European Union (EU) – in integrated format Rev.2.0.1 (31 October 2018).

Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Midazolam.
Pharmacotherapeutic group(s) (ATC Code)	Psycholeptics, benzodiazepine derivatives (N05CD08).
Marketing Authorisation Holder (MAH)	Neuraxpharm Pharmaceuticals, S.L.
Medicinal products to which this RMP refers	4
Invented name(s) in the European Economic Area (EEA)	BUCCOLAM.
Marketing authorisation procedure	Centralised procedure (EMEA/H/C/002267).
Brief description of the product	**Chemical class** Midazolam hydrochloride (MDZ) is a water-soluble imidazobenzodiazepine derivative (known as a benzodiazepine) that is a short acting sedative, sleep inducing, anxiolytic, anticonvulsant, and muscle relaxant drug. It is chemically related to diazepam.
	Summary of mode of action The pharmacological action of MDZ is characterised by short duration because of rapid metabolic transformation. MDZ has an anticonvulsant effect. It also exerts a sedative and sleep- inducing effect of pronounced intensity and an anxiolytic and muscle relaxant effect. After intramuscular (IM) or intravenous (IV) administration, anterograde amnesia of short duration occurs.
	Important information about its composition Not applicable.
Hyperlink to the Product Information	Please refer to the product information text in module 1.3.1.
Indication(s) in the EEA	**Current** Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years). The product must only be used by parents/carers where the patient has been diagnosed to have epilepsy.

	For infants between 3-6 months of age treatment should be in a hospital setting where monitoring is possible and resuscitation equipment is available.
	Proposed Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years). The product must only be used by parents/carers where the patient has been diagnosed to have epilepsy. For infants between 3-6 months of age treatment should be in a hospital setting where monitoring is possible and resuscitation equipment is available. Buccolam 10 mg is indicated for the treatment of prolonged, acute, convulsive seizures in adults.
Dosage in the European Economic Area (EEA)	**Current** <u>Infants, Toddlers, Children and Adolescents:</u> • *Children < 3 months*: not indicated for use. • *Children 3-6 months (hospital setting)*: 2.5 mg (yellow label). • *Children >6 months to < 1 year*: 2.5 mg (yellow label). • *Children 1 year to < 5 years*: 5 mg (blue label). • *Children 5 years to < 10 years*: 7.5 mg (purple label). • *Children 10 years to < 18 years*: 10 mg (orange label). The product is not indicated for use in adults.
	Proposed <u>Infants, Toddlers, Children, Adolescents and Adults:</u> • *Children < 3 months*: not indicated for use. • *Children 3-6 months (hospital setting)*: 2.5 mg (yellow label). • *Children >6 months to < 1 year*: 2.5 mg (yellow label). • *Children 1 year to < 5 years*: 5 mg (blue label). • *Children 5 years to < 10 years*: 7.5 mg (purple label). • *Children 10 years to < 18 years and* • *Adults*: 10 mg (orange label).
Pharmaceutical form(s) and strengths	**Current** MDZ is a cl ear, colourless, ready-to-use solution (containing 5mg MDZ [as hydrochloride] per ml) presented in single-use, amber, pre-filled, age-specific, color-coded oral syringes available in the following strengths, for buccal administration: • <u>BUCCOLAM 2.5 mg oromucosal solution</u> Each pre-filled oral syringe contains 2.5 mg MDZ (as hydrochloride) in 0.5 ml solution.

	• BUCCOLAM 5 mg oromucosal solution Each pre-filled oral syringe contains 5 mg MDZ (as hydrochloride) in 1 ml solution. • BUCCOLAM 7.5 mg oromucosal solution Each pre-filled oral syringe contains 7.5 mg MDZ (as hydrochloride) in 1.5 ml solution. • BUCCOLAM 10 mg oromucosal solution Each pre-filled oral syringe contains 10 mg MDZ (as hydrochloride) in 2 ml solution.
	Proposed Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No.

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication

The product is intended for the treatment of prolonged, acute, convulsive seizures in children from 3 months, adolescents (<18 years) and adults.

Incidence and Prevalence

Epilepsy is a disease of the brain characterised by an enduring predisposition to generate seizures and by the neurobiologic, cognitive, psychological, and social consequences of seizure recurrences. It is one of the most common neurological diseases and affects people of all ages, races, social classes, and geographical locations [Beghi, 2020].

Incidence

Overall, the pooled incidence rate of epilepsy was 61.4 per 100,000 person-years (95% Confidence Interval (CI) 50.7–74.4), being higher in low/middle-income countries than in high-income countries [Beghi, 2020]. The incidence is bimodally distributed, being highest in younger and older age groups and increases steadily after 50 years of age [Huff, 2023], and also in men compared to women [Beghi, 2020].

Amongst children (under 15 years of age), infants younger than 12 months have the highest incidence and frequency of the disease [Sander, 1990; DeLorenzo, 1996; Hesdorffer, 1998; Coeytaux, 2000; Dura, 2007; Raspall-Chaure, 2007; Govoni, 2008;].

The annual incidence of CSE is 17–23 episodes per 100,000 children, more than in adults (4–6 per 100,000 individuals), based on published data from the North London Status Epilepticus in Childhood Surveillance Study (NLSTEPSS) estimated that the ascertainment-adjusted incidence was between 17 and 23 episodes per 100,000 children (less than 16 years old) per year in North London, United Kingdom (UK) [Chin, 2006]. The incidence is higher in the first year of life (51/100,000 children/year) and declines until approximately 5 y ears of age. than in older age groups (29, 9, 2/ 100,000/year in the age ranges 1–4, 5–9 and 10–15 years, respectively). This is probably related to the fact that in the first year of life the brain is more susceptible to seizures in response to acute insults (electrolyte imbalance, fever, infections, and so on) [DeLorenzo, 1996; Chin, 2006; Capovilla, 2013]. The high incidence of Convulsive Status Epilepticus (CSE) in children younger than 1 year was particularly notable in the acute symptomatic group. Within each age group, the incidence was similar for boys and girls. The age-adjusted incidence of CSE was also similar in boys and girls [Chin, 2006].

Prevalence

The prevalence of epilepsy differs significantly among countries depending on the local distribution of risk and aetiologic factors, the number of seizures at diagnosis and if considering only active epilepsy (active prevalence) or including also cases in remission (lifetime prevalence). The point prevalence of active epilepsy was 6.38 per 1,000 (95% CI 5.57–7.30), showing a higher prevalence in males and low/middle-income countries [Beghi, 2020].

Regarding children, generalised seizure and epilepsy/syndrome types were more prevalent in children 0-6 years of age and partial/ localisation-related in children 6-15 years of age [Eriksson, 1997].

Demographics of the population in the authorised indication

Epilepsy is the most common neurological condition affecting people of all ages, race and social class. However, it is important to point out that epilepsy is slightly frequent in men, and in low/middle-income countries [Beghi, 2020]. Seizures have also bimodal age distribution that occurs in infants, secondary to febrile illness, and patients older than 75 years, secondary to structural damage due to stroke or trauma [Kodankandath, 2023].

Risk factors for the disease

Identified causes that can be set as risk factors for epilepsy, tend to vary with patient age. Overall, inherited syndromes, congenital brain malformations, infection, and head trauma are leading causes in children. Head trauma is the most common known cause in young adults. Strokes, tumours, and head trauma become more frequent in middle age, with stroke becoming the most common cause in the elderly, along with Alzheimer disease and other degenerative conditions [Ko, 2022].

History with epilepsy is the strongest single risk factor for generalised CSE. Between 15%- 27% of patients with epilepsy will experience at least one episode of Status Epilepticus (SE); 25%-40% of SE occurs in patients with epilepsy. Other risk factors include young age, genetic predisposition and acquired brain insults [Dodson, 1993; Shinnar, 1996; Berg, 1999; Fountain, 2000].

Central Nervous System (CNS) infections are a common cause of paediatric SE, accounting for 1%-12% of subjects in a series from developed countries [Neligan, 2010]. Infections include acute bacterial meningitis, acute viral meningitis or encephalitis, and subacute viral, bacterial, fungal or parasitic meningitis [Smith, 2016]. Other common causes of CSE in children include fever, antiepileptic drug noncompliance or medication change, acute systemic and metabolic illness, and congenital CNS abnormalities. In about 10% of cases, no cause can be identified [Watson, 1991].

SE secondary to autoimmune aetiologies is less common. In a recent prospective cohort study in adults, autoimmune and paraneoplastic aetiologies accounted for 2.5% of cases of SE [Spatola, 2015].

Main existing treatment options

The goal of treatment in patients with epileptic seizures is to achieve a seizure-free status without adverse effects [Ko, 2022]. In children, to control, stop, or decrease the frequency of the seizures without interfering with the child's normal growth and development is also deemed necessary.

Although many pharmacological treatments are available for SE in hospital settings, there are very limited choices in community settings owing to the lack of IV access in patients. Transfer of a patient from home to hospital can delay treatment substantially, resulting in a reduction of the chance of successful response to a single medication. It has been recognised that early treatment of seizures in the community with drugs that can be administered by non-medical staff should be beneficial [NHS Guideline, 2013; NHS Policy, 2013]. Currently, rectal diazepam is the medication most commonly used in the community setting and is authorised for this indication [Brigo, 2015]. However, the rectal route of administration is not always practical, acceptable or convenient. Reasons for this include the need to remove clothing and the route of administration itself which is deemed to be socially embarrassing or unacceptable. Additionally, administration is difficult during tonic clonic seizures and for wheelchair users, and constipation and bowel movements can interfere with absorption and delay treatment substantially [Wilson, 2004; Brigo, 2015].

Therefore, it has been recognised that there is an unmet need for an effective, fast acting treatment that can easily be administered by a more convenient route and suitable for use in both the community and

hospital settings [Scott, 1999]. In fact, to fulfil such unmet needs, it has been common practice to administer MDZ buccally (oromucosal administration of other MDZ formulations) off-label for the treatment of SE and the National Institute for health and Care Excellence (NICE) guideline recommends that "administering buccal MDZ as first-line treatment and administering rectal diazepam if preferred or if buccal MDZ is not available" [NICE, 2012].

Benzodiazepines such as diazepam, MDZ, or lorazepam are acceptable as the first-line medications for continuing seizures [Beghi, 2020]. In this context, BUCCOLAM presentation provides major advantages over these unauthorised/off-label buccal MDZ preparations currently used and over other formulations of authorised rescue medication (such as rectal, IM or IV routes of administration).

In addition to using antiepileptic medications, the treatment of seizures aims at correcting any identifiable causative process [Beghi, 2020].

Natural history of the indicated condition in the untreated population, including mortality and morbidity

The prognosis of patients with seizures depends mostly on any underlying cause [Beghi, 2020]. Impairment of consciousness during a seizure may unpredictably result in morbidity or even mortality [Ko, 2022]:

- Regarding *morbidity*, trauma is not uncommon among people with generalized tonic-clonic seizures. Injuries such as ecchymosis; hematomas; abrasions; tongue, facial, and limb lacerations; and even shoulder dislocation can develop as a result of the repeated tonic-clonic movements. Atonic seizures are also frequently associated with facial injuries, as well as injuries to the neck. Worldwide, burns are the most common serious injury associated with epileptic seizures.
- Regarding *mortality*, seizures cause death in a small proportion of individuals. Most deaths are accidental and result from impaired consciousness. However, Sudden, Unexpected Death In Epilepsy (SUDEP) is a risk in persons with epilepsy, and it may occur even when patients are resting in a protected environment (ie, in a bed with rail guards or in the hospital). The risk of SUDEP increases in the setting of uncontrolled seizures and in people with poor medication compliance.

On the other hand, SE, a seizure with a duration equal to or greater than 30 minutes or a series of seizures in which the patient does not regain normal mental status between seizures, is a life threatening neurologic emergency [Dham, 2014; Wylie, 2023]. Complications of SE can be separated into medical and neurological complications and also immediate and delayed complications [Wylie, 2023]:

- *Medical complications* include cardiac arrhythmia, cardiac damage because of catecholamine surge, respiratory failure, hypoventilation, hypoxia, aspiration pneumonia, pulmonary oedema, fever, and leukocytosis.
- *Neurological complications* include progression to chronic epilepsy and recurrent SE. In cases of prolonged refractory SE, there can be permanent neurological damage induced by the hyper-metabolic activity in regions of the brain undergoing prolonged and abnormal electrical activity.

Important co-morbidities

Epilepsy may affect all age groups suffering from a wide range of comorbidities; some of them being triggers of the condition.

As previously mentioned, inherited syndromes, congenital brain malformations, infection, and head trauma are leading causes in children [Ko, 2022]. Indeed, febrile SE is the most common cause in paediatric patients [Wylie, 2023]. Head trauma is the most common known cause in young adults. Strokes, tumours, and head trauma become more frequent in middle age, with stroke becoming the most common cause in the elderly, along with Alzheimer disease and other degenerative conditions [Ko, 2022].

Additionally, many different metabolic disorders can also cause seizures, some as a result of a metabolic disturbance such as hypoglycaemia or acidosis and some as a primary manifestation of the seizure disorder [Ko, 2022].

A significant proportion of both children (16 to 38%) and adults (42 to 50%) with SE have a history of epilepsy [Wylie, 2023].

Part II: Module SII - Non-clinical part of the safety specification

No Company-owned pharmacological or toxicological safety evaluation studies have been performed by Neuraxpharm nor Takeda. Therefore, a summary of the available literature on the pharmacological activity and the toxicological potential of MDZ-containing products is provided below:

Toxicity

- *key issues identified from acute or repeat-dose toxicity studies*

Prolonged exposure toxicity

The potential for commonly used anaesthetics and sedatives to induce neuroapoptosis and other neurodegenerative changes in the developing mammalian brain has become evident in animal studies over the past 15 years. This concern has led to a number of retrospective studies in human infants and young children, and some of these studies observed an association between exposure to general anaesthesia as an infant, and later neurobehavioral problems in childhood. This association is particularly evident for prolonged or repeated exposures. Because of the significant growth of foetal interventions requiring sedation and analgesia for the foetus, or because of maternal anaesthetic effects, this concern about anaesthetic neurotoxicity is relevant for the foetus [Andropoulos, 2018].

In response to the accumulation of evidence from animal and clinical studies, the Food and Drug Administration (FDA) issued a safety communication regarding the potential adverse effects in children less than 3 years of age. The warning distributed by the FDA focused only on repeated or lengthy use of general anaesthetics and sedation. It was noted in this communication that relatively short exposure to general anaesthetics and sedative drugs in infants or toddlers is unlikely to have negative effects on behavior or learning [FDA, 2016a; FDA,2016b].

Subsequently, the FDA enacted changes to the labels of general anaesthetic and sedative drugs, classes of which included barbiturates, N- methyl-d-aspartate antagonists (ie, ketamine), and benzodiazepine (including MDZ) [FDA, 2016a; FDA, 2017].

In a review completed by Andropolous, The animal studies that have shown neurotoxic effects utilised doses and dosing regimens that exceed the posology used for Buccolam. In the study published by Xu et al (2018), juvenile mice were treated continuously at doses of 10 or 20 mg/kg by intraperitoneal injection once hourly for 12 hours for 5 consecutive days. As with previous animal studies that have demonstrated similar neurotoxic effects, the route of administration used (intraperitoneal, intravenous, inhalation) at doses that maintain a prolonged surgical plane of anaesthesia, are not relevant for comparison to Buccolam, as the route of administration for Buccolam is oromucosal. Due to t he acute, intermittent clinical exposure of Buccolam (2.5 to 10 mg buccally), the applicability of the findings reported by Xu et al (2018) to the safety assessment of Buccolam are limited [Xu, 2001].

Reproductive/developmental toxicity

Insufficient data available on MDZ to assess its safety during pregnancy. Animal studies do not indicate a teratogenic effect, but foetotoxicity was observed as with other benzodiazepines. No data on exposed pregnancies are available for the two trimesters of pregnancy.

The administration of high doses of MDZ in the last trimester of pregnancy or during labour has been reported to produce maternal or foetal adverse effects (inhalation risk in mother, irregularities in the foetal heart rate, hypotonia, poor sucking, hypothermia and respiratory depression in the neonate).

The risk for neonates should be taken into account in case of administration of MDZ in the third trimester of pregnancy.

Safety pharmacology

- *Renal toxicity*

No non-clinical studies were conducted specifically to assess renal toxicity.

In renal failure, 1-hydroxyMDZ, the active metabolite of MDZ can be expected to accumulate prolonging the pharmacological effects [Vinik, 1983; Bolon, 2001; Swart, 2005].

The Company is not aware of studies of MDZ in children with chronic renal failure.

- *Hepatotoxicity*

No non-clinical studies were conducted to assess hepatotoxicity.

The Company is not aware of studies of MDZ in children with chronic liver disease. Studies in adults show that chronic hepatic disease alters the pharmacokinetics of MDZ [MacGilchrist, 1986; Pentikainen, 1989].

- *Congestive Heart Failure*

No non-clinical studies were conducted to assess this risk.

The Company is not aware of studies of MDZ in children with heart failure. The study in adults indicated that the predominant effect of congestive heart failure was on the clearance of MDZ which was decreased by 30% [Patel, 1990].

Other toxicity-related information or data

- *Mechanisms for Drug Interactions*

No non-clinical studies were conducted to assess risks associated with drug interactions.

The metabolism and clearance of MDZ may be affected by a wide range of drugs that inhibit or induce CYP450 3A as this will interfere with the metabolic removal of MDZ. In addition, since the primary metabolite of MDZ, 1-hydroxyMDZ, is pharmacologically active, the relationship between plasma drug concentrations and drug effects becomes more complex after oral MDZ administration where the metabolite levels are relatively high compared to parenteral routes of administration. The reported studies have not evaluated the effect of other drugs on the formation and elimination of 1-hydroxyMDZ making dose adjustment recommendations difficult [FDA, 1998].

Drug-drug interaction studies reported in the literature have been conducted in healthy adult volunteers. The Company is not aware of any formal drug-drug interaction studies of MDZ in children.

Part II: Module SIII - Clinical trial exposure

The original clinical package to support the efficacy of BUCCOLAM comprised bibliographic data only.

Subsequently, 2 controlled studies of efficacy and safety have been conducted in Japan by previous MAH, to support the use of the product in the Japanese population (**SHP615-301** and **SHP615-302**). An additional study carried out in the same country is ongoing (**TAK-815-5001**). Overall, a total of 75 patients have been exposed to MDZ in Japanese sponsored clinical trials.

Additionally, one *bioequivalence study* (**BLCL-MDZ-EU-01**) have been completed in 2023 in Europe. The aim of this study was to evaluate the pharmacokinetics of a single dose of midazolam oromucosal solution (Buccolam®) compared to MDZ solution for intramuscular injection (Hypnovel®) in healthy volunteers under fasting conditions. A total of 23 patients were finally enrolled in this sponsored clinical trial (16 women and 7 men), mainly adults (≥18 years of age) (n= 20) and elderly patients (≥65 years of age) (n=3).

A systematic literature review was conducted in April 2008 to define a specific dataset for evaluation. As recommended by the European Medicines Agency (EMA) in 2008 [EMA, 2008], the search included all studies (regardless of route of administration) of MDZ used for treatment of seizures in children and studies in adults with MDZ administered buccally. These searches comprised the original dataset, and the dataset was augmented via further searches performed in June 2010 and September 2016. The efficacy and safety of buccal MDZ are currently supported by the 16 studies from the literature shown in Table SIII.1 below. The overall exposure of these subjects to MDZ is summarised in Table SIII.2.

Importantly, the authorised parenteral formulation of MDZ hydrochloride (ex Roche - Hypnovel 10 mg/2mL ampoules) was used for the oromucosal MDZ treatment in all 4 of the Randomised (RD)-controlled studies in children in the original dataset. Since the BUCCOLAM formulation is the same as the authorised Hypnovel 10mg/2mL ampoules formulation, these 4 controlled studies vs RD in children were considered to be directly supportive of the efficacy and safety of BUCCOLAM and were presented as the pivotal studies. Since only one small uncontrolled study in adults was identified in the original literature search, the supportive data from adults (as recommended for inclusion by EMA scientific advice [EMA, 2008]) was minimal. However, the dataset from studies in children was considered sufficiently robust in its own right. Subsequent reviews provided additional data for this dataset, see from Table SIII.3 to Table SIII.6 below.

Table SIII.1: Studies of Buccal MDZ in Treatment of Acute Seizures

Study Type	Population			Total (Unique Studies)
	Paediatric		Adult	
	Route of Comparator to Buccal MDZ			
	Rectal	IV	Rectal	
Controlled Studies	4 Studies: Baysun et al (2005) McIntyre et al (2005)	2 Studies: Talukdar and Chakrabarty (2009) Tonekaboni et al (2012)	1 Study: Nakken and Lossius (2011)	7 Studies
	Mpimbaza et al (2008) Scott et al (1999)			
Uncontrolled, Supportive Studies	8 Studies (typically no comparator, or INM comparator): Ashrafi et al (2010[a]) Frelih et al (2007) Khan et al (2014) Kutlu et al (2003) Muchohi et al (2008) Trajano et al (2009[a,b]) Vlaskamp et al (2014) Wilson et al (2004)		1 Study (no comparator): Melendez et al (2006)	9 Studies
Total (Unique studies)	**14 Studies**		**2 Studies**	**16 Studies**

[a] Unblinded Randomised Controlled Trial (RCT)
[b] Trajano et al (2009) contained both rectal and IV comparators and therefore represents just 1 unique study. The IV comparator in the study was IV MDZ, whereas the other 2 studies with IV comparators employed diazepam.

Table SIII.2: Overall Exposure to MDZ

Age group	Route of Administration	Number of Patients Treated[a]
Children	Buccal	approximately 663
	Parenteral	306
	Intranasal	approximately 542
Total Children		**approximately 1,511**

Age group	Route of Administration	Number of Patients Treated[a]
Adults	Buccal	44
	Parenteral	596
	Intranasal	approximately 190
Total Adults		**approximately 830**

Abbreviation: approx.=approximately. Where number of children or adults per treatment was not specified in a study, it was assumed that approximately half of total patients were treated with MDZ, and the number of patients is preceded by "approximately.

MDZ (adults)

Adults have been exposed to single doses of 5 mg (n=18) and 10 mg (n=10) buccal MDZ. Sixteen (16) adults were exposed to an unspecified dose of buccal MDZ.

A total of 69 further single dose (5 mg) treatments (range 3 to 14 per adult) have been administered for subsequent seizures in 6 adults.

MDZ (children)

- *Buccal MDZ (children)*

Approximately 663 children have been exposed to single doses of buccal MDZ ranging from 0.2 to 0.6 mg/kg, and up to a 10 mg dose. The majority of children (440/approximately 679, 65%) have been exposed to a fixed dose, banded by age (approximately 0.25 to 0.5 mg/kg). A total of 43 further single dose treatments (range 1 to 11 per child) have been administered for subsequent seizures in approximately 17 children (actual numbers not specified).

In the majority of studies with buccal MDZ in children for the treatment of seizures, subjects were only treated for 1 seizure episode. However, in a few studies, patients were re-entered into the study for subsequent seizures and thus treated with a single dose on more than 1 occasion. The number of patients treated per particular number of seizures (i.e., per particular number of re- treatments) is not specified in all publications but the overall extent of exposure to a single dose is indicated by the total number of episodes treated per dose.

Table SIII.3: Exposure to Single Dose of Buccal MDZ by Number of Patients - Children

Reference	No. of children treated with a single dose (mg/kg) (No. of children treated on more than one occasion)						
	0.2	0.25	0.3	0.4	Fixed dose (~0.25 - ~0.5)	0.6	10 mg
Mpimbaza et al (2008)	-	-	-	-	165	-	-
McIntyre et al (2005)	-	-	-	-	92(~12)[a]	-	-
Scott et al (1999)	-	-	-	-	-	-	14[b] (~5)[c]
Baysun et al (2005)	-	23	-	-	-	-	-

Reference	No. of children treated with a single dose (mg/kg) (No. of children treated on more than one occasion)						
	0.2	**0.25**	**0.3**	**0.4**	**Fixed dose (~0.25 - ~0.5)**	**0.6**	**10 mg**
Talukdar and Chakrabarty (2009)	60						
Muchohi et al (2008)			8				
Frelih et al (2007)	21[d]	-	-	21[d]	-	-	-
Wilson et al (2004)	~20[e]	-	-	-	-	-	-
Kutlu et al (2003)	-	-	13			6	-
Ashrafi et al (2010[a])					49 [f]		
Tonekaboni et al (2012)					32[f]		
Vlaskamp et al (2014)					39[f]		
Khan et al (2014)					34[f]		
Trajano et al (2009[a,b])					13		
Therakind Limited, 2010 (MID001)	53						
TOTAL PER DOSE	**~154**	**23**	**21**	**21**	**424**	**6**	**14**
OVERALL TOTALS	**~663 children exposed to a single dose ~17 children re-treated on separate occasions**						

a Re-recruitment (repeat treatment) (N): 25* both treatments (MDZ N not specified [assumed ~12, i.e. half of total 25]): 7 within 1 week, 4 within 1 month, 14 after > 2 months; Max number of retreatments (either treatment) =5 (i.e. total of 6 separate treatments).
b All subjects were over 5 years old (range 5-19 years, majority [56%] >12years). Thus, dose represents~0.5 mg/kg.
c Re-recruitment (repeat treatment) (N): 10 both treatments (MDZ N not specified [assumed ~5, i.e. half of total 10]): 1 subject re-treated 11 times, 1 subject retreated 7 times, i.e. total exposure 12 and 8 treatments (other specific re-treatments and time period between re-treatments not specified).
d Doses: children <20kg: 0.4 mg/kg; >20kg: 0.2 mg/kg – Number per dose not specified, assumed half of total number (42) per dose.
e Number of children given buccal MDZ not specified (assumed half of total (40) – alternative treatment was intranasal MDZ).
f Dose not specified or dose within range.

Table SIII.4: Exposure to Single Doses of Buccal MDZ by Number of Doses – Children

Reference	No. of single doses per dose (mg/kg)						
	0.2	**0.25**	**0.3**	**0.4**	**Fixed dose (~0.25 - ~0.5)**	**0.6**	**10 mg**
Mpimbaza et al (2008)	-	-	-	-	165	-	-

Reference	No. of single doses per dose (mg/kg)						
	0.2	**0.25**	**0.3**	**0.4**	**Fixed dose (~0.25 - ~0.5)**	**0.6**	**10 mg**
McIntyre et al (2005)	-	-	-	-	109	-	-
Scott et al (1999)	-	-	-	-	-	-	40
Baysun et al (2005)	-	23	-	-	-	-	-
Talukdar and Chakrabarty (2009)	60						
Muchohi et al (2008)			8				
Frelih et al (2007)	21[a]	-	-	21[a]	-	-	-
Wilson et al (2004)	~20[b]	-	-	-	-	-	-
Kutlu et al (2003)	-	-	13			6	-
Ashrafi et al (2010[a])					49[c]		
Tonekaboni et al (2012)					32[c]		
Vlaskamp et al (2014)					39[c]		
Therakind Limited, 2010 (MID001)	53						
Trajano et al (2009[a,b])					13		
Khan et al (2014)					34[c]		
TOTAL PER DOSE	**~154**	**23**	**21**	**21**	**441**	**6**	**40**
OVERALL TOTAL	**~706 single dose exposures**						

a Doses: children <20kg: 0.4 mg/kg; >20kg: 0.2 mg/kg – Number per dose not specified, assumed half of total number (42) per dose.
b Children given buccal MDZ not specified (assumed half of total (40) – alternative treatment was intranasal MDZ).
c Dose not specified or dose within range.

- *Parenteral MDZ (children)*

A total of 306 children have been exposed to parenteral MDZ at a variety of doses and routes of administration. The majority of children (263/306 [86%]) have been exposed to a dose of 0.2 mg/kg IM.

Table SIII.5: Exposure to a Single Dose of Parenteral MDZ by Number of Patients – Children

Reference	Number of Children Treated with a Single Dose			
	0.06 mg/kg IV bolus + 0.15 mg/kg infusion	**0.2 – 0.5 mg/kg IM**	**0.2 mg/kg IV bolus + 0.002 to 0.01 mg/kg infusion**	**0.4 mg/kg IV bolus + 0.2 mg/kg infusion**
Chamberlain et al (1997)	-	13	-	-
Singhi et al (2002)	-	-	21	-
Boylan et al (2004)	3	-	-	-
Shah and Deshmukh, (2005)	-	50	-	
Mahmoudian and Najafian (2006)	-	-	-	19
Silbergleit et al (2012)	-	75[a]	-	-
Momen et al (2015)	-	49[b]	-	-
Portela et al (2015	-	16[c]	-	-
Welch et al (2015)	-	60	-	-
Total per Dose	**3**	**263**	**21**	**19**
Overall Totals	**306 children exposed to a single dose**			

Abbreviations: IM=intramuscular; IV=intravenous.
a Study population defined as subjects up to 20 years of age.
b One of the 50 patients treated in this study mistakenly received 0.6 mg/kg IM and is not included in this table.
c One patient in this study had a SE that lasted 55 minutes and did not respond to MDZ treatment. The patient then received IV diazepam. Cessation was achieved after rectal diazepam and an additional dose of IM MDZ.

- *Intranasal MDZ (children)*

Approximately 542 children have been exposed to single doses of IN MDZ ranging from approximately 0.1 to 0.3 mg/kg. The majority of children (approximately 378/542, 70%) have been exposed to a dose of 0.2 mg/kg. A total of approximately 222 further treatments (range: 1 to 28 per child) have been administered for subsequent episodes in more than 22 children (actual number not specified).

Table SIII.6: Exposure to a Single Dose of Intranasal MDZ by Number of Patients **– Children**

Reference	Number of Children Treated with a Single Dose (Number of children treated on more than 1 occasion)			
	Approx. 0.1 - 0.2 mg/kg	**0.2 mg/kg**	**0.2 - 0.3 mg/kg**	**Approx. 0.3 mg/kg**
Gunawan et al (2015)	-	30 (NS)	-	-
Dao et al (2014)	75 (NS)	-	-	-
Thakker and Shanbag, (2013)	-	27 (NS)	-	-
Javadzadeh et al (2012)	-	30 (NS)	-	-
Holsti et al (2010)	-	50 (NS)	-	-
Bhattacharyya et al (2006)	-	approx. 23 (NS)[a]	-	-
Mahmoudian and Zadeh, (2004)	-	35 (NS)	-	-
Lahat et al (2000)	-	21 (NS)[b]	-	-
Mittal et al (2006)	-	approx. 38 (NS)[a]	-	-
Fisgin et al (2002)	-	23 (NS)	-	-
Kyrkou et al (2006)	-	-	51 (NS)[c]	-
Harbord et al (2004)	-	-	22 (NS)[d]	-
Conroy et al (2000)	-	20 (NS)	-	-
Fisgin et al (2000)	-	16 (NS)	-	-
Kutlu et al (2000)	-	-	-	9 (2)
Scheepers et al (2000)	6[e] (3[f])	-	-	-
Jeannet et al (1999)	-	26[g] (16[h])	-	-
Lahat et al (1998)	-	20 (NS)	-	-
Kendall et al (1997)	-	-	-	1 (1)[i]
O'Regan et al (1996)	-	19 (NS)	-	-
Total per Dose	**81**	**approx. 378**	**73**	**10**
Overall Totals	**Approximately 542 children exposed to a single dose More than 22 children re-treated on separate occasions**			

Abbreviations: approx.=approximately; NS=not specified.

a Where number per treatment not specified in a comparator study, assumed that approximately half of total patients were treated with MDZ.

b Maximum of 3 re-treatments per patient.

c Doses included: Up to 16 kg (1-4 years) – 2.5 mg; 16-32 kg (4-10 years) – 5 mg; >32 kg (>10 years) – 10 mg.

d Maximum of 5 re-treatments per patient.

e Doses: 5 mg for patients <50 kg, 10 mg for patients > 50 kg.
f Maximum of 8 re-treatments per patient.
g Two children treated by sublingual route.
h Maximum of 28 re-treatments per patient.
i Dose: up to 4 mg in 2-year-old patient.

In Silico Investigation of Systemic Exposure and Pharmacokinetic Linearity of BM in Children

Given the assumptions and limitations of the *in vitro/in vivo* extrapolation process, the *in silico* simulation study demonstrated no evidence of pharmacokinetics (PK) non-linearity over the BM dose range studied (0.05 - 1 mg/kg) in any of the age bands from 1 day to 18 years of age. Specifically, this study predicts:

- Dose linearity of Bone Marrow (BM) PK in the range 0.05-1 mg/kg across the paediatric age range 0-18 years. This suggests that PK data generated in the BM PK study using a dose of 0.2 mg/kg (MID001) can be extrapolated linearly to the approved doses (fixed doses banded by age [range ~0.25 to ~0.5 mg/kg]).
- Systemic exposure in the dose range 0.05-1 mg/kg is significantly greater in the age range 0-3 months. However, between 3 months and 18 years, there appears to be no significant difference in the predicted exposure. Thus, in the case of MDZ, the influence of CYP3A enzyme ontogeny on systemic exposure is limited to children less than 3 months of age. Therefore, there is no need for maturation related dosage adjustments for children greater than 3 months of age.
- Two (2) of the published studies, 1 in children and 1 in adults, provide comparative bioavailability data and both of these studies used the Hypnovel 10 mg/2 mL formulation for all routes of administration.

Comparative Bioavailability

- Published study in 31 paediatric patients (with malaria) using Hypnovel formulation - buccal vs IV vs IM [Muchohi, 2008].
- The results of this small open-label, uncontrolled, non-randomised, comparator study demonstrated a larger and earlier Cmax {Tmax ~10 minutes) by the IV route compared to that of the buccal and IM routes which were similar (Tmax values ~15 minutes). The BM bioavailability was estimated at 87%.
- Published study in 8 healthy adults using Hypnovel formulation - buccal vs IV [Schwagmeier, 1998].
- The results of this small non-randomised, double dummy, cross-over comparator study demonstrated a larger and earlier C_{max} (T_{max} < 3 minutes) by the IV route compared to that of the buccal route (T_{max} ~30 minutes). In this study, the mean BM bioavailability was determined to be 74.5%. As this was a cross-over study, this value for absolute bioavailability is more reliable than that estimated in the above Muchohi et al (2008) study, albeit in adults. This study addresses the point raised by the EMA scientific advice to ensure sufficient bioavailability of the formulation (via a study in adults).

Bioequivalence

- The 4 pivotal RD-controlled clinical efficacy/safety studies of BM in children, which have been submitted in the Paediatric Use Marketing Authorisation (PUMA) application to support the product indication, used the Hypnovel 10 mg/2 mL formulation for the BM treatment. As the formulation is essentially similar to the Hypnovel 10 mg/2 mL formulation, a bridging PK study to demonstrate relative bioavailability or bioequivalence to the formulation used in the pivotal studies (i.e. a pharmacokinetic comparison of the BUCCOLAM formulation to the Hypnovel formulation delivered buccally) was not required.

Data from Company-Sponsored Trials

In total, 25 patients have been exposed to MDZ in open-label Company-sponsored clinical trials. The exposure data from these trials (**SHP615-301** and **SHP615-302**) are presented below in Table SIII.7 to Table SIII.9.

Table SIII.7: Age group and gender

Estimated Cumulative Subject Exposure to SHP615 from Clinical Trials SHP615-301 and SHP615-302, by Age and Gender:			
Age range	**Number of Subjects**		
	Male	**Female**	**Total**
< 1 year	1	2	3
1 to < 5 years	4	9	13
5 to < 10 years	3	4	7
10 to < 18 years	1	1	2
Total	**9**	**16**	**25**

Table SIII.8: Dose

Cumulative for all doses of exposure:		
Dose of exposure	**Patients**	**Percentage**
2.5 mg	3	12.0
5 mg	13	52.0
7.5 mg	7	28.0
<10 mg	1	4.0
10 mg	1	4.0
Total	**25**	**100.0**

Dose of Exposure is the planned dose when the drug administration was documented to be complete on the study drug administration eCRF form.
*One Subject received "<10 mg" as the drug leaked a little after the full amount of the drug was injected into each side of mouth.

Table SIII.9: Race

Cumulative exposure in Company CTs by Race:		
Ethnic origin	**Patients**	**Percentage**
Asian	25	100.0
Total	**25**	**100.0**

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The clinical package to support the efficacy and Marketing Authorisation Application (MAA) of BUCCOLAM comprised bibliographic data only. This section is not applicable.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical package to support the efficacy and MAA of BUCCOLAM comprised bibliographic data only. This section is not applicable.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not available.

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women Breastfeeding women	Not included in the clinical development program. No cases of exposure during pregnancy were reported in the published clinical studies. The SmPC, Section 4.6 Fertility, Pregnancy and Lactation, contains the following information: *Insufficient data are available on MDZ to assess its safety during pregnancy. Animal studies do not indicate a teratogenic effect, but fetotoxicity was observed as with other benzodiazepines. No data on exposed pregnancies are available for the first two trimesters of pregnancy. The administration of high doses of MDZ in the last trimester of pregnancy or during labour has been reported to produce maternal or foetal adverse reactions (inhalation risk in mother, irregularities in the foetal heart rate, hypotonia, poor sucking, hypothermia and respiratory depression in the new-born infant). MDZ may be used during pregnancy if clearly necessary. The risk for new-born infants should be taken into account in the event of administration of MDZ in the third trimester of pregnancy.* MDZ passes in low quantities (0.6%) into breast milk. As a result it may not be necessary to stop breast feeding following a single dose of MDZ. Animal studies did not show an impairment of fertility.
Children	BUCCOLAM was specifically designed as a single, age-specific dose formulation for children. The population studied overall

Type of special population	Exposure
	across the published studies was broadly representative of the population intended to receive the product after marketing, reflecting the target age range (children aged 3 months - < 18 years) and disease type and duration. Both sexes were equally represented across all studies. Several of the studies were conducted in non-European races. The published clinical studies referred to in the Application were conducted in the hospital emergency care setting and in one study in a residential centre for children with epilepsy. It is intended that BUCCOLAM will be used in both the community and hospital settings.
Elderly	Not applicable.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients Patients with a disease severity different from inclusion criteria in clinical trials	**Patients with Hepatic Impairment** Paediatric patients with impaired hepatic function were not studied in the pre-authorisation phase. **Patients with Chronic Renal Failure** Paediatric patients with chronic renal failure were not studied in the pre-authorization phase. **Patients with Other Relevant Comorbidity** Patients with other relevant comorbidity were not studied in the pre-authorisation phase. **Patients with a Disease Severity Different from the Inclusion Criteria in the Clinical Study Population** The clinical package to support the efficacy of BUCCOLAM comprises bibliographic data only. This section is not applicable.
Population with relevant different ethnic origin	The metabolism and clearance of MDZ may be affected by a wide range of drugs that inhibit or induce cytochrome P450 3A as this will interfere with the metabolic removal of MDZ. In addition, since the primary metabolite of MDZ, 1- hydroxyMDZ, is pharmacologically active, the relationship between plasma drug concentrations and drug effects becomes more complex after oral MDZ administration where the metabolite levels are relatively high compared to parenteral routes of administration. Although ethnic differences in CYP3A polymorphisms are known to exist, there is insufficient evidence to date to suggest that the major polymorphic variants in CYP3A4 have any association with CYP3A4 activity [Keshava, 2004]. The results from the

Type of special population	Exposure
	studies above conducted in India, UK, Uganda and Turkey provided consistent results and did not reveal any potential differences in efficacy or safety due to ethnic differences. Therefore, no difference in dosing based on race is recommended.
Subpopulations carrying relevant genetic polymorphisms	A genetic component to the aetiology of epilepsy is well recognised but the mechanism of inheritance and the genes involved are yet to be fully established [Chioza, 2009]. This section is not applicable.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

As per Summary of Product Characteristics (SmPC), MDZ is indicated for the treatment of prolonged, acute, convulsive seizures in children (from 3 months), adolescents and adults. 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. On the contrary, in patients with controlled epilepsy, MDZ can be kept at home as a safety measure for breakthrough acute seizures.

Since MDZ is used in acute seizure treatment and the frequency will differ between patients, it is accepted to express exposure as the number of boxes distributed as noted in the Periodic Safety Updated Report (PSUR) assessment report (dated 12 March 2015).

SV.1.2 Exposure

Hence, sales figures in available units of boxes sold are provided to estimate patient exposure. These figures are shown in the following table:

Table SV.1: Exposure table: Commercially marketed product (MDZ)

Dosages Distributed	Number of Boxes Distributed* Cumulatively, through November 2023
2.5 mg	319,659
5 mg	790,256
7.5 mg	774,422
10 mg	2,136,270
***Total boxes distributed**	**4,020,607**

*each box contains 4 pre-filled oral syringes.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

It is unlikely that the product could be misused for an illegal purpose such as a recreational drug or for facilitating assault etc. BUCCOLAM is only available subject to a medical prescription.

No evidence of abuse, misuse or diversion was noted in the clinical trials and no incidence of diversion of study materials was reported. The potential for misuse for illegal purposes is difficult to estimate at present.

The potential for anterograde amnesia and the availability of the product in the community poses the risk of drug-facilitated sexual assault (also known as date rape) of adults and children. It is inappropriate to mention this risk in the SmPC or Patient Information Leaflet (PIL) as these documents are searchable by the general public on the internet and this would increase the potential for such illegal use of the product.

Accordingly, the SmPC states under Section 4.4, Special Warnings and Precautions for Use: "*MDZ may cause anterograde amnesia"*. Prescribers, alerted to this general precaution for all benzodiazepines, will need to consider the potential for the patient's caregivers to deliberately or inadvertently divert the product for such purposes. No specific educational materials are proposed because this is a general issue for all benzodiazepines.

Prescribers of any benzodiazepine such as MDZ should be aware that, when introduced into the community, these drugs as a class have the potential for abuse as a recreational drug or to facilitate sexual assault (due to their ability to cause anterograde amnesia). Accordingly, the SmPC states under Section 4.4, Special Warnings and Precautions for Use: *"MDZ may cause anterograde amnesia."* However, the potential for abuse is not considered appropriate for the SmPC or PIL, because the provision of this information to the general public via the internet could have the unintended opposite effect of increasing the potential for misuse. Likewise, no specific educational materials are proposed, since this is a general risk of benzodiazepine.

The MAH considers it unlikely that the product MDZ will be misused for such illegal purposes, for several reasons: First, BUCCOLAM is available by prescription only. Prescribers will need to consider the potential for diversion, whether intentional or unintentional. Further, the prescription of single-use containers will limit the amount of product available for diversion. These factors may explain why no evidence of abuse, misuse, or diversion have been noted in the clinical trials, and no incidence of diversion of study materials has been reported.

A review of the global safety database searching for the following Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs): *Drug abuse, Intentional product misuse, Drug diversion, Drug dependence, Dependence, Product tampering* and *Intentional product use issue* was performed. The search derived 29 Individual Case Safety Report (ICSRs) with 33 adverse events of abuse or diversion cumulatively. Where age was provided, drug abuse or diversion were more consistent with drug use in unapproved age group. These events were coded as reported in Table SVI.1

Table SVI.1:Events of abuse or diversion

Preferred Terms (PTs)	Serious (n)	Non-serious (n)	Total (n)
Drug abuse	10	0	10
Drug dependence	8	0	8
Drug diversion	2	1	3
Intentional product misuse	9	3	12
TOTAL	**29**	**4**	**33**

The review of reports did not identify any new trend or safety concern. The safety data review did not provide new significant information impacting the cumulative knowledge in relation to the potential risk of abuse or diversion in relation to MDZ. Routine pharmacovigilance was deemed sufficient for continued monitoring of such events.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable as this is an update of the RMP.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable as this is an update of the RMP.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risks: None.

Important Potential Risk: Aspiration/aspiration pneumonia *(MedDRA PTs: Aspiration, Pneumonia, Pneumonia aspiration)*

Potential mechanisms:

Direct aspiration, possibly leading to infectious process (pneumonia).

Evidence source(s) and strength of evidence:

No data pertaining to aspiration/aspiration pneumonia is available from literature with regards to paediatric dosing of MDZ via buccal route of administration.

Characterisation of the risk:

No data pertaining to aspiration/aspiration pneumonia is available from literature with regards to paediatric dosing of MDZ via buccal route of administration.

- Clinical experience

According to the safety database, no serious adverse events associated aspiration/aspiration pneumonia from patients enrolled in clinical studies have been received.

- Post-marketing experience

According to the company safety database, four (4) cases associated with MDZ involving a total of four (4) adverse events associated with 'Aspiration/aspiration pneumonia' were cumulatively received: Aspiration (2), Pneumonia (2).

PTs	Serious	Non-serious	Total
Aspiration	2	0	2
Pneumonia	2	0	2
Total	**4**	**0**	**4**

Based on this information, the reporting rate for these events when calculated per 100,000 patients exposed is 0,09 [95% CI 0,03 – 0,25].

Risk factors and risk groups:

Epileptic seizures and oromucosal administration are risks factors. Moreover, a convulsing child is at risk of aspiration from their own secretions. Also, patients prone to vomiting are at an increased risk.

Aspiration of oropharyngeal and gastric contents caused by a reduced level of consciousness, upper airway weakness, recurrent seizures, and the sedative effect of antiseizure medications may contribute to the high frequency of pneumonia in this population [Hawkes, 2018].

Buccal administration of the product does not increase the risk of aspiration. Rapid treatment is the most important aspect to ensure the risk of aspiration from the seizure itself is minimised.

Preventability:

Aspiration following buccal administration of MDZ has not been identified in the pivotal clinical studies in 294 children with seizures nor in the pharmacokynetic study (MID001) conducted by the previous MAH in 53 children. The maximum dose volume to be administered (2 mL) is small. The convulsing child will be positioned on his side and the product administered buccally thereby reducing any possible risk of aspiration of the administered solution.

As stated in section 4.2 of the SmPC, the full amount of solution should be inserted slowly into the space between the gum and the cheek. Laryngo-tracheal insertion should be avoided to prevent accidental aspiration of the solution. If necessary (for larger volumes and/or smaller patients), approximately half the dose should be given slowly into one side of the mouth, then the other half given slowly into the other side. In addition, section 4.6 of the SmPC indicates that the administration of high doses of MDZ in the last trimester of pregnancy or during labour has been reported to produce maternal or foetal adverse reactions such as risk of aspiration of fluids and stomach contents during labour in the mother.

Impact on the risk-benefit balance of the product:

A convulsing child is at risk of aspiration from their own secretions. Buccal administration of the product does not increase the risk of aspiration. Rapid treatment is the most important aspect to ensure the risk of aspiration from the seizure itself is minimised. Inadequate treatment can lead to life threatening or fatal outcome; as such, the balance of benefit to risk remains positive.

Public health impact:

The potential impact on public health is expected to be low.

Important Potential Risk: Choking/asphyxiation on syringe cap (*MedDRA PTs: Choking, Foreign body aspiration, Asphyxia, Foreign body in respiratory tract, Foreign body in gastrointestinal tract, Accidental exposure to product packaging by a child, Accidental exposure to product packaging)*

Potential mechanisms:

Choking and asphyxiation on syringe cap if it remains on the syringe during administration.

Evidence source(s) and strength of evidence:

There is no information in the literature about choking/asphyxiation on the syringe cap for MDZ.

Characterisation of the risk:

- Clinical experience

According to the safety database, no serious adverse events associated with choking/asphyxiation on the syringe cap from patients enrolled in clinical studies have been received.

- Post-marketing experience

According to the company safety database, eight (8) cases associated with MDZ involving a total of eight (8) adverse events associate with 'Choking/asphyxiation on the syringe cap' were cumulatively received: Accidental exposure to product packaging (1), Asphyxia (1), Choking (3), Foreign body aspiration (1), Foreign body in gastrointestinal tract (1) and Foreign body in respiratory tract (1).

PTs	Serious	Non-serious	Total
Accidental exposure to product packaging	0	1	1
Asphyxia	1	0	1
Choking	3	0	3
Foreign body aspiration	1	0	1
Foreign body in gastrointestinal tract	0	1	1
Foreign body in respiratory tract	1	0	1
Total	**6**	**2**	**8**

Based on this information, the reporting rate for these events when calculated per 100,000 patients exposed is 0,19 [95% CI 0,09 – 0,39].

Risk factors and risk groups:

No specific risk group. Occurrence of choking on the syringe cap could occur if the caregiver did not remove the syringe cap prior to MDZ administration.

Preventability:

As stated in section 4.2 of the SmPC, the oral syringe cap should be removed before use to avoid risk of choking. In addition, section 6.6 details step-by step the administration of the product.

The introduction of a syringe single piece tip-cap to increase patient safety is approved on 23 June 2022 following a Post-Authorisation Commitment (PACs) requested by the Committee for Medicinal Products for Human Use (CHMP).

Impact on the risk-benefit balance of the product:

Choking on the cap can delay treatment and lead to life threatening or fatal outcome. The benefit of treatment outweighs the risk of this occurring, and the product labelling adequately instructs patients and caregivers to remove the cap prior to administration.

Public health impact:

The potential impact on public health is expected to be low.

Important Potential Risk: Medication errors *(MedDRA Standardised MedDRA Query (SMQ): Medication Errors)*

Potential mechanisms:

Not applicable.

Evidence source(s) and strength of evidence:

Several cases involving medication errors have been cumulatively received.

Characterisation of the risk:

- Clinical experience

According to the safety database, no serious adverse events associated with medication error from patients enrolled in clinical studies have been received.

- Post-marketing experience

According to the company safety database, 657 cases associated with MDZ involving a total of 742 adverse events associated with 'Medication errors' were cumulatively received. The most frequently reported events were: Incorrect dose administered (37), Product administered to patient of inappropriate age (39), Product prescribing error (40), Product prescribing issue (37), Product storage error (30), Product use in unapproved indication (48) and Product use issue (256).

PTs	Serious	Non-serious	Total
Accidental exposure to product	0	5	5
Accidental exposure to product by child	0	2	2
Accidental exposure to product packaging	0	1	1
Accidental overdose	3	3	6
Accidental underdose	0	1	1
Circumstance or information capable of leading to medication error	1	7	8
Drug ineffective for unapproved indication	3	3	6
Expired product administered	1	11	12
Extra dose administered	0	1	1
Inappropriate schedule of product administration	0	12	12
Incorrect dosage administered	0	2	2
Incorrect dose administered	2	35	**37**
Incorrect dose administered by product	0	1	1
Incorrect product administration duration	0	1	1
Incorrect route of product administration	1	27	28

PTs	Serious	Non-serious	Total
Intercepted accidental exposure to product by child	0	1	1
Intercepted medication error	0	2	2
Intercepted product administration error	0	1	1
Intercepted product dispensing error	0	1	1
Intercepted product prescribing error	0	5	5
Intercepted product storage error	0	2	2
Labelled drug-drug interaction medication error	1	1	2
Medication error	2	9	11
Overdose	14	7	21
Poor quality device used	0	1	1
Poor quality product administered	0	4	4
Prescribed overdose	0	6	6
Prescribed underdose	0	5	5
Product administered to patient of inappropriate age	3	36	**39**
Product administration error	2	10	12
Product appearance confusion	0	1	1
Product communication issue	0	1	1
Product delivery mechanism issue	0	1	1
Product dispensing error	1	6	7
Product dispensing issue	0	1	1
Product dose confusion	0	1	1
Product dose omission issue	0	6	6
Product label confusion	0	2	2
Product label issue	0	3	3
Product lot number issue	0	1	1
Product packaging difficult to open	0	1	1
Product packaging issue	0	6	6
Product prescribing error	1	39	**40**
Product prescribing issue	0	37	**37**
Product storage error	0	30	**30**
Product temperature excursion issue	0	5	5
Product use complaint	0	5	5
Product use in unapproved indication	8	40	**48**
Product use issue	7	249	**256**
Syringe issue	1	7	8
Therapeutic product ineffective for unapproved indication	2		2
Underdose	1	17	18
Wrong dose	1	1	2
Wrong product administered	0	1	1
Wrong technique in product usage process	2	21	23
Total	**57**	**685**	**742**

Based on this information, the reporting rate for these events when calculated per 100,000 patients exposed is 18,45 [95% CI 17,15 – 19,83].

Risk factors and risk groups:

Patients or caregivers of patients who are misinformed about the correct dosing and administration of the medication.

Preventability:

The SmPC of the products provides information on dosing, method of administration, and precautions to be taken before administering the product under the section 4.2.

Impact on the risk-benefit balance of the product:

The potential risk of medication errors can be serious. Medical attention should be immediately sought for patients who have been exposed to more than the recommended dose.

Public health impact:

The potential impact on public health is expected to be low.

SVII.3.2. Presentation of the missing information

Missing information: children under 6 months of age

Evidence source:

According to the SmPC, given the higher metabolite to parent drug ratio in younger children, a delayed respiratory depression as a result of high active metabolite concentrations in the 3-6 months age group cannot be excluded. Therefore, the use of MDZ in the 3-6 months age group should be limited for use only under the supervision of a health care professional where resuscitation equipment is available and where respiratory function can be monitored and equipment for respiratory assistance, if needed, is available.

Anticipated risk/consequence of the missing information:

Respiratory function can be compromised, therefore as stated in the SmPC the use of MDZ should be limited for use only under the supervision of a health care professional.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of 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.

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities are in place, namely adverse reactions reporting and signal detection.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities will be conducted to assess the effectiveness of risk minimisation measures.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

No planned or on-going post-authorisation efficacy studies have been imposed.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Aspiration/aspiration pneumonia	Routine risk communication: *SmPC section 4.2 Posology and method of administration.* Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only.
Choking on a syringe cap / Asphyxiation	Routine risk communication: *SmPC Section 4.2 Posology and method of administration.* *SmPC Section 6.6 Special precautions for disposal and other handling.* *PIL: Section 5. Method and Route(s) of administration.* Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only.
Medication Errors	Routine risk communication: *SmPC Section 4.2 Posology and method of administration.* *SmPC Section 4.9 Overdose.* Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only.
Use in children < 6 months of age	Routine risk communication: *SmPC Section 4.4 Special warnings and precautions for use.* *SmPC Section 5.1 Pharmacodynamic properties.* Routine risk minimisation activities recommending specific clinical measures to address the risk: None.

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of 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.* Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	None.	*None.*

Part VI: Summary of the risk management plan

Summary of risk management plan for BUCCOLAM (midazolam)

This is a summary of the Risk Management Plan (RMP) for BUCCOLAM. The RMP details important risks of BUCCOLAM, how these risks can be minimised, and how more information will be obtained about BUCCOLAM 's risks and uncertainties (missing information).

BUCCOLAM's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how BUCCOLAM should be used.

This summary of the RMP for BUCCOLAM should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of BUCCOLAM's RMP.

I. The medicine and what it is used for

BUCCOLAM is authorised for the treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years), and also, in adults. (see SmPC for the full indication). It contains MDZ as the active substance and it is given by oromucosal route of administration.

Further information about the evaluation of BUCCOLAM's benefits can be found in BUCCOLAM's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage*:* https://www.ema.europa.eu/en/medicines/human/EPAR/buccolam

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute ***routine risk minimisation measures***.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute ***routine pharmacovigilance activities***.

If important information that may affect the safe use of BUCCOLAM is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of BUCCOLAM are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of BUCCOLAM. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
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.

II.B Summary of important risks

Important potential risk: Aspiration/aspiration pneumonia	
Evidence for linking the risk to the medicine	No data pertaining to aspiration/aspiration pneumonia is available from literature with regards to paediatric dosing of MDZ via buccal route of administration.
Risk factors and risk groups	Epileptic seizures and oromucosal administration are risks factors. Moreover, a convulsing child is at risk of aspiration from their own secretions. Also, patients prone to vomiting are at an increased risk. Aspiration of oropharyngeal and gastric contents caused by a reduced level of consciousness, upper airway weakness, recurrent seizures, and the sedative effect of antiseizure medications may contribute to the high frequency of pneumonia in this population [Hawkes, 2018]. Buccal administration of the product does not increase the risk of aspiration. Rapid treatment is the most important aspect to ensure the risk of aspiration from the seizure itself is minimised.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2.* Additional risk minimisation measures: *None.*

Important potential risk: Choking/asphyxiation on syringe cap	
Evidence for linking the risk to the medicine	There is no information in the literature about choking/asphyxiation on the syringe cap for MDZ.
Risk factors and risk groups	No specific risk group. Occurrence of choking on the syringe cap could occur if the caregiver did not remove the syringe cap prior to MDZ administration
Risk minimisation measures	Routine risk minimisation measures: *SmPC Section 4.2.* *SmPC Section 6.6.* *PIL: Section 5.* Additional risk minimisation measures: *None.*

Important potential risk: Medication errors	
Evidence for linking the risk to the medicine	Several cases involving medication errors have been cumulatively received.
Risk factors and risk groups	Patients or caregivers of patients who are misinformed about the correct dosing and administration of the medication.
Risk minimisation measures	Routine risk minimisation measures: *SmPC Section 4.2.* *SmPC Section 4.9.* Additional risk minimisation measures: *None.*

Missing information: Use in children < 6 months of age	
Risk minimisation measures	Routine risk minimisation measures: *SmPC Section 4.4.* *SmPC Section 5.1.* Additional risk minimisation measures: *None.*

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of BUCCOLAM.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for BUCCOLAM.

Part VII: Annexes

Table of contents

Annex 7 – Other supporting data (including referenced material)

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