EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 February 2022
EMA/190723/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 29(4) of Directive 2001/83/EC

Nasolam and associated names

INN/active substance: midazolam

Procedure number: EMEA/H/A-29(4)/1511

Note:

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

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Table of contents

List of abbreviations

AUC	Area Under the Curve
AUC_{INF}	AUC from time 0 extrapolated to infinite time
C_{max}	Maximum Concentration
CMDh	Co-ordination group for Mutual recognition and Decentralised procedures
CMS	Concerned Member State
CNS	Central Nervous System
EPAR	European Public Assessment report
GABA	gamma-aminobutyric acid
IB	intrabuccal
IN	intranasal
MDZ	midazolam
OAA/S	Observer's Assessment of Alertness/Sedation
PD	pharmacodynamic
PK	pharmacokinetic
popPK	population pharmacokinetic
popPK-PD	population pharmacokinetic-pharmacodynamic
RfP	reference product
SmPC	Summary of Product Characteristics
SPV	Saccadic Peak Velocity
SRTT	Simple Reaction Time Task
T_{max}	Time take to reach C_{max}
VAS	Visual Analogue Scale

1. Information on the procedure

An application was submitted under the decentralised procedure for Nasolam and associated names, 2.5 mg, 3.75 mg and 5 mg nasal spray, solution, in a single-dose container on 29 January 2020.

The legal basis under which the application was submitted is Article 10(3) of Directive 2001/83/EC as amended, hybrid application.

The application was submitted to the Reference Member State (RMS): NL and the concerned Member States (CMS(s)): DK, DE, FI, IE, NO, SE, UK (NI).

The decentralised procedure NL/H/5089/001-003/DC started on 21 February 2020.

On day 210, major issues on efficacy and safety, raised by Sweden, remained unresolved; hence the procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), under Article 29, paragraph 1 of Directive 2001/83/EC, by The Netherlands on 17 June 2021. The CMDh 60-day procedure was initiated on 26 July 2021.

Day 60 of the CMDh procedure was on 23 September 2021, and as no agreement could be reached, the procedure was referred to the CHMP. Sweden raised in view of the proposed indication "treatment of prolonged, acute, convulsive seizures, both in adults and children from 2 years" objections on the pharmacokinetic (PK) comparison to intrabuccal administered midazolam and identification of a dose window that combines sufficient effectiveness with adequate safety for a broad target population treated by lay-persons in a prehospital setting that were considered to be a potential serious risk to public health.

On 24 September 2021 the RMS, the Netherlands, therefore triggered a referral under Article 29(4) of Directive 2001/83/EC.

2. Scientific discussion

2.1. Introduction

Product details

Midazolam is a derivative of the imidazobenzodiazepine group with a mechanism of action similar to other benzodiazepines. Midazolam has a sedative and sleep-inducing effect of pronounced intensity. It also exerts an anxiolytic, an anticonvulsant and a muscle-relaxant effect. After administration anterograde amnesia of short duration occurs (the patient does not remember events that occurred during the maximal activity of the compound). Midazolam 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; therefore, the pharmacological action of midazolam is of short duration.

Nasolam is a nasal spray containing midazolam in the strengths 2.5 mg, 3.75 mg and 5 mg. The reference product in this hybrid application is Dormicum 5mg/mL solution for injection (Cheplapharm Arzneimittel GmbH). Differences compared to the reference product are the therapeutic indications, pharmaceutical form, strength and route of administration. The proposed indications are those of the reference medicinal product (conscious sedation and premedication) plus an extra indication i.e. "the treatment of prolonged, acute, convulsive seizures, both in adults and children from 2 years".

The applicant proposed the below indications at the stage of the CMDh procedure:

"[Product name] is a short-acting sleep-inducing and anticonvulsive drug that is indicated in:

- *Conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia*
- *Premedication before induction of anaesthesia*

[Product name] must only be used by healthcare professionals for conscious sedation or premedication

- *Treatment of prolonged, acute, convulsive seizures.*

[Product name] must only be used by parents/care givers where the patient has been diagnosed to have epilepsy.

[Product name] is indicated in adults and children > 12 kg and aged 2 years and older. "

Currently only marketing authorisations for the following midazolam containing formulations have been granted in the EU: tablets (for insomnia), solution for injection/infusion (for conscious sedation and premedication before anaesthesia), oral solution (for conscious sedation and premedication before anaesthesia in children) and solution for oromucosal use (intrabuccal administration for seizures in children (Buccolam)).

Currently, midazolam nasal sprays are already available in two strengths as magistral formulations, known as Midazolam 2.5 mg or 5 mg unit dose nasal spray in the Netherlands or Midazolam HCl 2.5 mg or 5 mg nasal spray unit dose in Sweden, which are prescribed for various indications, including cessation of seizures/ prevention of status epilepticus in various settings.

Claimed benefits of intranasal midazolam over other routes of administration relate to the fast absorption into the systemic circulation as the nasal mucosa is only one cell-layer thick and highly vascularised. Moreover, due to the fast absorption from the nasal mucosa, no gastrointestinal absorption nor hepatic first-pass effect occurs for intranasally administered midazolam.

This referral procedure was triggered due to disagreement as regards the benefit-risk of the product in the indication 'Treatment of prolonged, acute, convulsive seizures', which was questioned by Sweden. The other indication (conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia) was already agreed by all concerned Member States.

The concerns raised by Sweden during the application procedure that led to the triggering of the CMDh Article 29(1) of Directive 2001/83/EC referral are:

- Similarity based on PK comparison to intrabuccal administered midazolam has not been demonstrated and efficacy and safety can therefore not be bridged.
- It is not self-evident that a dose window can be identified that combines sufficient effectiveness with adequate safety for a broad target population treated by lay-persons in a pre-hospital setting

The overall concern was that safety and efficacy of a posology to be used by lay persons outside hospital had not been demonstrated based on the literature data provided.

As the CMDh could not reach an agreement on the above concerns, The Netherlands, triggered a referral under Article 29(4) of Directive 2001/83/EC.

On the basis of the grounds that led to the triggering of this Article 29(4) referral procedure, the CHMP asked the applicant to address the following issues:

- The bridging of data on efficacy and safety between Nasolam and Buccolam in view of non-similar exposure profiles (earlier and higher C_{max}, subsequent lower exposure, risk of underdosing in heavier subjects due to decreasing exposure with increasing body weight),

- The treatment of prolonged, acute, convulsive seizures' in adults in view of pharmacokinetic comparison to intrabuccal administration (which is not approved for this indication in adults),
- The lower exposure in subjects with a higher body weight and the safety profile of intranasal use
- The need for a dose adjustment in the anticonvulsive indication in elderly in view of the lower dose in the conscious sedation indication.
- The effectiveness of the proposed educational programme as an effective risk minimisation for respiratory compromise.
- The proposed posology regarding the need to obtain medical advice prior to the administration of a second dose if patients do not respond to the first dose.

Clinical data

The data package submitted in support of the application included a four-way crossover, double-blind, double-dummy, randomised, placebo-controlled clinical pharmacokinetic-pharmacodynamic study in healthy subjects aged 18-53 years, comparing the sedative effects in terms of time to onset of effect and size of the effect. The comparator arm was Dormicum/Hypnovel, i.e. 2.5mg intravenous midazolam. Two doses of intranasal midazolam were used, i.e. 2.5mg and 5mg. The sedative effects were measured using Saccadic Peak Velocity (SPV), the Bond and Lader Visual Analogue Scale (VAS) for sedation (alertness, calmness and mood), the Simple Reaction Time Task (SRTT) and the Observer's Assessment of Alertness/Sedation (OAA/S).

A population pharmacokinetic (popPK) model and a population pharmacokinetic-pharmacodynamic (popPK-PD) model for midazolam after intravenous (IV) and intranasal (IN) administration was developed based on this clinical therapeutic equivalence study.

For the anti-epileptic indication, eight in silico PK-PD simulation analyses were performed using popPK and popPK-PD models in adults (PDV404007 and PDV404012), in paediatric patients (PDV 404008 and DV404009), in elderly (PDV404010 and PDV404013) and in special populations (PDV404011 and PDV404014). Simulations were performed using intravenous midazolam administered intrabuccally (IB). Data from the Buccolam EPAR was used to construct the model for simulations.
The applicant provided literature data to further support the use in adults for the treatment of prolonged, acute, convulsive seizures.

2.2. Assessment of the issues raised as a potential serious risk to public health

Bridging to efficacy and safety data of Buccolam as the exposure profiles of Nasolam and Buccolam differ - summary of applicant's responses

The safety threshold proposed by the applicant is based on the concentration for which respiratory depression is reported in the literature (see figure 7 below). The efficacy threshold is based on a landmark study on the efficacy of midazolam in the management of acute seizures (Silbergleit 2012). The average time to cessation seizures after 10 mg IM midazolam in adults and children weighing <40kg was 3.3 minutes (see Figure 3). In a quantitative study on the PK of IM midazolam, the midazolam concentration at 3.3 minutes was estimated at 17 ng/mL, as based on visual interpolation of the mean profile. Therefore, it is concluded by the applicant that the average efficacious concentration for midazolam is 17 ng/mL (see figure 1 and 2 below).

Figure 1: The time from active treatment to cessation of convulsions for IM midazolam is 3.3 minutes. Asterisks indicate means, boxes interquartile ranges, bold vertical lines within boxes medians, I bars 1.5 times the interquartile range, and circles outliers. For details see *Silbergleit et al. 2012*

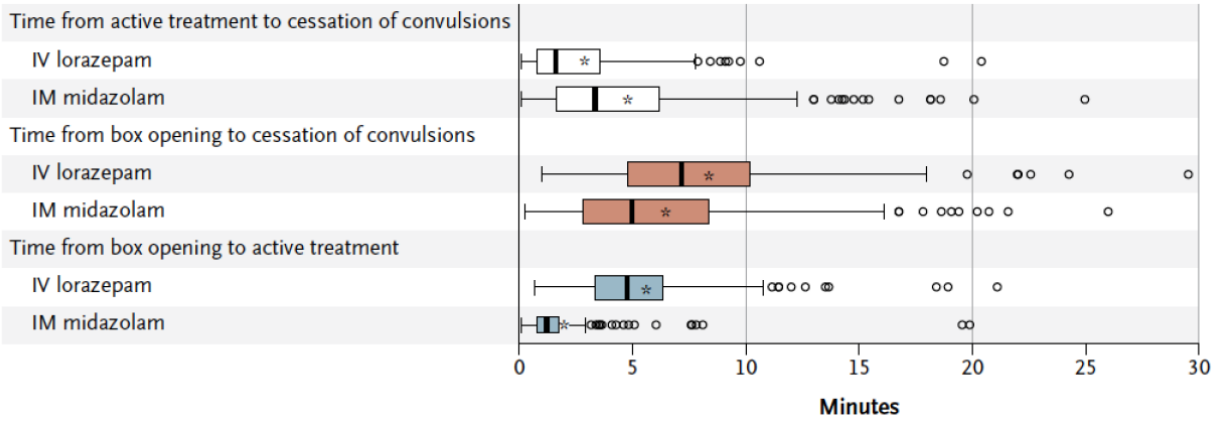
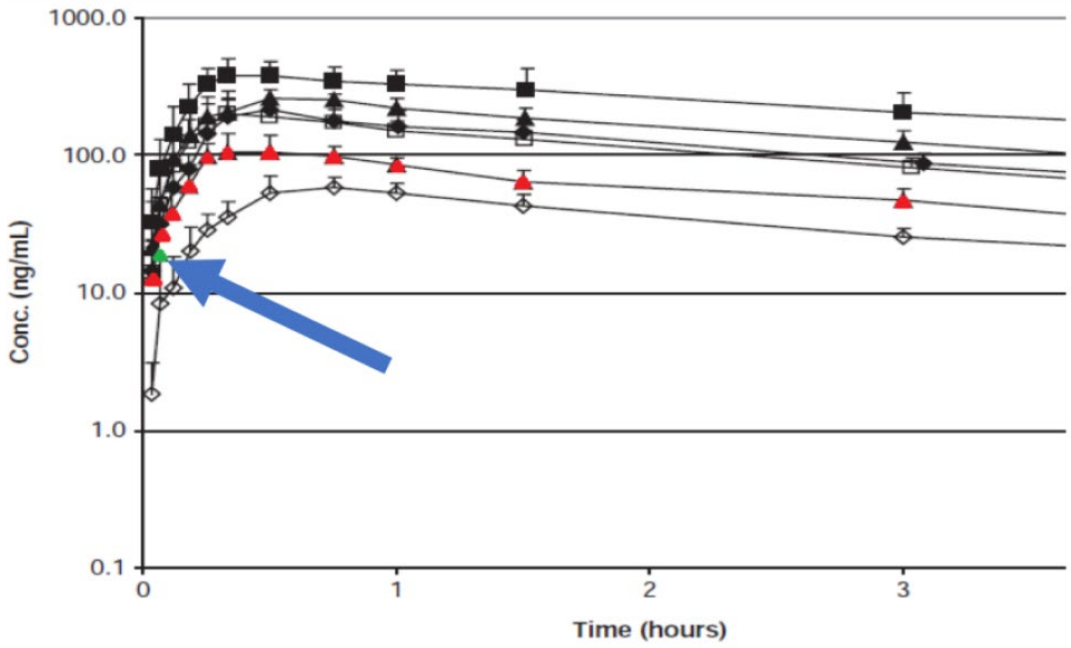


Figure 2: Linear interpolation of the PK following 10 mg IM midazolam administration (triangles, see Figure 2 in Reichard 2010) indicates that the average midazolam concentration at 3.3 minutes is 17 ng/mL (as indicated by the green triangle and the blue arrow).

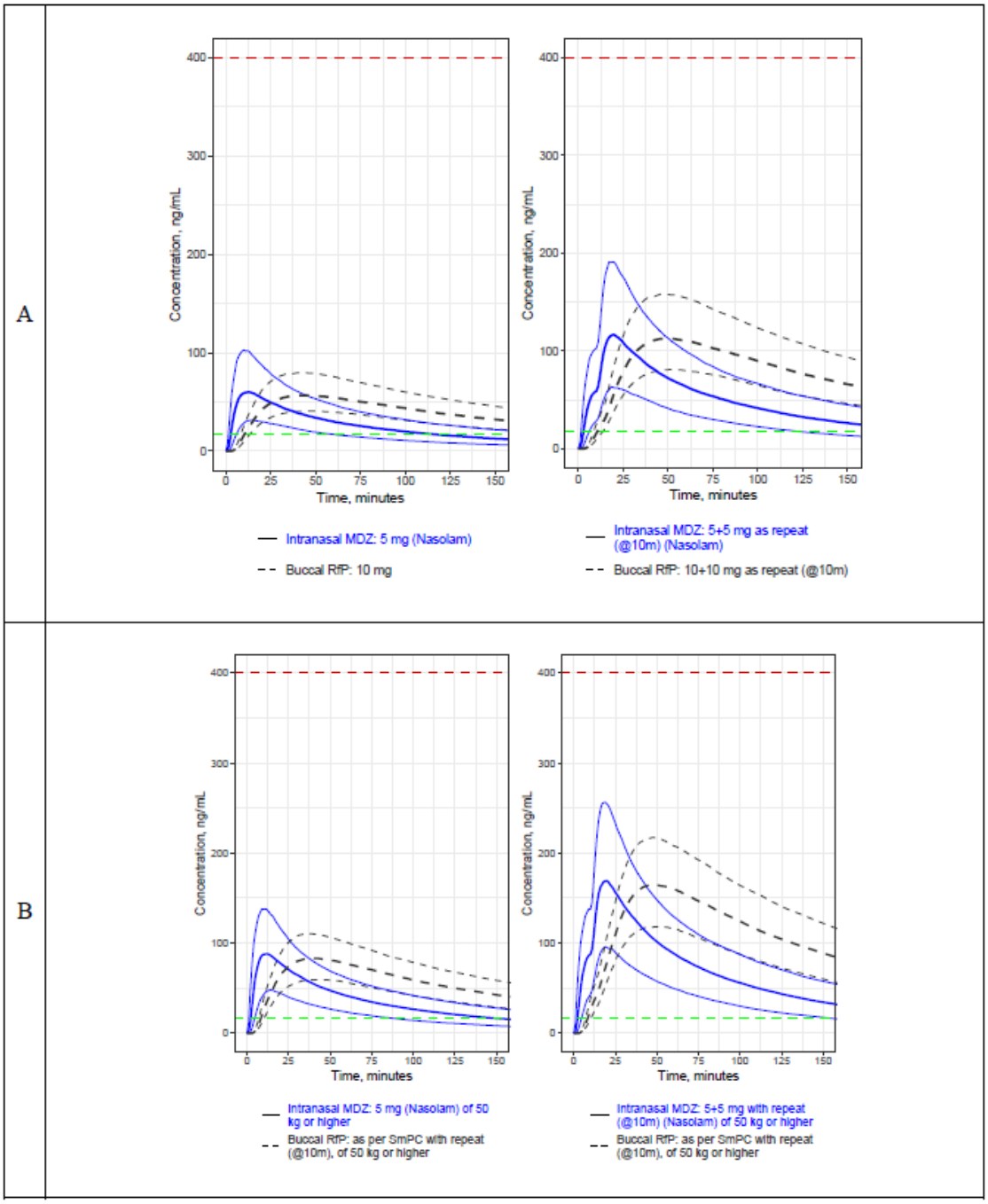


The complete concentration-time profile and distribution (variability) of concentrations (as indicated by 80% percentiles (upper and lower lines)) in adults, adolescents and children, at any given time is shown in Figure 1 below for the buccal administration of the reference product (RfP) and IN midazolam (Nasolam). To be noted, in the left figure the single administration is shown, and in the right figure the profile in case a second administration is given after 10 min., both for buccal and IN administration. The simulated C_{max} and AUC_{INF} versus body weight is shown in Figures 2 and 3. The PK profile for IN

midazolam in adults based on clinical study CHDR1012 vs. bibliographic data is shown in Figure 4 and Table 1.

When PK profiles of midazolam after buccal and IN administration are compared an earlier C_{max} for IN administration relative to buccal administration of midazolam is observed (figure 3).

Figure 3: PK profiles of midazolam after buccal and IN administration (see below). Simulated concentration-time profile in adults (panel A), children weighing > 50 kg (panel B), children weighing 19 kg to 44 kg (panel C), and children weighing < 19 kg (panel D) including 80% percentiles at any given time for the buccal administration of the RfP and IN midazolam (Nasolam) after a single dose (left panel) and a subsequent second dose at 10 minutes after the first dose (right panel). The efficacy and safety thresholds are indicated by a green and red line.



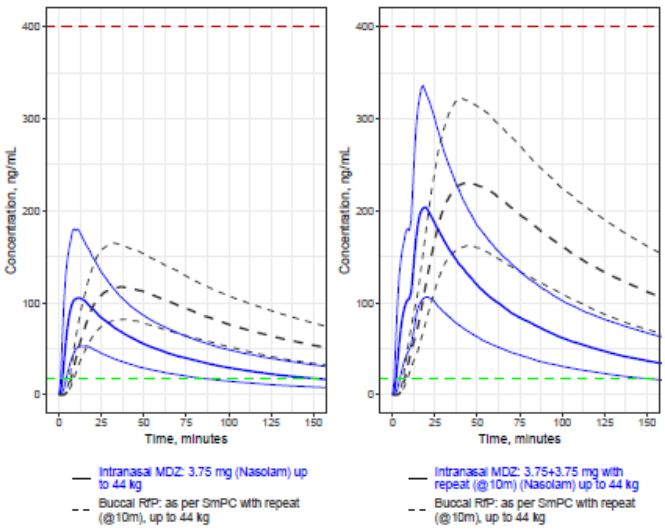
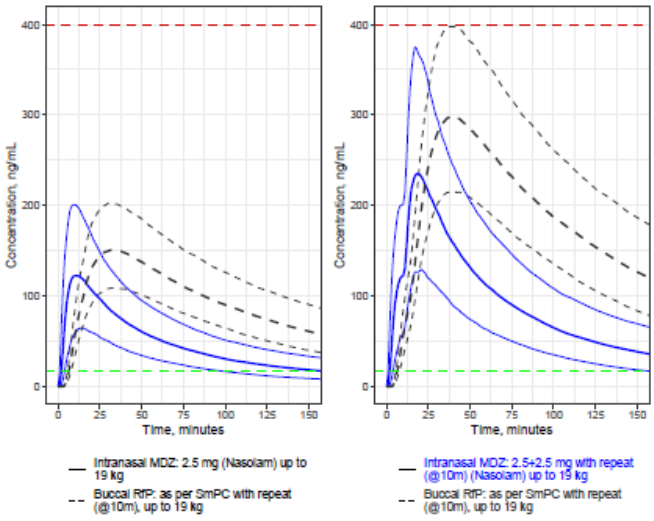
C	 Concentration, ng/mL Time, minutes Intranasal MDZ: 3.75 mg (Nasolam) up to 44 kg Buccal RfP: as per SmPC with repeat (@10m), up to 44 kg Intranasal MDZ: 3.75+3.75 mg with repeat (@10m) (Nasolam) up to 44 kg Buccal RfP: as per SmPC with repeat (@10m), up to 44 kg
D	 Concentration, ng/mL Time, minutes Intranasal MDZ: 2.5 mg (Nasolam) up to 19 kg Buccal RfP: as per SmPC with repeat (@10m), up to 19 kg Intranasal MDZ: 2.5+2.5 mg with repeat (@10m) (Nasolam) up to 19 kg Buccal RfP: as per SmPC with repeat (@10m), up to 19 kg

Figure 4 and figure 5 show that the relation for C_{max} and AUC_{INF} for body weights up to 100 kg is comparable for buccal and IN midazolam as requested (see below). To be noted, in the "A" figures the single administration is shown, and in the "B" figures the profile in case a second administration is given after 10 min., both for buccal and IN administration.

Figure 4: Simulated C_{max} versus body weight in accordance with the EMA Q&A on Modelling and simulations. The efficacy and safety thresholds are indicated by a green and red line.

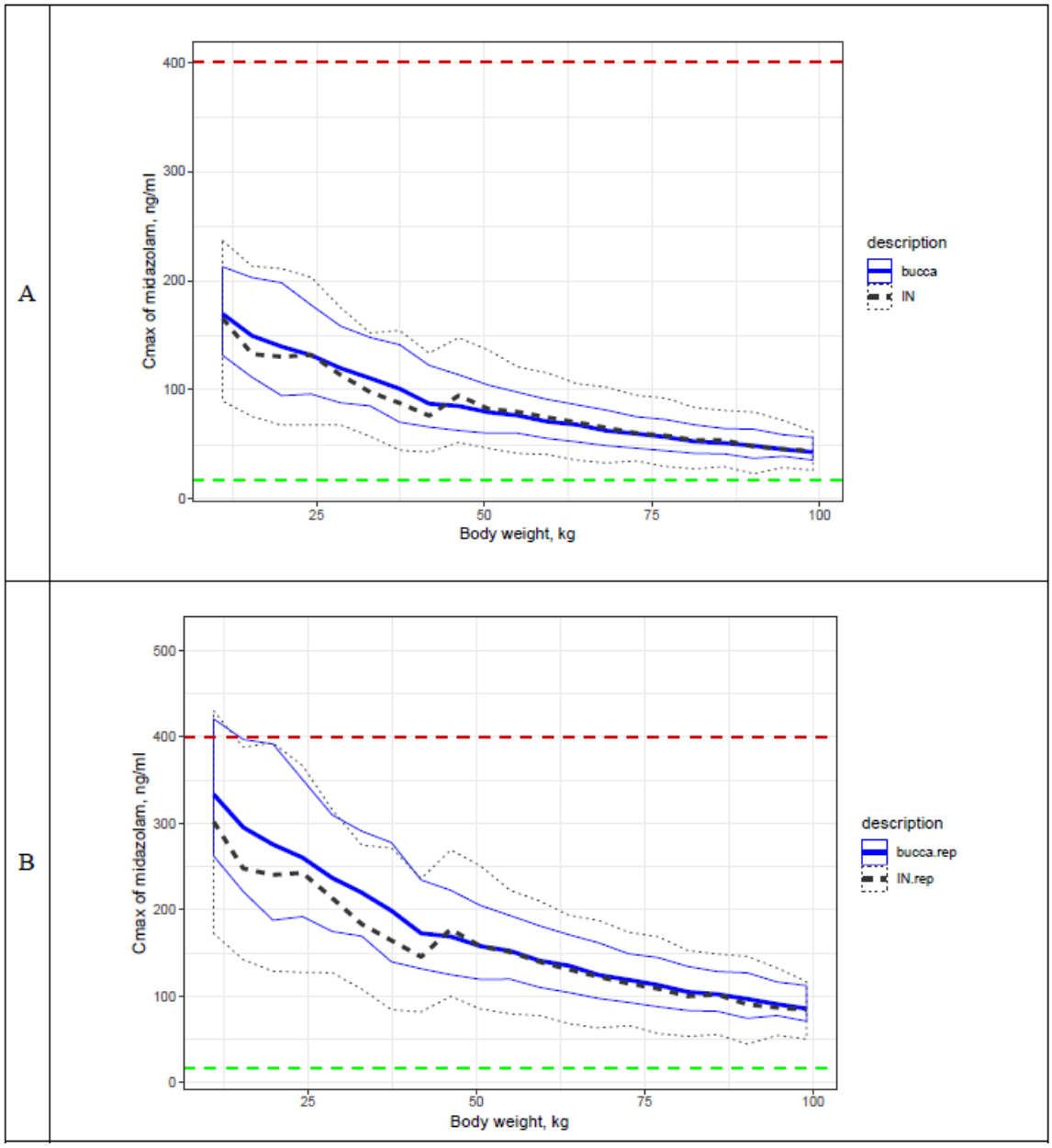


Figure 5: Simulated AUC_{INF} versus body weight. The efficacy and safety thresholds are indicated by a green and red line

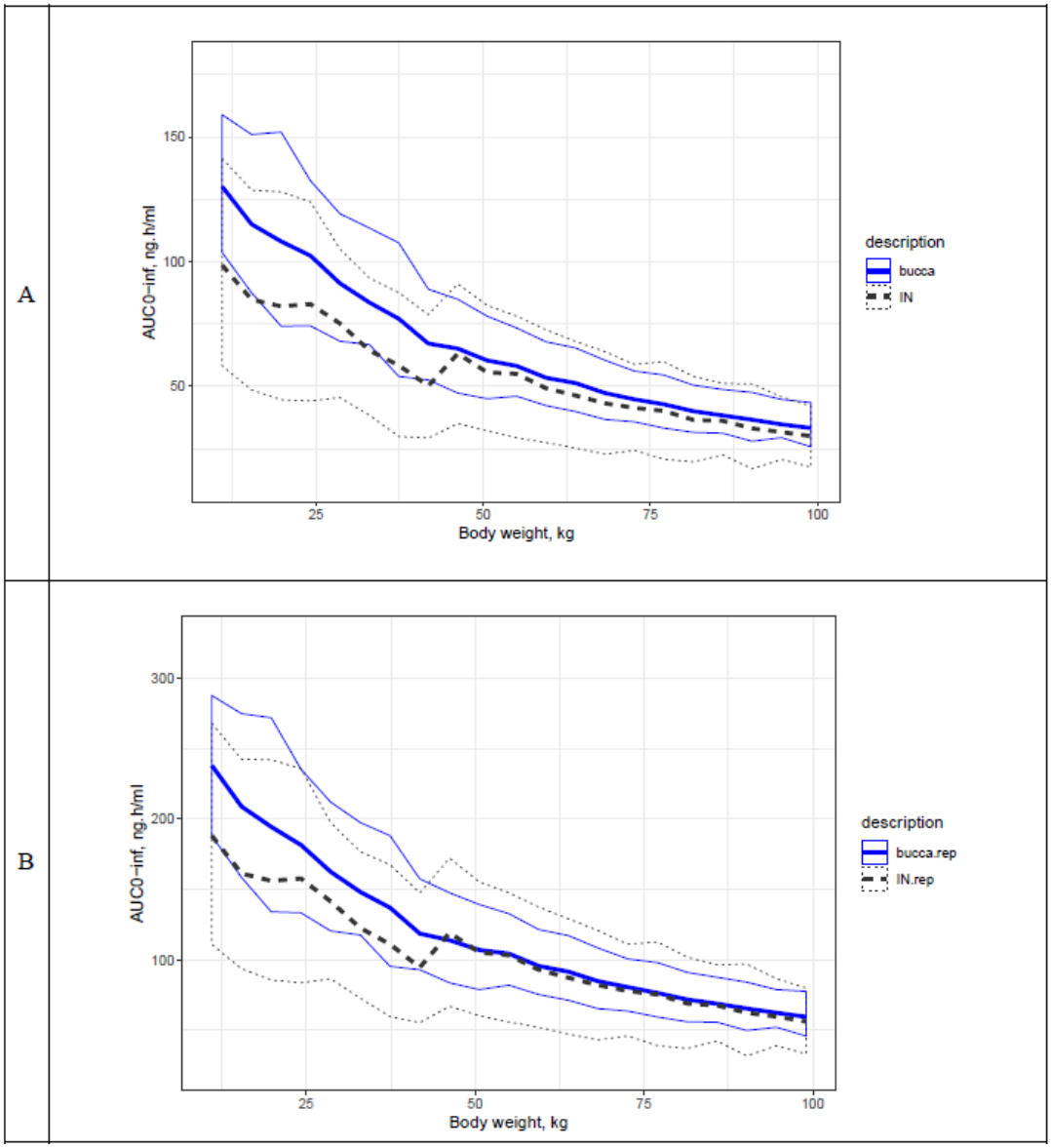


Figure 6 and table 1 also confirm according to the applicant that the PK for IB and IN midazolam is comparable with the exception of an earlier C_{max}.

Figure 6: PK profiles in adults are shown for IN midazolam (blue circles, based on clinical study CHDR1012) and bibliographic data on the PK of buccal midazolam (grey squares, based on bibliographic data). The applicant claims that the PK profiles of buccal and IN midazolam below confirm the simulated PK profiles in Figure 3.

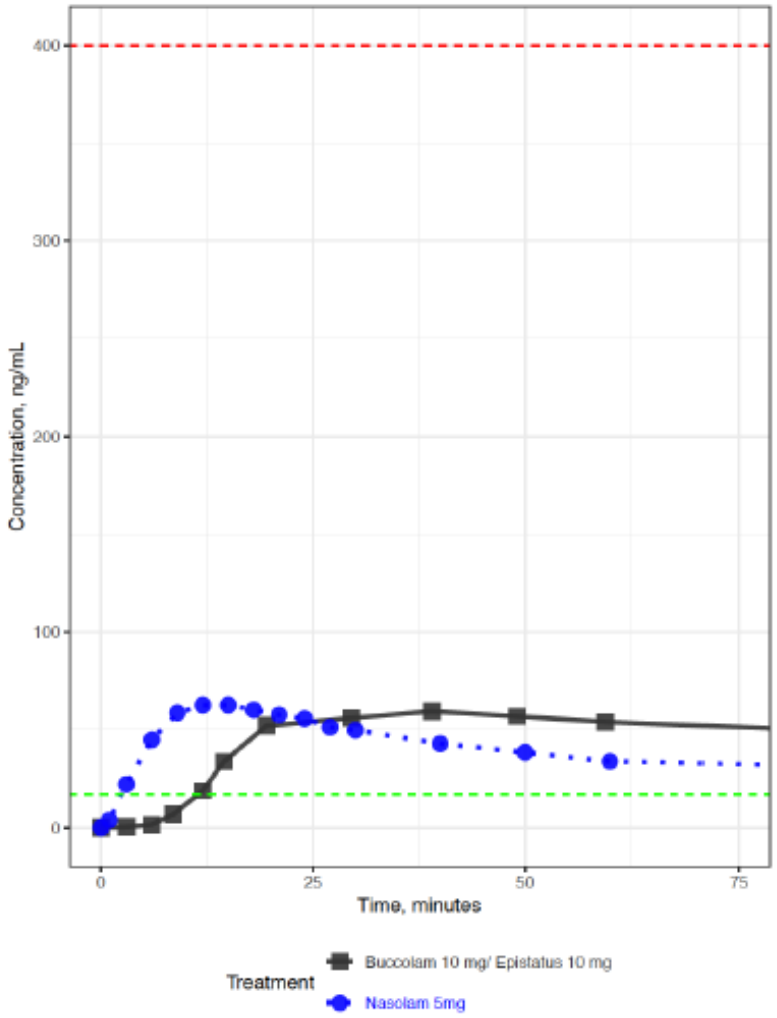


Table 1. Midazolam C_{max} values after buccal and of IN midazolam (Nasolam) administration of a single dose in adults. Data reported as mean ± SD or mean (range).

Administration route	Tmax (min)	Cmax (ng/mL)
Buccal midazolam 10 mg (Epistatus) [b]	48 ± 24	63.9 ± 19.0
IN midazolam 5 mg (Nasolam)[a]	14 (9 – 24)	66.2 ± 20.9
Buccal midazolam 10 mg (Dormicum/Hypnovel/Buccolam)[b]	54 ± 36	73.3 ± 27.5

[a] Clinical study CHDR 1012 / Module 2.5 [b] Epistatus UKPAR

The applicant indicated that based on the PK profiles in Figures 3 to 6, it can be concluded that the C_{max} and AUC_{INF} of buccal and IN midazolam are comparable except for an earlier C_{max} for IN midazolam.

Discussion on bridging to efficacy data of Buccolam

The CHMP considered that the PK profiles following a single dose are not identical to the buccal administration as the C_{max} is earlier and has a higher 80% predicted interval than buccal administration (see figure 3). However, the mean C_{max} values (middle line in figure 3) are comparable.

Efficacy threshold

The efficacy threshold was justified based on data from Silbergleit et al. 2012, a double-blind, randomised, noninferiority trial wherein the efficacy of IM midazolam was compared to that of IV lorazepam for children and adults in status epilepticus treated by paramedics. The median time for seizure cessation in both adults and children treated with 10mg IM midazolam was 3.3 minutes. The concentration of midazolam at this timepoint was 17ng/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 is considered appropriately justified.

Figure 4 shows that the PK levels can be reached following a single dose, i.e. levels are above the justified efficacy threshold necessary for seizure cessation. It was noted that the PK profiles no longer display an overlap after 20-50 minutes between IN and IB administered midazolam (see figure 3). Moreover, the plasma concentration following IN administration also drops below the efficacy threshold (see figure 3). Based on these two notions, further substantiation on efficacy, including reoccurrences was required.

All literature data discussed during the procedure showed that following a single IN administration of midazolam, seizure cessation occurred < 5 minutes in 57%-82% of the seizures and < 10minutes for 58-87% of the seizures. This is comparable to a single IB administration of midazolam, where seizure cessation occurred < 5 minutes for ~ 40-75% of the seizures and < 10 minutes 56-85% of the seizures. Therefore, it can be concluded that IN midazolam is as effective as IB midazolam for treating acute prolonged seizures.

Figure 4 shows that the concentrations of midazolam remained above the minimum efficacy threshold for efficacy up to 50-75 minutes post-dose. Therefore, the applicant has been requested to discuss the risk of reoccurrences. In response, the applicant submitted literature data describing the seizure free period after IB and IN midazolam administration. The proportion (%) seizure freedom 6 hrs post-dose was 58-75% for IN midazolam, indicating that the risk of reoccurrence is low. This proportions are acceptable as they are comparable to IB midazolam where 56-70% without recurrence within 1hr is reported. Although the time measured after treatment is different for both formulations, the proportion of seizure freedom is comparable between IB and IN midazolam. Therefore, the observed decrease of midazolam plasma concentration below the defined efficacy threshold after a single dose is not considered an issue as it does not result in a higher recurrence rate.

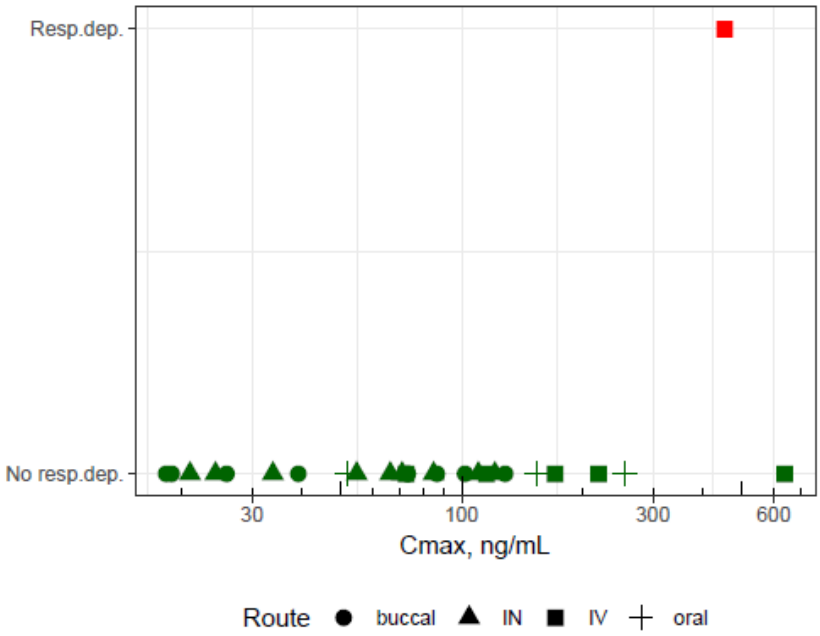
The effect of weight on the exposure of midazolam is considered comparable between IN and IB administered midazolam, as absorbed midazolam would undergo the same distribution/elimination pattern both for IB and IN administered midazolam. This is confirmed by Figures 2 and 3, which show comparable mean values in heavier subjects for IN and IB midazolam. The lower C_{max} and AUC described for IN midazolam compared to IB midazolam is not a concern as the efficacy threshold as the effect on seizure cessation and reoccurrences is comparable (see previous comments).

Safety justification for the earlier C_{max} - summary of applicant's responses

The following justification is provided by the applicant to indicate that an earlier C_{max} does not lead to a different safety profile as compared to IB midazolam:

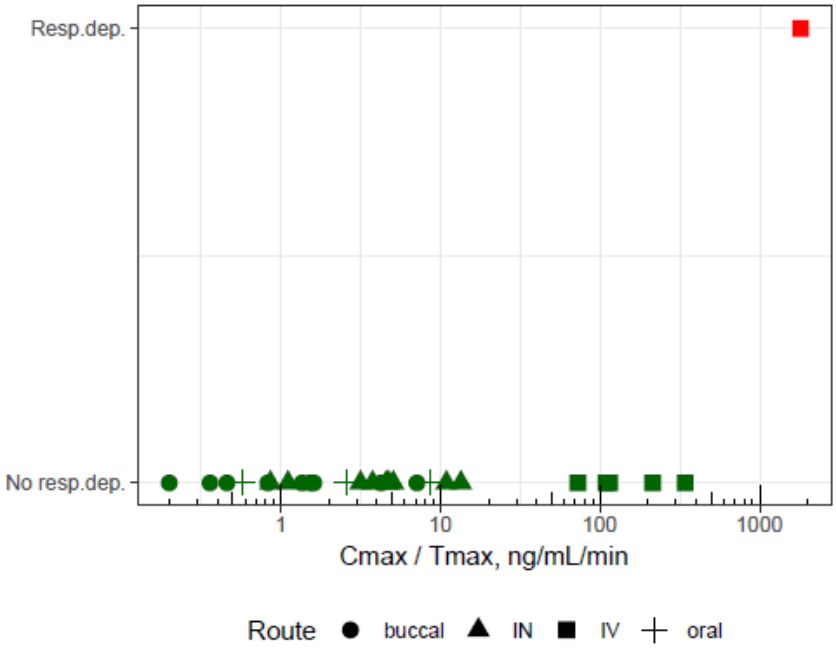
1) Differences in T_{max} are caused by an absorption lag time.
2) The time to reach plateau levels (as shown in figure 6 above) is comparable between IN administration (14min) and IB administration (19min).
3) The PK exposure of IN midazolam is far below PK exposure associated with respiratory depression (see figure 7 below).

Figure 7: Relation between C_{max} and respiratory depression after oral, buccal, IN and IV midazolam administration for studies where respiratory depression was investigated after midazolam administration. Midazolam concentrations up to 400 ng/mL do not lead to respiratory depression.



4) A steep increase in midazolam concentration is associated with the occurrence of respiratory depression. To quantify/characterise the steepness the applicant presented a C_{max}/T_{max} curve.

Figure 8: Relation between the C_{max} / T_{max} ratio and respiratory depression after oral, buccal, IN and IV midazolam administration and respiratory depression. No clinically relevant respiratory depression is observed after midazolam administrations that lead to C_{max}/T_{max} ratios below 341 ng/ml/min.



5) Maintaining airway patency in fitting patients is not related to benzodiazepines (Silbergleit 2012). As maintaining airway patency is not related to benzodiazepine exposure, the earlier C_{max} of IN administration is unrelated to this risk. Note: The Package Leaflet includes instructions for "turning patients sideways".

6) Both IB midazolam and IN midazolam aim to treat acute seizures before these develop into sequela of continued seizures lasting for longer periods of time that can result in muscle fatigue and therefore losing airway patency (Hirsch 2012).

7) The earlier C_{max} is hypothesised to lead to a faster onset of efficacy and therefore also a faster reduction of seizure duration, thereby further preventing the occurrence of any muscle fatigue, thus reducing the risk of losing airway patency. This is supported by an expert opinion submitted by the applicant.

8) The earlier C_{max} in IN midazolam compared to IB can cause an earlier termination, which is the primary goal of acute seizure treatment. Therefore, an earlier C_{max} is considered favourable.

9) The PL and SmPC include instruction to turn the patient sideways as soon as feasible to maintain airway patency.

10) The device is ready to use and does not require assembly, and therefore does not have risks associated with the assembly of the device by laymen.

11) The low volume of IN midazolam allows relative easier administration, full absorption by the nasal mucosa and does not lead to any risk of aspiration or loss of airway patency.

The applicant argued that acute seizures that do not develop into self-sustaining seizures generally last less than 5 minutes (Hirsch 2012), and seizures lasting longer than 5 minutes require immediate treatment for preventing the seizures from becoming self-sustained (Hirsch, 2012). This makes the PK exposure during the first 10 minutes after seizure initiation the most important period for assessing the efficacy of IN and buccal midazolam.

Figure 3 (D) shows that the PK exposure of IN midazolam is above the midazolam efficacy threshold concentration of 17 ng/mL (for details see appendix B) for over 75 minutes. As acute seizures generally do not last longer than 5 minutes (Hirsch 2012), and seizures lasting longer than 5 minutes require immediate treatment for preventing the seizures from becoming self-sustained (Hirsch, 2012), it is concluded that IN midazolam is efficacious in the treatment of acute seizures.

Figure 3 (D) also shows that the PK exposure of IN midazolam is higher than buccal midazolam during the first 18 minutes (for the lowest IN midazolam percentile) to 150 minutes (for the highest IN midazolam percentile). Therefore, it can be concluded that the efficacy of IN midazolam is comparable to buccal midazolam for 18 minutes to 150 minutes. Because this duration is longer than the duration of acute seizures, it is concluded that the efficacy of IN and buccal midazolam for the treatment of acute seizures is comparable.

It is hypothesised by the applicant that the earlier C_{max} may lead to an earlier onset of efficacy of IN midazolam relative to buccal midazolam. This can shorten the seizure duration. Shortening the seizure duration is important to the patient for two reasons. The first reason is that a shorter seizure will cause less (irreversible) brain damage. The second reason is that longer seizures have a higher chance to become self-sustained (Hirsch 2012), causing potentially fatal damage to the brain.

Discussion on safety threshold

In view of the safety threshold the applicant reviewed literature on respiratory depression showing a midazolam concentration of 452ng/ml, which further supports the proposed safety threshold of 400 ng/ml calculated by the applicant for the risk of respiratory depression.

The applicant further discussed literature data wherein IN midazolam is compared head-to-head to rectal diazepam in several studies. The results indicated a better effect of IN midazolam with a comparable safety profile to rectal diazepam.

The C_{max} following the second IN dose is not higher than following the second IB dose in subjects with a body weight of <40kg. In the heavier subjects the variability of the C_{max} is greater, however no safety concerns have been reported in head-to-head comparison to other products across weight ranges (e.g. rectal diazepam).

Safety was further substantiated by a discussion on the risk for respiratory depression and effects on maintaining airway patency. Regarding the risk of respiratory depression, the applicant reiterates that the exposure following IN midazolam is lower than what has been seen for IV midazolam and is comparable to IB midazolam. Therefore, no additional risks are associated with IN midazolam compared to IB midazolam. This is graphically shown in figure 7, where the C_{max} and reported respiratory depression are represented, and both IB midazolam and IN midazolam have comparable C_{max} ranges.

To further substantiate that the difference in absorption time does not cause respiratory depression, the applicant divided the C_{max} by the T_{max} to quantify the steepness of the increase in plasma concentration (figure 8). The steepness analysis shows that IN and IB midazolam have a comparable steepness as the IN data points (circles) are surrounded by the IB data points (triangles).

Bibliographic data is available for the safety of IN midazolam administration in patients (Scheepers (2000), Loftsson (2001), Gudmundsdottir (2001), Knoester (2002), Rudy (2002), Dale (2006), Wermeling (2006; 2009), de Haan (2009), Haschke (2010), Noll (2011), Banck (2015), Kay (2015) Schrier (2016), Berg (2017), Detyneicki (2019), Kay (2019), Wheless (2019) and Spencer 2020). in total, 938 patients were treated with IN midazolam, and only one patient was suspected of having respiratory depression. It is noted that the suspected respiratory depression may have been caused by an inadequate positioning of the pulse oximeter or the displacement of the oximeter during ictal movements where the body position of the patient was changed (Von Blomberg 2020).

The applicant's notion that the risk for a loss of airway patency is related to the seizure itself rather than the use of benzodiazepines is supported. Therefore, the loss of airway patency is not considered a concern related to the use of IN midazolam specifically. Although the risk is associated with the seizure, the PL adequately recommends putting patient into a stable side position as soon as possible to maintain airway patency, thereby reducing this risk.

Taken together, there appears to be no additional risk for IN midazolam given as a single dose as compared to IB midazolam or rectal diazepam, which are treatments that are currently available and recommended

Overall, the CHMP considered that the applicant has adequately substantiated that the exposure between IN and IB midazolam is comparable, except for an earlier and higher C_{max} (for some weight groups). However, these differences in the PK profiles do not lead to differences in efficacy as both the effect on seizures cessation and reoccurrences is comparable between the formulations. The earlier C_{max} of IN midazolam could be considered an advantage over IB midazolam as this may lead to an earlier cession of seizures. Moreover, the earlier and higher C_{max} is not expected to lead to an increased risk of respiratory depression.

Finally, the C_{max} of a single dose of IN midazolam never exceeds the C_{max} of 2 doses of Buccolam administered safely and more easily be administered by a lay-person in an outpatient setting. Thus, the higher C_{max} is no longer considered a potential safety concern.

Substantiation of adult indication - summary of applicant's responses

The applicant states that the adult indication was not included in the registration of buccal midazolam (Buccolam), because the product was registered via a paediatric-use marketing authorisation (PUMA), i.e. exclusive use in paediatric patients. However, there is extensive data 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 (Shankar 2021; Kadel 2018; Nakken 2011; Scott 1999). and by the recommendation for buccal midazolam in national of NL, DK, FI, DE, IE, NO, SE and UK, which are all involved in the procedure.

Bibliographic data on the use of IB and IN midazolam in adults

Regarding the use IN midazolam in adults, the applicant indicates that this formulation is also recommended for adults in these national guidelines (see table appendix A), with comparable efficacy and safety profiles to buccal midazolam as demonstrated in the literature (see table 4).

A tabulated overview was also submitted describing the recommendations in DE, DK, FI, NL, NO, SE and UK guidelines on the use of both IB midazolam and IN midazolam in adult and paediatric patients (see references). In these, the same doses are recommended for adults as for the heavier/older paediatric subjects.

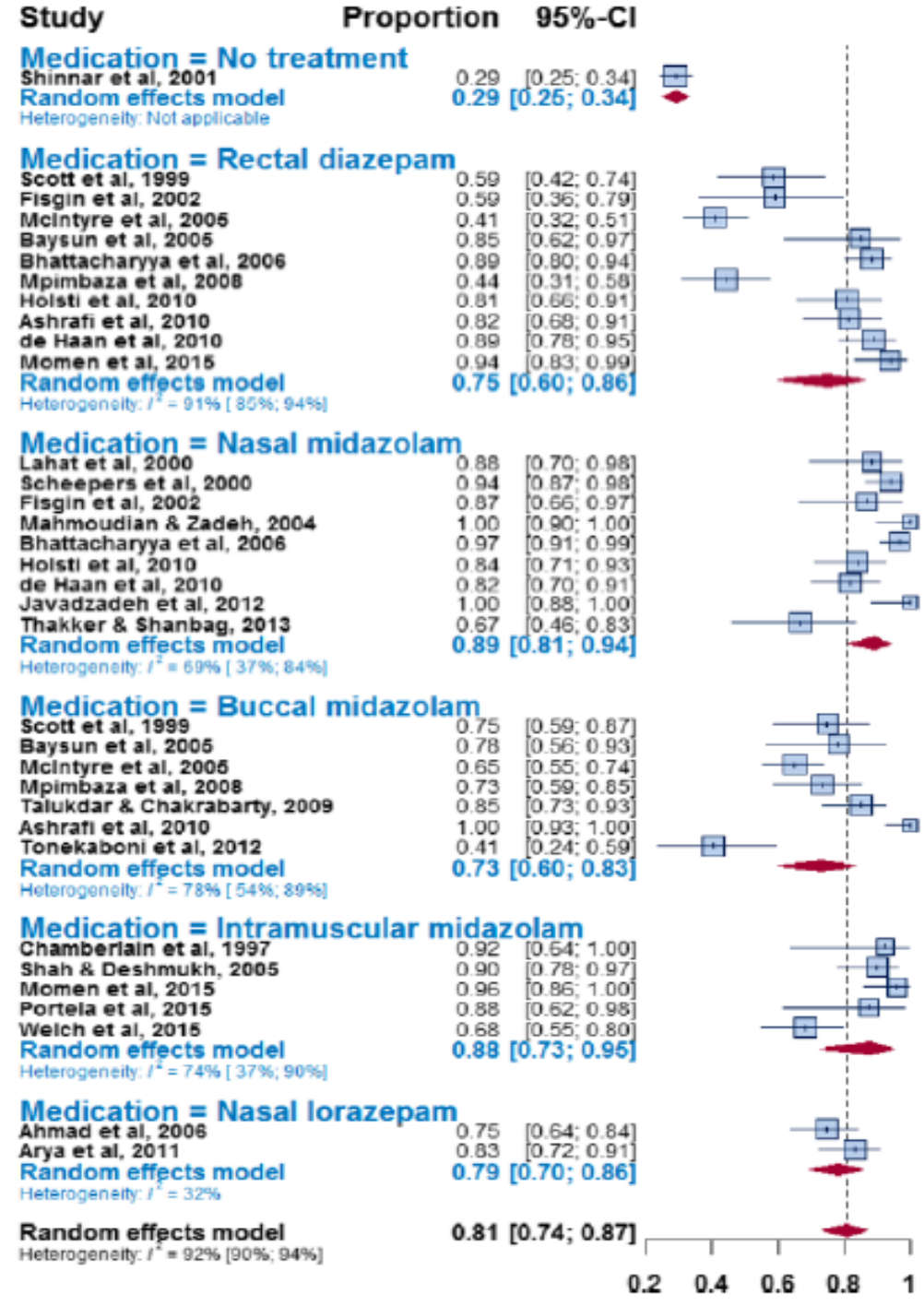
Table 2. Bibliographic data supporting the safety and efficacy of IN midazolam in adults for the management of acute seizures as obtained in a total of 664 patients.

Year	First author	Number of subjects	IN dose (mg)	Success rate %
2020	Von Blomberg	243	5	94
2019	Detyniecki	134	5	81
2019	Wheless	104	5	88
2019	Kay	42	5.7	57
2019	Owusu	23	3	70
2015	Kay	75	5.1	75
2009	De Haan	21	10	82
2000	Scheepers	22	10	94
		Total 664	Average dose 5 mg	

The applicant presented also a meta-analysis by Sanches et al. 2017[1] which shows the effectiveness of treatment with several benzodiazepines with different routes of administration. The results from this meta-analysis (grade II) is displayed in the figure 9 below.

[1] Epilepsia. 2017 Aug;58(8):1349-1359. doi: 10.1111/epi.13812. Epub 2017 Jun 16.

Figure 9: Effectiveness for no treatment, rectal diazepam, IN midazolam, buccal midazolam, IM midazolam and nasal lorazepam (Sanchez 2017). The average proportion of stopped seizures and the 95% confidence interval is shown for each study.



In this figure, the average proportion of stopped seizures (i.e. 1 corresponds to 100%) and the 95% confidence interval is shown. Data includes studies in both adult and paediatric populations. Additional literature data was submitted previously and partially repeated here in the applicant response.

Similar pharmacology of midazolam in adolescents and adults

The applicant concluded that that pharmacology of midazolam is similar for adolescents and adults based on the following considerations:

- The posology of the RfP (Dormicum) recommends the same dose in adults as in adolescents aged 12 to 18 years.
- The licensed adolescent buccal dose (10 mg, see SmPC Buccolam) is similar to the unlicensed adult buccal dose (10 mg) as recommended in national guidelines for the management of acute seizures.

These conclusions are supported by the observation that buccal midazolam (Epistatus) is registered for adolescents (aged 10 to 18 years) in Europe (UK, Germany, Hungary and Sweden) on the basis of similarity of PK data in adults and *in silico* simulations based on the well-known pharmacology of midazolam in adults and adolescents. Therefore, the applicant concluded that the safety and efficacy of buccal midazolam in adolescents aged 10 to 18 years can be predicted on the basis of data from adults and vice versa.

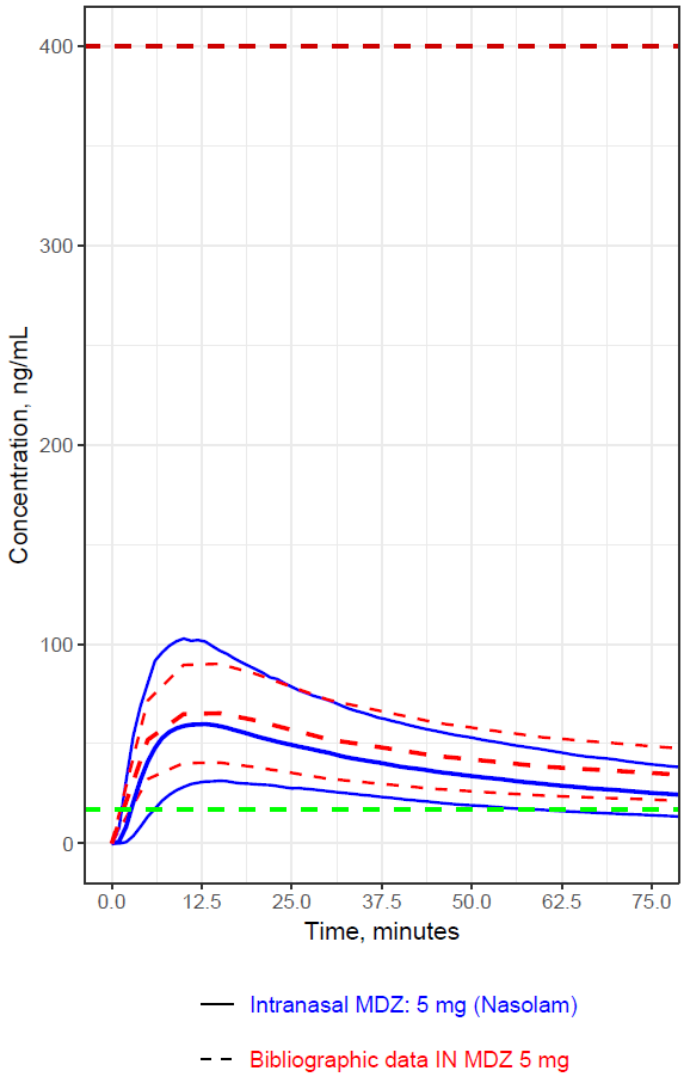
As acute seizures that do not develop into a sequela of continued seizures generally last less than 5 minutes (Hirsch 2012), and seizures lasting longer than 5 minutes require immediate treatment for preventing the seizures to become self-sustained (Hirsch, 2012). For this reason, the PK exposure during the first 10 minutes after seizure initiation is more relevant than the PK exposure thereafter, thus, the applicant argues that the efficacy and safety of midazolam in the management of acute seizures are C_{max} related rather than AUC.

Data from the clinical study CHDR1012 show that the C_{max} of 5 mg IN midazolam is comparable to bibliographic data on the C_{max} of 10 mg buccal midazolam (see UKPAR Epistatus) (see Figure 3 before). Furthermore, the C_{max} of 10 mg buccal and 5 mg IN midazolam is comparable across different body weights (see Figure 4 before). Therefore, the applicant concluded that the safety and efficacy of 10 mg buccal and 5 mg IN midazolam in adults is similar.

Safety and efficacy of IN midazolam in adults- summary of applicant's responses

IN midazolam (Nayzilam) is authorised for use in adults in the US by laypersons in an outside hospital setting (see FDA label for Nayzilam). Figure 10 shows the PK profile of the IN midazolam licensed in the US (Nayzilam) and the PK profile of the IN midazolam of the current application (Nasolam). Based on Figure 10 it is concluded that the PK profiles of Nayzilam and Nasolam are similar.

Figure 10: The PK exposure and 80% percentile intervals of the IN midazolam licensed in the US (Nayzilam) and the PK profile of the IN midazolam (Nasolam).



The efficacy and safety thresholds are indicated by a green and red line (see above for their determination).

Over 50,000 units IN midazolam (Nasolam) have been dispensed since 2017 in the Netherlands, Norway and Sweden. Over 1 million units magisterially prepared IN midazolam (known as the Knoester formulation) have been dispensed in the Netherlands over the last 20 years without leading to reports on an elevated risk of respiratory depression to the Dutch authorities. Prescribers and dispensing pharmacists in the Netherlands by law are obliged to report any side effects of medication that is prescribed and dispensed as specialty product. Therefore, the absence of reported side effects is supportive for the inferences above. The PK exposure of the Knoester formulation is by the applicant be considered similar to the PK exposure of IN midazolam (Nasolam) in view of the available data from Knoester et al 2002.

In addition, IN midazolam is recommended for adults in national guidelines (see also tabulated overview above).

Extrapolation of efficacy to adults:

Although simulations indicate an approximately 50 % lower median C_{max} at a body weight of 100 kg as compared to 40 kg (see figure 4 and 5 above), efficacy in adults can be considered to be extrapolated from efficacy in children. In the SmPC of Buccolam the C_{max} values after the buccal administration of the RfP are listed for different age groups, and the C_{max} decreases with age from 148 ng/mL in children aged 1 to 5 years, to 87 ng/mL in children aged 10 to 18 years. This is despite the administration of a two times higher dose of children aged 10 to 18 years (10 mg), relative to the dose in children aged 1 to 5 years (5 mg).

The applicant concluded that midazolam C_{max} decreases with increasing age in the proposed age groups of 2 to 18 years. Furthermore, because older children are heavier than younger children, the applicant concluded that midazolam C_{max} decreases with increasing weight. Therefore, the applicant concludes that the approximately 50% lower median C_{max} at a body weight of 100 kg relative to 40 kg would demonstrate that the simulations accurately reflect the PK of midazolam in different weight and age categories.

Effective concentration in adults

The threshold concentration for onset of effect in adults is 17 ng/mL (for details see appendix B and question 1). Furthermore, the PK in heavier subjects differs from non-heavy subjects as the elimination phase of the PK curve is prolonged only at concentrations below 8 ng/mL, which is a sub-clinical level in normal subjects and heavier subjects. An example that illustrates that the differences in PK in heavier subjects are not clinically relevant is shown in Figure 11 below.

Figure 11: Plasma midazolam concentrations after IV and oral administration of midazolam to a heavier subject (136 kg) and a match controlled non-heavy subject (61 kg). For details see *Greenblatt 1984*

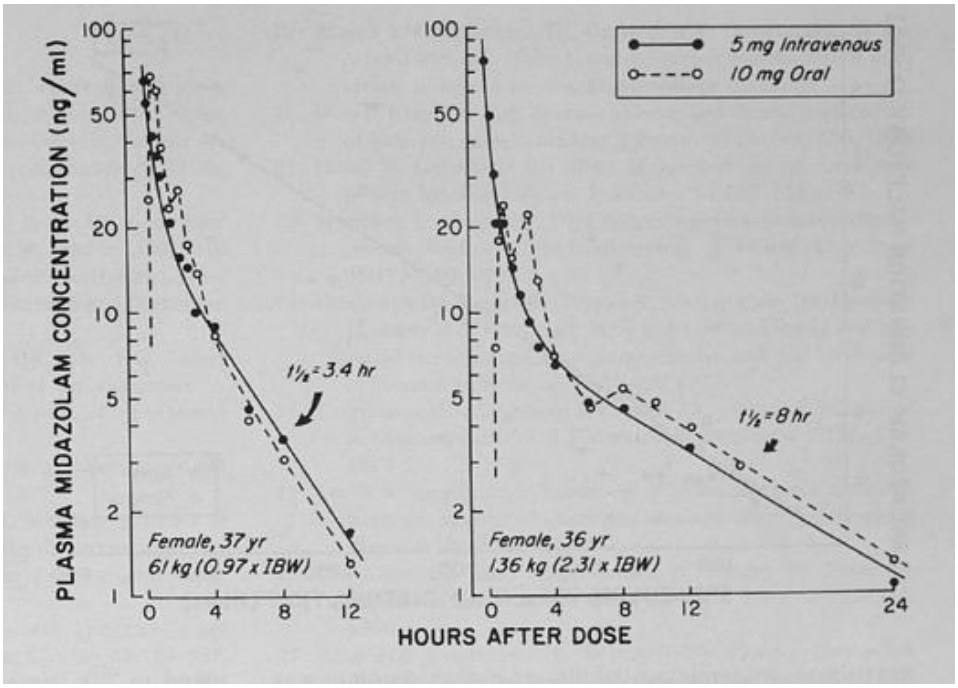
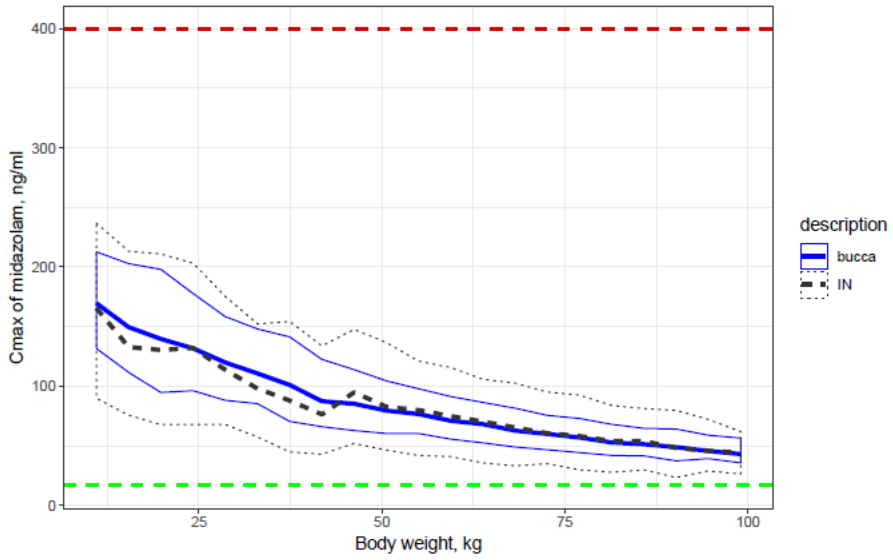


Figure 11 shows the plasma midazolam concentrations after 5 mg IV and 10 mg oral administration of midazolam for a heavier subject (136 kg) and a match-controlled non-heavy subject (61 kg). Based on Figure 2, it can be concluded that that differences in the shape of the PK curve occur after 4 hours at

midazolam concentrations below 8 ng/ml. The prolongation of the elimination PK phase is related to the release from midazolam from a so-called deep PK compartment, as is confirmed by the higher volume of distribution in heavier patients in the absence of a difference in clearance. These differences in the midazolam PK exposure in heavier adults after IN midazolam are not clinically relevant. First, the differences in heavier adults are below the minimal effective midazolam concentration of 17 ng/mL and will not lead to differences in the efficacy profile of IN midazolam in heavier subjects. Second, the differences are far below the midazolam safety threshold of 400 ng/mL (for details on the safety threshold, see Question 1) and will not lead to differences in the safety profile of IN midazolam in heavier subjects. Furthermore, simulated data indicate that the IN midazolam concentrations are above the minimal effective midazolam concentration for body weights ranging from 19 kg to 100 kg (see figure 12 below). Therefore, the administration of IN is concluded midazolam is efficacious for these body weights.

Figure 12: Simulated C_{max} versus body weight in accordance with the EMA Q&A on Modelling and simulations. The efficacy and safety thresholds are indicated by a green and red line.



Based on these considerations, it is concluded by the applicant that the changes on midazolam concentrations in heavy subjects are not clinically relevant as these only occur beyond 4 hours following administration and at midazolam concentrations that are not clinically relevant.

The applicant also substantiates the safety threshold based on the concentrations of midazolam at which respiratory depression is reported in the literature. Respiratory depression was reported at a midazolam concentration of 452ng/ml when given IV (Gross 1983).

Discussion on substantiation of the use in adults as part of the indication

The CHMP considered that after the first intranasal administration, relatively comparable median C_{max} values are obtained compared to buccal administration.

For the anticonvulsive indication, extrapolation based on comparable exposure, i.e. PK values, is considered acceptable. The anticonvulsive effect of midazolam and corresponding dose ranges are extensively described in the literature and considered well known. In addition, the applicant has

performed a bioavailability PK study to substantiate exposure after IN administration. The use in adult for the seizure indication is acceptable based on the consistency between the results observed from literature studies and PK simulations. Although a lower exposure is observed in heavier subjects, IN midazolam concentrations are still above the threshold concentration for onset of effect in adults and comparable to that of IB midazolam.

Moreover, the use of IN midazolam and IB midazolam is supported across available European treatment guidelines (see tabulated overview A above). In these guidelines, dose recommendations for adults are the same as for adolescents. Given that the exposure of IN midazolam is similar for both these age-groups the proposed posology is considered substantiated.

The lack of reporting of adverse events related to respiratory depression is reassuring; however the absence of cases cannot be seen as evidence for an absence of risk, and it is agreed that spontaneous reporting may not be the most reliable form to assess the incidence of respiratory compromise from midazolam. Hence, this can only be considered as supportive information. The C_{max} is within the range of intrabuccal midazolam (see table 1 comparison of C_{max} and T_{max} of oral, IN and IV midazolam administration) and the literature data confirms the well-established PK profile of midazolam.

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.

Overall, based on the consistency of the overall submitted data package, i.e. literature data on adults and adolescents, PK simulations and profile in adults and adolescents and the same dose recommendation in adults and adolescents, the use of midazolam intranasal in adults can be considered acceptable.

Discussion on administration of second dose after medical advice

No differences are anticipated compared to Buccolam where a second dose may lead eventually to a successful intervention in this serious condition that may have detrimental consequences. In the majority of cases a single IN midazolam dose is sufficient to achieve seizure cessations, similar to the response reported for IB midazolam. However, in case the seizure has not stopped within 10 minutes or do reoccur after an initial response it is desirable to include an option for a second dose, which should however be given only after obtaining medical advice, and in the case of young children, respiratory impaired patients and elderly, only in the presence of a healthcare professional.

The posology for the treatment of prolonged, acute, convulsive epileptic seizures has during the procedure been brought in line with the product information of Buccolam 2.5, 5, 7.5, 10 mg oromucosal solution in pre-filled syringes. The SmPC and Package Leaflet have been updated accordingly.

In the updated text, the carer is instructed to administer only a single dose of midazolam. Additionally, the carer is instructed to seek emergency medical assistance if the seizure has not stopped within 10 minutes after administration of midazolam. The carer must give the empty nasal spray device to the healthcare professional to provide information on the dose received by the patient.

Instructions for administration of a second dose by a lay person for the treatment of prolonged, acute, convulsive epileptic seizures have been amended to state that they should not administer a second dose to young children, patients with respiratory impairment and elderly patients, as for these patient's populations, the second dose should only be administered in the presence of a health care professional.

Dose recommendation in elderly subjects and effectiveness of the educational program- summary of applicant's responses

For the management of acute seizures, the applicant's proposed dosing for IN midazolam (Nasolam) in elderly and special populations is based on national guidelines for the management of acute seizures in the RMS and CMS countries. For the sedation indication, the proposed dosing for IN midazolam (Nasolam) in elderly and special populations is based on the SmPC for the IV administration of the RfP for procedural sedation and premedication.

The differences in dose reduction for elderly and special populations for the sedation and epilepsy indication are related to differences in Benefit / Risk (B/R) evaluations concerning the consequences of underdosing. For sedation, the consequences of underdosing are limited, allowing for a conservative dosing approach in elderly and special populations. For the epilepsy indication, the consequences of underdosing include the occurrence of (fatal) brain damage, leading to a dose recommendation that considers the implications of the risk of overdosing and the impact of underdosing.

It is concluded that the dose recommendations for the management of acute seizures are more relevant for the use of IN midazolam (Nasolam) in the management of acute seizures than the dose recommendations in the SmPC of the reference product for the use of IV midazolam in the sedation indication. The Product Information also has measures in place to maintain airway patency before administering the product in order to mitigate the risk of airway obstruction due to the seizure itself.

Discussion on dose recommendation in elderly subjects and effectiveness of the educational programme

The applicant indicates that the dose recommendation in the elderly for the sedation indication is based on the posology of IV midazolam which is indicated for conscious sedation. The anticonvulsive dose recommendation in the elderly is based on the dose required for seizure cessation in adults. No dose adjustment is proposed for this patient subpopulation. The B/R for the treatment of seizures, where midazolam is given as a single dose, is different as compared to conscious sedation. Cessation of prolonged seizures is an acute medical emergency setting, which is different from conscious sedation/premedication, a planned and controlled setting. The use of midazolam nasal spray for prolonged seizures is a potentially life-saving intervention to prevent further development of the seizures into status epilepticus. Thus, the benefit of seizure cessation (i.e. prevent development into status epilepticus) outweighs any potential risks on the use of IN midazolam in the elderly population.

Current treatment options for prolonged seizures and status epilepticus in adults in a pre-hospital setting include midazolam IM or rectal diazepam, which have the same safety risks for elderly subjects.

Previous PK simulations have already shown that a 5 mg dose followed by a second 5 mg dose after intranasal administration in elderly subjects suggests no pharmacokinetic issues, i.e. no overexposure compared to buccal administration. Safety data regarding the use of buccal midazolam in elderly was also discussed previously by the applicant, with no unexpected or additional safety findings compared to adolescents or adults.

However, a dose reduction from the initially proposed 5.0 mg to 3.75 mg for elderly in the seizures reduction was considered necessary by the CHMP to avoid the risk of respiratory depression in this vulnerable population (reflecting a similar approach taken for the sedation indication), while still maintaining an adequate level of midazolam exposure. The other alternative of a lower dose (2.5 mg) would however be too low to treat prolonged, acute, convulsive seizures, especially as a repeat dose may only be possible once a health care professional is on site for this population.

3. Benefit-risk balance

A seizure is defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Prolonged seizures are known to occur with epilepsy, and it is acknowledged to pose a serious health risk to the patient if left untreated, i.e. potential (neuronal) damage or progression to status epilepticus.

Midazolam is a benzodiazepine that exerts its anti-epileptic effects by the inhibition of the spread of seizure activity. The current product concerns an intranasal (IN) formulation of midazolam, for which approval is sought through an Article 10 (3) hybrid application with Dormicum 5mg/mL solution for injection (Cheplapharm Arzneimittel GmbH) as reference product. The proposed epilepsy indication is: "*the treatment of prolonged, acute, convulsive seizures, both in adults and children from 2 years*". For a similar indication, midazolam is currently approved as a buccal formulation both centralised (Buccolam, EMEA/H/C/002267) as well as decentralised (Epistatus, [SE/H/1958/001] approved in UK (NI), Germany, Hungary and Sweden) for use in paediatric and adolescent patients. The use of midazolam, including both the buccal and intranasal routes of administration, for the cessation of prolonged seizures, is considered well established and incorporated in epilepsy treatment guidelines across Europe (The Netherlands, Denmark, Finland, Germany, Ireland, Norway, Sweden and UK).

Four issues were raised in the referral procedure triggered by Sweden which pertained to 1) further substantiating the PK bridge between IN midazolam and the efficacy and safety data of Buccolam due to differences in the exposure profiles, 2) further substantiating the adult indication as this could not be based on PK comparisons to intrabuccal administration as this is not approved in adults taking into account the impact of body weight, 3) justifying whether a dose adjustment for elderly subjects is not considered necessary and 4) the proposed posology on the necessity to obtain medical advice prior to second dose administration should be justified.

The argumentation put forward by the applicant to support the PK bridge between Buccolam and IN midazolam is considered sufficient for the following reasons: While the PK profiles are not fully identical between the formulations, the earlier and higher C_{max} of IN midazolam is not considered a safety risk. The C_{max} of IN midazolam is below the C_{max} of two doses of buccal midazolam (in accordance with Buccolam/Epistatus SmPC); hence the risk for respiratory depression is no different than for buccal midazolam. Loss of airway patency is not considered an issue related to midazolam itself, rather as a consequence of the prolonged seizures if left untreated. In this respect, the earlier C_{max} could be considered a possible advantage over buccal administration, leading to an earlier cessation of seizures.

As stated previously, Buccolam and Epistatus are approved for paediatric and adolescent patients only. Simulations have been discussed by the applicant to substantiate the posology in adults, accompanied by scientific literature. Based on this data use of midazolam in adults, including heavier subjects, is not considered an issue. Moreover, the use of IN midazolam is supported across European treatment guidelines. In these guidelines, dose recommendations for adults are the same as for adolescents and given that the exposure of IN midazolam is similar for both these age-groups the proposed posology can be considered substantiated.

For the sedation indication, a dose reduction is recommended for elderly subjects. Based on the provided simulations by the applicant, there seems to be no overexposure after IN administration compared to buccal administration in elderly subjects, however due to the potentially increased risk of respiratory compromise, an adaptation of the dose to 3.75 mg was considered relevant to reduce this risk while still maintaining efficacious treatment. In the acute (outpatient) treatment of prolonged seizures, the benefit-risk should be weighed differently than in a routine medical setting. The benefit of seizure cessation in this medical emergency, preventing possible conversion into status epilepticus and subsequent neuronal damage, outweighs the potential safety risk. No distinction has been made in

dose recommendations for this age population in the national treatment guidelines. In addition, the same safety risks have also been accepted for other benzodiazepines used within the same setting, such as intramuscular midazolam or rectal diazepam.

In the SmPC that was part of the CMDh procedure, it was initially advised to obtain medical advice prior to administering the second dose of IN midazolam in case seizures did not stop after the initial dose. In view of the available data on development of respiratory compromise the need to seek medical advice before a second dose was strengthened, and it was added that especially vulnerable patient groups at risk of respiratory compromise (young children, patients with respiratory impairment and elderly patients) should receive a second dose only in the presence of a healthcare professional.

Taken together, the efficacy and safety of IN midazolam for the cessation of prolonged seizures in both adults and paediatric patients has been adequately substantiated by the applicant. Midazolam must be administered in the emergency outpatient setting as soon as possible, as prolonged seizures could lead to status epilepticus and subsequent (neuronal) damage. The intranasal route allows for an easy route of administration by caregivers while the risks remain comparable to other midazolam products. The use of IN midazolam is also widely accepted in the treatment of epilepsy, as reflected in several European treatment guidelines. Hence, in this emergency setting, the benefits of IN midazolam outweigh any potential risks associated with the use of the product across all age groups claimed in the indication when used in accordance with the product information.

4. Risk management

The applicant has submitted a risk management plan (V.1.8), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to Nasolam.

Safety specification

The applicant proposed the following list of safety concerns (and added Respiratory depression as important potential risk) in RMP v1.8, which was considered acceptable:

Important identified risks	None
Important potential risks	Respiratory depression
Missing information	Exposure during pregnancy

4.1. Risk minimisation measures

The CHMP considered that amendments to section 4.2 of the SmPC were necessary to include the information of this review. The Package Leaflet was amended accordingly.

The CHMP, having considered the data submitted in the application agreed that the following risk minimisation measures included by the applicant in the RMP are necessary for the safe and effective use of the medicinal product.

Educational material for caregivers/ patients in order to minimize the risk of respiratory depression by including emergency instructions regarding

- how to recognise respiratory depression
- how to act in case of a respiratory depression: call medical assistance and what can be done immediately, how to perform a head tilt-chin lift to secure free airway of patient.

This instruction materials (i.e. card, booklet or letter), including reference to the PIL, would be printed in a "credit card format" and enclosed in each marketed Nasolam packaging. This distribution path would assure that the caregiver (i.e. in case of infants) receives them accordingly within each Nasolam prescription.

5. Grounds for Opinion

Whereas,

- The Committee considered the referral under Article 29(4) of Directive 2001/83/EC
- The Committee considered the totality of the data submitted by the applicant in relation to the objections raised as potential serious risk to public health.
- The Committee considered that the currently available data, including pharmacokinetic and literature data on the use of midazolam to treat seizures, was acceptable to support efficacy in terms of seizure cessation within the relevant timeframe and safety especially in view of respiratory compromise which may occur.
- In view of a lower dose used in sedation for patients above 60 years of age, the Committee considered a reduction of the dose in this population also for the seizures indication to reduce the risk of respiratory compromise.
- Furthermore, in view of the available data on the risk of respiratory compromise, which may increase after a second dose due to higher exposure, the advice to seek medical advice before a second dose was strengthened, and vulnerable patient groups (young children, patients with respiratory impairment and elderly patients) should receive a second dose only in the presence of a healthcare professional. The key messages in the educational material for caregivers/ patients in order to minimize the risk of respiratory depression were considered acceptable.
- The Committee was of the view that the benefits of Nasolam in stopping prolonged acute convulsive seizures in epilepsy patients outweigh its risks when the first dose is given by a parent or carer, and the second dose only after seeking medical advice, however for vulnerable patient groups the second dose should be given in the presence of a healthcare professional.

The Committee, as a consequence, considers that the benefit-risk balance of Nasolam and associated names is favourable and therefore recommends the granting of the marketing authorisation(s) for the medicinal products referred to in Annex I of the CHMP opinion subject to the agreed amendments to the product information as set out in Annex III of the CHMP opinion and other risk minimisation measures as described above.

Appendix 1

Divergent positions

Article 29(4) of Directive 2001/83/EC

Procedure No: EMEA/H/A-29(4)/1511

Nasolam and associated names (INN: midazolam)

Divergent statement

The following CHMP Members consider that the benefit/risk of Nasolam in the treatment of prolonged, acute, convulsive seizures in adults and children > 12 kg and aged 2 years and older is not favourable based on the following grounds:

- In the context of an Art. 10(3) application, a reliable bridge to the reference product (buccal midazolam) has not been established.
- Pharmacokinetic similarity to buccal midazolam for the paediatric population has not been demonstrated. Intranasal C_{max} is observed earlier, higher, and the plasma concentration decreases more rapidly as compared to buccal administration. There is consistently larger variability for the intranasal product compared to Buccolam. As exemplified in subjects <19 kg the lower bound of C_{max} is ~40% lower compared to Buccolam. This raises concern for lack of efficacy and recurrence of seizures compared to Buccolam.
- At the proposed posology, there is a substantial decrease in C_{max} with increased weight and consequently a risk for underdosing of heavier adults. Efficacy in the subgroup of heavier adults has not been demonstrated.
- Safety of the earlier and higher C_{max} compared to Buccolam for treatment by lay persons in a community/home setting has not been demonstrated. The risk for loss of airway patency and respiratory depression may be increased. The methodology behind the proposed exposure threshold for safety concerning potential respiratory comprise is not scientifically sound. The collected 35-year long experience from midazolam and studies of PK/PD relationship indicates that no such clinically meaningful threshold can be defined. The dose needs to be titrated to effect and vigilance is needed to deal with respiratory compromise at any dose. This is well reflected in the SmPC core text agreed by the CHMP in an Art. 30 referral 2002.
- The proposed exposure threshold for efficacy is not accepted. The methodology behind the proposed threshold is not scientifically sound. The basis for the calculation is the median 3.3 minutes to cessation of the seizures in the RAMPART study and using a separate PK study to extract a corresponding concentration. Using the median time to termination of seizures and not accounting for variability within and across studies, and spontaneous termination of seizures early on, means that less than 50% of patients have stopped seizing at this time point. In other studies, longer median times to seizure termination are reported. Accepting this as an effectiveness threshold would be to accept a very high non-response rate and that doses of benzodiazepines for seizure control are very much higher than needed. This is unreasonable given that doses are generally titrated to effect, and non-interventional studies have used intranasal midazolam doses titrated between 2.5 – 15 mg. The face validity of the proposed threshold level for efficacy is very low.
- Literature presented do not provide sufficient support for efficacy and safety of Nasolam when critically appraised regarding study design, outcomes estimated, risk of bias, precision, relevance to the proposed target population, setting, and dose.

- Reference to the licensed use of 5 mg intranasal midazolam Nayzilam in the US does not provide robust support for efficacy and safety of Nasolam. The indication for Nayzilam is different from that proposed for Nasolam. The greater variability of the Nasolam exposure profile has not been justified. Two placebo-controlled randomised trials are referred to:
    - In Detyniecki 2019 <40% of seizure types characterizing the study population are related to the proposed indication for Nasolam, no subgroup analysis presented relevant for the proposed indication, no patient <12 or >64 years of age.
    - The Spencer 2020 study is negative against placebo.
- The posology for older and frail patients is a concern. The proposed dose in patients > 60 years is higher compared to the dose proposed for procedural sedation, where special monitoring and support facilities are recommended. Proposed additional risk minimisation measures are not expected to be effective in mitigating respiratory compromise.

Based on the presented clinical and bioequivalence evidence in their totality, we are of the following opinion:

In conclusion, for the proposed indication for treatment of prolonged epileptic seizures, by lay persons outside the healthcare setting, acceptable PK similarity has not been demonstrated for bridging of efficacy and safety from other midazolam formulations. Differences in exposure profiles have not been justified so that a beneficial benefit/risk balance can be concluded for a fixed posology to be used by lay persons outside hospital. The benefit/risk balance remains negative.

CHMP Members expressing a divergent opinion:

- Agnes Gyurasics
- Simona Badoi
- Elita Poplavska
- Armando Genazzani
- Kristina Dunder
- Alexandre Moreau
- Ondřej Slanař
- Blanka Hirschlerova

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