COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Nasolam 2.5 mg, 3.75 mg and 5 mg nasal spray, solution in single-dose container (midazolam hydrochloride)

NL/H/5089/001-003/DC

Date: 22 February 2023

This module reflects the scientific discussion for the approval of Nasolam 2.5 mg, 3.75 mg and 5 mg nasal spray, solution in single-dose container. The procedure was finalised on 1 April 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
AUC	Area under curve
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
IB	Intrabuccal
IN	Intranasal
IV	Intravenous
Log K_{ow}	Octanol/water partition coefficient
MAH	Marketing Authorisation Holder
OAA/S	Observer's Assessment of Alertness/Sedation
PBT	Bio-accumulative toxic
PD	Pharmacodynamics
PEC	Predicted environmental concentration
PECsw	Predicted environmental concentration for surface water
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PL	Package Leaflet
PopPK model	Population pharmacokinetics model
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SPV	Saccadic Peak Velocity
SRTT	Simple Reaction Time Task
TSE	Transmissible Spongiform Encephalopathy
VAS	Visual Analogue Scale

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Nasolam 2.5 mg, 3.75 mg and 5 mg nasal spray, solution in single-dose container, from Medir Europe B.V.

The product is a short-acting sleep-inducing and anticonvulsive drug that is indicated in adults and children ≥12 kg and aged 2 years and older for:

- conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia;
- premedication before induction of anaesthesia, (the product must only be used by healthcare professionals for conscious sedation or premedication);
- treatment of prolonged, acute, convulsive seizures, (the product must only be used by parents/care givers where the patient has been diagnosed to have epilepsy).

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the European Reference Product (ERP) Dormicum 5mg/mL midazolam solution for injection (NL RVG 10064) which has been registered in the Netherlands by Cheplapharm Arzneimittel GmbH since 19 July 1984 through a mutual recognition procedure (DE/H/3599/002). Dormicum is also marketed in other European countries under the brand name Hypnovel. An unlicensed magisterially prepared product is available in the Netherlands, Norway and Sweden.

The concerned member states (CMS) involved in this procedure were Denmark, Germany, Finland, Ireland, Norway, United Kingdom (Northern Ireland), and Sweden.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC as 'hybrid' of a reference medicinal product, with changes to the therapeutic indications, pharmaceutical form, strength and route of administration compared to the reference product.

Scientific advice

Scientific advice on the clinical development of Nasolam was obtained from the Dutch Medicines Evaluation Board (MEB) and from the European Medicines Agency (EMA) in 2010 and 2013, respectively, regarding multiple quality, efficacy and safety aspects.

II. QUALITY ASPECTS

II.1 Introduction

Nasolam is a clear, slightly yellow solution, to be used as a single-dose nasal spray with a pH range of 3.3-3.8 . The nasal spray is hypertonic, due to the use of propylene glycol. Each

millilitre of solution contains midazolam as hydrochloride equivalent to 50 mg midazolam for all strengths:

- each 2.5 mg Nasolam single-dose container holds one dose (50 µL) of 2.5 mg midazolam (as hydrochloride).
- each 3.75 mg Nasolam single-dose container holds one dose (75 µL) of 3.75 mg midazolam (as hydrochloride).
- each 5 mg Nasolam single-dose container holds one dose (100 µL) of 5 mg midazolam (as hydrochloride).

The products are packed in single-dose containers consisting of a clear glass vial with a rubber stopper, integrated in a polypropylene spray container packed in a blister.

The excipients are water, propylene glycol and ethanol.

II.2 Drug Substance

The active substance is midazolam hydrochloride, which is a well-known drug substance. Midazolam is described in the European Pharmacopoeia. The drug substance is a crystalline powder and practically insoluble in water, freely soluble in ethanol (96%), soluble in methanol and hydrochloric acid. Polymorphism is not relevant for this product, since it concerns a solution.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the MAH or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists of seven chemical reaction steps followed by a salt formation and a purification step. No metal catalysts or class 1 solvents are used during manufacture. The potentially genotoxic impurities have been adequately addressed.

Quality control of drug substance

The active substance specification is has been established in-house by the MAH. The acceptance criteria for description, identification (infrared), solubility, colour, water, assay, an impurity and related substances comply with the Ph. Eur. monograph for midazolam. Additional tests for related substance glycol ether and residual solvents (including class 1 solvents, contaminants of the solvents used in the last step of synthesis), with adequate acceptance criteria, are included in the specification. Batch analytical data demonstrating compliance with this specification have been provided for three production-scale batches.

Stability of drug substance

The stability of the drug substance has been assessed in ICH long-term and accelerated conditions. The re-test period of the substance is 5 years when stored in stated conditions. No specific temperature restrictions are necessary and it has been shown that the drug substance is photostable.

II.3 Medicinal Product

Pharmaceutical development

The products are of an established pharmaceutical form (solution), but they have a new method of administration for midazolam hydrochloride (nasal spray). The choice of excipients has been justified in view of the target patient groups. The development of the products has been adequately described in line with the requirements from EMA's guideline on the quality of nasal products. It has been demonstrated that the delivery device is suitable for administration of the drug product for the proposed indications. It has been demonstrated that the pH range for these drug products is critical and this pH range has been adequately justified and controlled. The excipients (ethanol, propylene glycol and purified water) are not usual for this type of dosage form. The efficacy of ethanol and propylene glycol as preservatives has been demonstrated.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques. The solutions are manufactured by mixing and filling. The manufacturing process of the bulk product and vial filling are adequately validated. Process validation data on the products have been presented in accordance with the relevant European guidelines for a bulk solution (which was comparable in volume to the commercial scale), for three batches of 2.5 mg and three batches of 5 mg. All strengths of vials are filled from one bulk solution.

Control of excipients

The excipients comply with Ph. Eur. requirements. These specifications are acceptable.

Microbiological attributes

The efficacy of ethanol (15% v/v) and propylene glycol (15% v/v) in the formulation as antimicrobial preservatives has been confirmed, making the product self-preserving. The test for micro-organisms as described in Ph. Eur. 5.1.3 (*Efficacy of antimicrobial preservation*) have been used to assess the efficacy. The results significantly exceed the recommended acceptance criteria from Ph. Eur. 5.1.3 for nasal preparations. Furthermore, the preservative effects of propylene glycol and ethanol are well-known. Batch validation included tests for microbiological contamination at the start, middle and end of filling the vials. The container closure system has been adequately described.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form and include tests for appearance, pack appearance, pH, osmolarity, uniformity of dosage units, identification (high-performance liquid chromatography and chlorides), assay, related substances, droplet size distribution and microbiological quality. Limits in the

specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life requirements are identical. Satisfactory validation data for the analytical methods have been provided. Batch analytical data for three full-scale bulk batches for the 2.5 mg and 5 mg strength and one batch for the 3.75 mg strength from the proposed production site have been provided, demonstrating compliance with the specification. An adequate nitrosamines risk evaluation report has been provided and no risk for presence of nitrosamines in the drug product was identified.

Stability of drug product

Stability data on the product have been provided for on three full-scale bulk batches of each strength stored at 25°C/60% RH (18 months), 30°C/65% RH (6 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. A shelf-life of 2 years can be granted. No special storage conditions are required for the drug product. The batches were stored in transparent Ph. Eur. type I glass vials with rubber plunger, placed in the polypropylene delivery device, as packaged for marketing. Results of photostability studies have been provided and no significant changes were observed.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Nasolam has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Midazolam is a well-known and widely used substance.. The literature submitted for the non-clinical part of this dossier is considered adequate to cover all aspects (pharmacology, pharmacokinetics and general toxicology). In addition, a study in rabbits was performed to assess local tolerance following the new intranasal (IN) administration route. The environmental risk assessment that was performed is discussed below.

III.2 Pharmacology

Midazolam is a derivative of the imidazobenzodiazepine group. Its mechanism of action is similar to other benzodiazepines. Midazolam has an anticonvulsant effect, a hypno-sedative effect, and an anxiolytic and muscle-relaxant effect. After intramuscular or intravenous administration, anterograde amnesia of short duration can occur. Midazolam's effects are mediated by enhancement of gamma- aminobutyric acid neurotransmission in limbic, thalamic and hypothalamic regions of the central nervous system. 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.

The literature submitted for the non-clinical part of this dossier is considered adequate to cover pharmacology.

III.3 Pharmacokinetics

After oral dosing, midazolam was rapidly absorbed with an absolute bioavailability of approximately 45%. Midazolam is extensively bound to plasma proteins (94-98%) and because it is a highly lipophilic molecule, it shows extensive distribution. The short duration of pharmacological effects is largely explained by its rapid metabolic biotransformation, mainly by CYP3A4. The principal metabolite is 1-OH-midazolam, which is rapidly conjugated with glucuronic acid. Midazolam is virtually entirely cleared via liver metabolism and mainly excreted by the renal route, with less than 1% of midazolam being excreted (unchanged) in the urine. Elimination half-life was under one hour in all species. The literature submitted for the non-clinical part of this dossier is considered adequate to cover pharmacokinetics.

III.4 Toxicology

The toxicity profile of midazolam is essentially similar to that of benzodiazepines in general. Repeated dose IV and oral toxicity studies in mice, rats, rabbits and dogs indicated that the liver is a target organ. Other adverse effects were e.g. changes in white blood cell counts, reduced red blood cells, body weight changes, urinary inflammation, increased adrenal cortical weight and adrenal cortical hypertrophy, increased thyroid and kidney weights.

Midazolam was negative in a standard battery of genotoxicity tests and no conclusive evidence for carcinogenic potential was seen in a 2-year oral bioassay in rats and mice.

No evidence of impaired fertility was observed in rats after IV doses of 10 times the recommended adult human dose. Animal studies indicate that during pregnancy midazolam is not expected to increase the risk of congenital anomalies. Use near delivery may result in neonatal respiratory depression. In view of the lack of controlled studies on the use of midazolam in early pregnancy, a cautionary approach is recommended.

<u>Local tolerance toxicology study in rabbits</u>
In addition to the submitted literature, a study in male rabbits was performed to assess local tolerance following the new intranasal administration route. Rabbits were intranasally dosed

daily for four days in the right nostril with placebo or 50 µL of active formulation (3 times the equivalent human volume based on comparison of the nasal surface and 8.9 times compared to humans based on metabolic body weight). The signs of local irritation of the respiratory epithelium (metaplasia, transitional hyperplasia, inflammatory cell infiltrates) appeared reversible. Although effects on olfactory epithelium were not completely reversed after two weeks, this is not considered relevant because, in contrast to rabbits, intranasal sprays are not expected to reach the olfactory cleft in humans.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Nasolam is a substitute for products currently available as tablets and solution for injection for the therapeutic indication sedation (Dormicum, Hypnovel) and currently available as oromucosal solution (Buccolam) for treatment of epileptic seizures. As the product is intended to be prescribed for the treatment of multiple indications (sedation, premedication and epileptic seizures), a phase I environmental risk assessment was performed. It does not contain components which result in additional hazards to the environment during storage, distribution, use and disposal.

The phase I ERA included a predicted environmental concentration (PEC) calculation, in which recent European prevalence data were used. Although the data for use in the epilepsy indication are older than 5 years, they are considered acceptable due to the absence of more recent European data. The total sum of the PEC for surface water (PECsw) for use in sedation, premedication and epilepsy is below the threshold. Due to the low log K_{ow} (octanol/water partition coefficient) of midazolam (a parameter for predicting the distribution of a substance in the environment), further screening for persistence, bioaccumulation and toxicity was not required.

Table 1. Summary of ERA study results

Substance (INN/Invented Name): midazolam hydrochloride (Nasolam)			
CAS-number (if available): --			
PBT* screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Shake-flask method	2.73	Potential PBT (~~Y~~/N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.73	B/not B
	BCF**	< 2000	B/not B
Persistence	DT50 or ready biodegradability	--	P/not P
Toxicity	NOEC or CMR	--	T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB*** ~~The compound is considered as vPvB~~ ~~The compound is considered as PBT~~		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surface water , default or refined (e.g. prevalence, literature)	~0.000002	µg/L	> 0.01 threshold (~~Y~~/N)
Other concerns (e.g. chemical	--	--	(~~Y~~/N)

class)			
** persistent bioaccumulative toxic* *** bioconcentration factor* **** very persistent and very bio-accumulative*			

Conclusion
The PECsw for midazolam hydrochloride is below the action limit of 0.01 µg/l and the substance is not persistent bio-accumulative toxic (PBT) as the log Kow does not exceed 4.5. Therefore, no Phase II ERA was required.

III.6 Discussion on the non-clinical aspects

Nasolam is a substitute for products currently available as tablets and solution for injection. The phase I ERA showed that Nasolam is not expected to pose a risk to the environment when used for the indications of sedation, premedication and epileptic seizures.

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

A clinical study (study 1) has been submitted to compare the pharmacokinetics (PK) and pharmacodynamics (PD) of midazolam after intranasal (IN) application versus intravenous (IV) administration. Based on the clinical therapeutic equivalence from study 1, a population PK model (study 2) for midazolam after IN and IV administration was developed. Using this model, eight computer simulation (*in silico*) analyses were performed in specific populations.

IV.2 Pharmacokinetics

Study 1 – bridging study, 2.5 mg and 5 mg IN administration versus 2.5 mg IV administration of midazolam (hydrochloride),
Design
The MAH conducted a bridging study in which the pharmacokinetic and pharmacodynamic profile of the test product Nasolam (Medir Europe B.V., The Netherlands) is compared with the profile of the reference product Dormicum (Cheplapharm Arzneimittel GmbH, Germany). This was a double blind, placebo controlled, double dummy, randomised, crossover trial to investigate the pharmacokinetics, pharmacodynamics and tolerability of the IN midazolam formulation in healthy adult subjects. Sixteen healthy subjects, (8 male and 8 female), aged 19 to 53 years were included.

Subjects on four occasions, at least 6 days apart, received single dose treatments of IN (Nasolam) and IV (Dormicum) midazolam in a randomised sequence:

- midazolam 2.5 mg IN + placebo IV
- midazolam 5.0 mg IN + placebo IV
- placebo IN + midazolam 2.5 mg IV
- placebo IN + placebo IV

Blood samples were taken at pre-dose and at 1 minute and 15 seconds, at every 3 minutes (until 30 minutes), every 10 minutes (until 60 minutes), every 30 minutes (until 2 hours), and at 3, 4, 6, 8 and 12 hours after drug administration.

Analytical/statistical methods
A validated technique (liquid chromatography with tandem mass spectrometry) has been applied for the analysis of midazolam and α-hydroxy-midazolam in plasma. The calibration curve for midazolam and α-hydroxy-midazolam ranged from 0.1 – 100 ng/mL. Quality control sample concentrations were 0.3, 3.0 and 75 ng/mL. The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Pharmacokinetic IV data for two subjects were not included in the overall evaluation, as abnormal high concentrations were found and the metabolite data could not confirm these. Contamination with midazolam was suspected to be the explanation, due to the samples being taken from the same infusion line at which the midazolam dose was given. The MAH carried out a sensitivity analysis by inclusion of the data and this was found to have no significant impact on the overall outcome. This resulted in 16 subjects in the IN group and 14 subjects in the IV group being included for statistical analysis.

Table 2. Pharmacokinetic parameters (non-transformed values) of midazolam.

Treatment	$AUC_{0-\infty}$ (ng.h/ml) mean (SD)	C_{max} (ng.h/ml) mean (SD)	t_{max} (minutes) median (range)	$t_{1/2}$ (h) mean (SD)	F (%) (SD)
Midazolam IV 2.5 mg n=14	93.9 (31.8)	219.2 (149.3)	2 (1-3)	3.59 (1.06)	100
Midazolam IN 2.5 mg n=16	65.6 (32.2)	30.6 (12.9)	11 (6-24)	6.31 (7.78)	74.42 (39.05)
Midazolam IN 5 mg n=16	131.9 (26.0)	66.2 (20.9)	14 (9-24)	4.35 (1.35)	76.41 (21.54)

Table 3. Pharmacokinetic parameters (non-transformed values) of α-hydroxy-midazolam.

Treatment	$AUC_{0-\infty}$ (ng.h/ml) mean (SD)	C_{max} (ng/ml) mean (SD)	t_{max} (minutes) median (range)	$t_{1/2}$ (h) mean (SD)	Metabolite/ parent AUC ratio* (%)
Midazolam IV 2.5 mg n=14	15.83 (5.84)	6.1 (2.3)	14 (9-21)	4.62 (2.10)	17
Midazolam IN 2.5 mg n=16	10.87 (5.89)	2.4 (1.3)	45 (24-240)	5.34 (2.14)	17

Midazolam IN 5 mg n=16	24.04 (9.02)	5.3 (1.8)	51 (21-121)	6.25 (2.76)	18
**principal metabolite = α-hydroxy-midazolam; parent drug = midazolam*					

Absorption
After IN administration, linear pharmacokinetics were observed over the 2.5 – 5 mg dose range, based upon administration of a 2.5 and 5 mg dose. As such, for the 3.75 mg dose a similar relative bioavailability is expected. Midazolam C_{max} values after IN administration were rapidly achieved with t_{max} values of 11 and 14 minutes. This may be of importance for a rapid onset of effect, i.e. the induction of sedation under acute circumstances, and may be even more important in epilepsy. As could be expected, lower C_{max} values (about -84%) are observed in IN compared to IV administration. In addition, C_{max} values after IN application showed a lower variability compared to IV application (32-42% vs. 68%). The absolute bioavailability is about 75% after IN administration. No second absorption peaks were observed after IN administration, which indicate absence of absorption of orally ingested midazolam. This is further supported by the similar AUC metabolite/parent ratio after IV and IN administration (see table 3). Midazolam after IN administration is subject to moderate inter-individual variability.

For the metabolite α-hydroxy-midazolam, C_{max} values after IN administration are achieved in about 50 minutes and are about 60% lower compared to IV administration. The metabolite/parent ratio was about 17%, it was comparable after IV and IN administration, and independent of the dose. No relevant contribution to the clinical effect by the metabolite α-hydroxy-midazolam is expected, considering the low concentrations observed after IN application and considering that a maximum of two doses may be administered, preventing possible accumulation. The C_{max} levels observed after IN administration appeared to be comparable to the C_{max} levels observed (in bibliographic data) after intrabuccal administration (IB, within the cheek). However C_{max} levels were achieved sooner (14 min versus 40 min). Moreover, the absolute bioavailability after IB administration is about 75% (reference: EPAR Buccolam), comparable to the absolute bioavailability observed after IN administration.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

<u>Study 2 – PopPK model & computer simulations</u>
A population PK (popPK) model was developed using the data of study 1. The structural model was a 3-compartmental model with a combined zero- and first-order process for IN absorption. Basic goodness-of-fit plots, a visual predictive check, a numerical predictive check and non-parametric bootstrap indicated that the model performs well. Using this popPK(-PD) model, eight in silico PK-PD simulation analyses (two in each group) were performed in: adults, paediatric patients, elderly and special populations.

For the conscious sedation/premedication indication, the MAH used Dormicum IV injection as comparator in the simulations. The aim was to determine appropriate dosing levels for

Nasolam by obtaining comparable C_{max} values between the two products using median, 10th and 90th percentiles, although it was expected that the IV C_{max} values would be higher.

Results of IN versus IV administration simulations are listed in tables 4. Intranasal dosing 1 – 10 min earlier compared to the IV dose would not lead to a significant difference in comparability of exposure, so time of IN dosing could follow that of IV dosing. Simulations with an incorrectly applied extra IN dose (on top of the first two IN doses) led to plasma levels below that of reference IV dosing.

Table 4. Simulated IN doses resulting in a comparable exposure to the simulated IV dose in special patient groups. The IV reference recommended dose is included for comparison.

Conscious sedation/ premedication:			
Patient population	**Simulated IN dose resulting in a comparable exposure to the simulated IV dose**	**Simulated IV dose**	**IV reference recommended dose**
Paediatrics: **12 – 18 years**	 5 mg 5 + 2.5 mg	 2.5 mg 2 + 1 mg	 2 – 2.5 mg 2 – 2.5 + 1 mg
6 – 12 years	2.5 mg 2.5 + 2.5 mg	0.0375 – 0.05 mg/kg 0.0375 + 0.025 to 0.05 + 0.025 mg/kg	0.025 – 0.05 mg/kg not indicated
2 – 6 years	2.5 mg	0.075 – 0.1 mg/kg	0.05 – 0.1 mg/kg
	2.5 + 2.5 mg	0.075 +0.05 to 0.1 + 0.05 mg/kg	not indicated
Elderly (>60 years)	2.5 mg 2.5 + 2.5 mg	1 mg 1 + 0.5 mg	0.5 - 1 mg 0.5 - 1 mg + 0.5 - 1 mg
Respiratory depression patients	2.5 mg 2.5 + 2.5 mg	1 mg 1 + 0.5 mg	0.5 - 1 mg 0.5 - 1 mg + 0.5 - 1 mg
Renal impairment	2.5 mg 2.5 + 2.5 mg	1 mg 1 + 0.5 mg	0.5 - 1 mg 0.5 - 1 mg + 0.5 - 1 mg
Hepatic impairment	2.5 mg 2.5 + 2.5 mg	1 mg 1 + 0.5 mg	0.5 - 1 mg 0.5 - 1 mg + 0.5 - 1 mg
Cardiac impairment	2.5 mg 2.5 + 2.5 mg	1 mg 1 + 0.5 mg	0.5 - 1 mg 0.5 - 1 mg + 0.5 - 1 mg
Critically ill patients	2.5 mg 2.5 + 2.5 mg	1 mg 1 + 0.5 mg	0.5 - 1 mg 0.5 - 1 mg + 0.5 - 1 mg
Obese (BMI 30 to 40 kg/m^2) and morbid obese (BMI > 40 kg/m^2)	5 mg 5 + 2.5 mg	2.5 mg 2 + 1 mg	0.5 - 1 mg 0.5 - 1 mg + 0.5 - 1 mg

For the treatment of prolonged, acute convulsive seizures indication, the MAH used midazolam solution for IB administration as comparator (Epistatus). Epistatus is only indicated in children and adolescent covering the age range of 3 months up to 18 years. The aim was obtaining a comparable early exposure between IN and IB administration, taking

into account the median, 10th and 90th percentiles of the C_{max}. Considering the shorter t_{max} after IN administration, C_{max} levels were expected to be reached earlier than those after IB administration.

The results are listed in table 5. Based upon simulations in subjects aged 12 – 60 years, t_{max} is about 9 minutes shorter than after IB administration, which may lead to a faster onset of efficacy. Over a longer time period, IN midazolam exposure is lower compared to that observed after IB administration. This may result in a lower efficacy over time and the need for an additional dose. Adolescent showed about 15 – 20% higher C_{max} and exposure compared to adults. For adults, no recommended IB dose is given in the SmPC, so the adolescents dose of 10 mg was extrapolated for the simulations in adults of special populations. In line with advice from the Committee for Medicinal Products for Human Use (CHMP), extrapolation between adult and adolescent doses was deemed reasonable, as for established midazolam products, including the reference products, dose recommendations are the same between 12 to 60 years age range. See section *VI. Overall conclusion, benefit/risk assessment and recommendation* for more details on the CHMP advice.

Table 5. Simulated IN doses resulting in a comparable exposure to the simulated IB dose in special patient groups. The IB reference recommended dose is included for comparison.

Prolonged, acute convulsive seizures:			
Patient population	**Simulated IN dose resulting in a comparable exposure to the simulated IB dose**	**Simulated IB dose**	**IB reference recommended dose**
Pediatrics: **12 – 18 years** **10 – 12 years** **5 – 12 years** **2 – 5 years**	 5 mg 5 mg 5 mg 3.75 mg	 10 mg 10 mg 7.5 mg 5 mg	 10 mg 10 mg 7.5 mg 5 mg
Elderly (>60 years)	5 mg	10 mg	not indicated
Respiratory depression patients	5 mg	10 mg	not indicated
Renal impairment	5 mg	10 mg	not indicated
Hepatic impairment	5 mg	10 mg	not indicated
Cardiac impairment	5 mg	10 mg	not indicated
Critically ill patients	5 mg	10 mg	not indicated
Obese (BMI > 30 kg/m^2 but BMI<40 kg/m^2) and morbid obese (BMI > 40 kg/m^2)	5 mg	10 mg	not indicated

Distribution, metabolism and elimination
Considering the absolute bioavailability of 75% after IN administration and the comparable AUC metabolite/parent ratio of about 0.17 after IN as well as after IV administration, the following could be concluded:

- *distribution* of midazolam is expected to be comparable between IN administration and IV administration. Midazolam plasma protein binding is about 96 – 98%. The major fraction of plasma protein binding is due to albumin. Midazolam is excreted in low quantities (0.6%) in human milk. As a result, it may not be necessary to stop breast feeding following a single or once repeated dose of IN midazolam.
- *metabolism* and *elimination* of midazolam is expected to be comparable between IN administration and IV administration. Midazolam is excreted mainly by the renal route (60-80% of the injected dose) and recovered as glucuro-conjugated α-hydroxy-midazolam. Less than 1% of the administered dose is recovered in urine as unchanged drug and the elimination half-life of α-hydroxy-midazolam is shorter than one hour. When midazolam is given by IV infusion, its elimination kinetics do not differ from that following bolus injection.

Midazolam is extensively metabolised by the CYP3A4. The principal metabolite is α-hydroxy-midazolam, which is biologically active and is rapidly conjugated with glucuronic acid, although a small proportion is further hydroxylated to 1,4-dihydroxymidazolam. The other metabolite is 4-OH-midazolam.

Interactions
Considering the expected similarities in metabolic and elimination pathways of IN compared to IV administered midazolam, it is acceptable to include the possible interactions observed for midazolam that is IV administered (Dormicum) and IB administered (Buccolam) in the SmPC of Nasolam. Specific interactions known for oral co-administration of midazolam have not been included in the SmPC. Although it is known that interactions known for oral administered midazolam may occur also systemically for IN administered midazolam, the magnitude of the effect remains unclear. The overall warnings for CYP inhibitors and inducers in the SmPC are considered sufficient to cover this.

Special populations
With regard to *gender* and *race*, no difference in pharmacokinetics is expected compared to the population aged 12 – 60 years. No specific dosing recommendations are therefore needed. With regard to the other groups, findings are discussed here (see table 4 and 5 for results).

Paediatrics
For paediatrics, dosing based on weight is considered more appropriate than extrapolating from adults as PK is dependent on weight and not age. This is in line with the IB administered product and it will allow for more accurate dosing in the paediatric population aged 2 to under 12 years. The weight-based dosing is based on commonly used age-weight charts. Simulations showed weight-based dosing leads to comparable or slightly lower plasma concentrations compared to age-based dosing. For the proposed dose in the anti-convulsive indication an amendment is requested, based on the clinical experience in the Netherlands

and several literature studies where a 0.2 – 0.3 mg/kg dose is recommended. Simulation results indicate that exposure after IN administration is comparable to that after IB administration and within those observed after IV administration. Thus, a comparable sedation and management of seizures can be expected. For PK data in children aged 2 – 12 years of age, the MAH referred to literature and other registered medicinal products. These data were used for simulations of exposures after IN administration (see tables 4 and 5). The paediatric PK models have been further validated by external data which were not used for the establishment of the model. Based upon this validation, the model predicts the exposure reasonable well after IN, IB, oral and IV administration.

Elderly

The lower recommended dose in elderly may be due to a lower midazolam clearance, a higher midazolam unbound fraction and higher midazolam potency, as described in literature.

Renal impairment

Pharmacokinetics of midazolam is not altered in patients with chronic renal failure (based on bibliographic data). But the main midazolam metabolite, α-hydroxy-midazolam glucuronide, which is excreted through the kidneys, accumulates in patients with severe chronic renal failure after long-term midazolam administration. This accumulation causes (prolonged) sedation. For Nasolam, in the setting of conscious sedation/premedication or the treatment of prolonged, acute convulsive seizures, a single dose or two doses of IN midazolam is unlikely to accumulate to the extent that the prolongation of pharmacological action is of great clinical significance. Nevertheless, Nasolam should be carefully administered to patients with renal impairment.

Hepatic impairment

The clearance in cirrhotic patients may be reduced and the elimination may be longer when compared to those in healthy volunteers (based on bibliographic data). The absolute bioavailability of Nasolam is expected not to be altered in patients with hepatic impairment after IN administration as midazolam is not subject to hepatic first-pass metabolism. The clearance in these patients may be reduced, which could lead to a prolonged pharmacological effect. From a safety perspective it is recommended not to use Nasolam in patients with severe hepatic impairment.

Patients with cardiac impairment

The elimination half-life of midazolam in patients with decompensated cardiac insufficiency is prolonged compared to healthy people (based on bibliographic data). Nasolam should be used with caution in these patients. In patients with cardiac impairment aged 12-60 years, Nasolam is dosed at 2.5 mg, instead of 5 mg. Patients aged 2-11 years or >60 years should use Nasolam only in a setting with cardiorespiratory monitoring and support facilities.

Critically ill patients

The elimination half-life in critically ill patients is prolonged up to 6 times (based on bibliographic data). Therefore, these patients aged 12-60 years should be dosed 2.5 mg, instead of 5 mg Nasolam. Critically ill patients 2-11 years or > 60 years should use Nasolam only in a setting where cardiorespiratory monitoring and support facilities are available.

Obese patients
The mean half-life is greater in obese than in non-obese patients (5.9 vs 2.3 hours). This is due to an increase of approximately 50% in the volume of distribution corrected for total body weight. The clearance is not significantly different in obese and non-obese patients (based on bibliographic data). For Nasolam, obesity is not expected to lead to marked differences in pharmacological activity other than the prolongation of the pharmacological effect of maximally 20 minutes in circa 20% of the obese population.

Conclusion
Overall, the pharmacokinetic exposure after the administration of IN midazolam was below the exposures of IV, IB, or oral midazolam administrations that generally are considered safe. Similarly, the exposure of IN midazolam followed by a second dose was shown to be safe. Considering that the simulations are not showing bioequivalence between IN versus IV or IB administration, further support is coming from clinical data, including popPK/PD simulations. Earlier exposure is obtained by the IN compared to IB administration, which may be considered favourable for a rapid onset of effect, but over a longer time period exposure is lower. However, comparable PK profiles are obtained following two doses of IN versus one dose IB. This indicates that for subjects from whom the seizures are not well controlled following one IN dose, a second dose may be needed. This is included in the SmPC. Overall, the posology in the SmPC is approved, as the second dose is only recommended if the seizure is not controlled after ten minutes following the first dose.

IV.3 Pharmacodynamics

The primary pharmacological effects of midazolam are anticonvulsant, sedation, sleep inducing, anxiolytic and muscle relaxant. The anticonvulsive effect and the dose ranges are extensively described in literature and well known. In addition, the MAH has performed a PK study (Study 1) and simulations (Study 2). Extrapolation based on comparable exposure is acceptable. Since the anti-epileptic indication of IB midazolam is only approved for the paediatric population, use in adults required further substantiation (see section *IV.4 Clinical efficacy*). The MAH provided a discussion on the sedative effect and the results of Study 1 (see section IV.4 *Clinical efficacy* below). Information on secondary pharmacology, e.g. psychological effects, is lacking, but accepted considering this is a hybrid application and the MAH relies on the data from the reference products.

IV.4 Clinical efficacy

Conscious sedation/ premedication indications
The MAH performed a therapeutic equivalence study (Study 1), comparing the sedative effects of midazolam in term of time to onset of effect and size of the effect of IN versus IV administration. The comparator arm was Dormicum 2.5 mg (IV). Two doses of IN midazolam were used, i.e. 2.5 mg and 5 mg. The sedative effects were measured using Saccadic Peak Velocity (SPV), the Bond and Lader Visual Analogue Scale (VAS) for sedation, the Simple Reaction Time Task (SRTT) and the Observer's Assessment of Alertness/Sedation (OAA/S). The magnitude of effect was consistent in all sedations, 2.5 mg IV midazolam consistently showed a profile between those of the 2.5 mg and 5 mg IN midazolam. A difference in time

to maximum effect is observed, which is particularly evident in the SPV, VAS and OAA/S. However, on the SRTT, which is considered the most accurate for sedation, no difference in time to effect is observed. Therefore, from a PD perspective equivalence between Nasolam (IN) and Dormicum (IV) is considered demonstrated. The conscious sedation and premedication indications are considered adequately demonstrated.

Anti-convulsive indication

For the anti-epileptic indication, the MAH performed computer simulations (Study 2) comparing IN and IB midazolam (see Table 5), after a single and adaptive dose. The simulations were performed on the PD sedation endpoints OAA/S and SPV. These simulations showed that profiles of IN midazolam and IB midazolam differ, especially in children 6-8 years of age, elderly and the special populations. The simulations consistently showed a more rapid response following IN administration, but a lower AUC (area under curve). These rapid responses correspond to the previous PK data, the findings from a meta-analysis by Sanchez Fernandez et al. from 2017 and the simulation findings for younger patients, adolescents and adults. A more rapid response compared to IB midazolam is considered favourable for an anti-convulsive indication. The lower AUC could imply that the anti-convulsive properties are not maintained long enough to fully counter act the seizures. However, based on the PK data from the computer simulations, adaptive dosing (i.e. two doses administered) showed high overlap with the profile of IB administered midazolam. It is noted that the sedative endpoints are considered explorative for an anti-convulsive indication.

Besides Study 2 simulations, the MAH submitted literature (ten studies) in support of the anti-epilepsy indication. In short, the studies reported a seizure cessation <5 minutes for 57%-82% of the seizures (De Haan et al.; 2010 Kay et al.; 2019; Owusu et al., 2019). It is noted that these studies had small numbers of subjects included, i.e. 20-75. Studies by Detyniecki et al. (2019) and Wheless et al. (2019) had more subjects included, i.e. 134 and 161 respectively and showed comparable seizures cessation in 80.6%-87.6% within 10 minutes. Overall these studies, dated from 2000 to 2020, showed a consistent effect on seizure cessation. The formulations described in these studies are comparable to Nasolam and therefore it is agreed that the efficacy and safety can be extrapolated. The previous submitted literature studies by Nakken et al. (2011) and Scott et al. (1999) are considered supportive. The treatment with IN midazolam for acute seizures in adults is recommended in national guidelines.

In conclusion, the anti-convulsive indication is considered acceptable, based on the comparable PK profile (in terms of C_{max} and AUC) between IB and IN midazolam, in conjunction with a consistent effect shown in literature data which also matches the performed simulations. To address the anti-convulsive indication in adults, the MAH has extended the bibliographic data on IN and IB midazolam. The MAH has indicated how the IN formulations have evolved over time, as in the past the retention capacity of the nasal mucosa was not included in studies. The formulations have also evolved to become water-based. These factors are important as they impact the efficacy and thereby the consistency of the effect reported in the literature over time.

Overall, the efficacy of IN midazolam in the proposed populations for the indications is sufficiently demonstrated.

IV.5 Clinical safety

The safety profile of midazolam is well known and can be extrapolated from the reference product Dormicum (IV midazolam), based on comparable systemic exposure. The MAH has conducted a tolerability test to assess the safety related to the route of administration. Adverse reaction related to the route of administration were sneezing and diplopia, blurred vision and excessive blinking and are included in the SmPC.

The exposure following IN midazolam is lower than seen for IB and IV midazolam, which is confirmed by the incidence of respiratory events reported in the study by Brigo (2015) and other literature data. The safety profile is comparable to that of rectal diazepam. Taken together there appears no additional risk for IN midazolam compared to other products currently available.

Potential administration errors (administration to the inappropriate administration site and priming of the device before use of the device) are reduced by warnings on the carton outer box and the single-dose container and by instructions for use in the PL with pictograms and specific text for the situation that the product is used in young children where the nozzle may not fully fit in the nostril.

Usability of the dosing device

The MAH has demonstrated sufficient usability of the Aptar Unit-Dose device in the adult population, based on its Human factor assessment, as well as on published usability studies (Krieter et al. 2016, Tippey et al. 2019) evaluating a comparable nasal device in acute opioid overdose setting using naloxone. It was demonstrated that the shot weight was independent of the orientation of the device when the drug product at issue was used. This enables fast administration to patients in any body position. In view of the provided information and the marketed products with the Aptar unit dose device, Nyxoid and Imigran (both for time critical use), the selection of the device can be accepted for adults.

To demonstrate usability of the Aptar Unit-Dose in young children where the nozzle can only be placed onto the nostril in case their nostril is too small for insertion, the MAH referred to forensic anthropology population data (Sforza et al. 2010) and inferred that the nozzle can fully enter the nostril in children aged 4 years and older. In children aged 2 – 4 years, where the nozzle tip can only be placed onto the nostril, the MAH explained that due to the spherical and conical shape of the nozzle tip, the nozzle will always protrude into the nostril to a certain extent and will result in an effective administration. Furthermore, the MAH referred to anecdotical stories (non-scientific literature) of children who were successfully revived following administration of Narcan (which has the same device) after an unintentional opioid overdose, in comparable stressful situations. In addition, the MAH provided expert opinions about the already available unlicensed product. Lastly, 14,400 units of 2,5 mg magisterially prepared IN midazolam have been dispensed to children aged 2 to <8 years, in the Netherlands, Sweden and Norway, without complaints from patients or caregivers about the efficacy and safety in the intended population known to the MAH.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Nasolam.

Table 6. Summary table of safety concerns as approved in RMP

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

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

For this authorisation, reference is made to clinical studies and experience with the innovator products Dormicum and Buccolam. Based on the submitted pharmacokinetic-pharmacodynamic clinical study, therapeutic equivalence between Nasolam and IV midazolam is considered demonstrated. The conscious sedation and premedication indication are therefore considered adequately demonstrated. The anti-epileptic indication is supported by PK simulations, and the indication in adults is acceptable based on the consistency between the results observed from literature studies and simulations.

The safety profile of midazolam is well known and can be extrapolated from the reference product, based on comparable systemic exposure. Safety related to the route of administration is substantiated by a tolerability test. The usability of the device both in adults and paediatric population is substantiated and potential administration errors are reduced by warnings on the carton outer box and the single-dose container and by instructions for use in the PIL. Risk management is adequately addressed.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was Dutch. The test consisted of a pre-test screening phase, a pilot test, followed by two test rounds with ten participants each. In both test rounds all of the questions were answered correctly by the participants. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Nasolam 2.5 mg, 3.75 mg and 5 mg nasal spray, solution in single-dose container have a proven chemical-pharmaceutical quality, and their efficacy and safety profile have been adequately demonstrated.

In the Board meeting of 3 June 2021, the specification of the active substance were discussed. All points were resolved positively before the end of the procedure.

Agreement was initially not reached by the member states on approval of the indication "treatment of prolonged, acute, convulsive seizures, both in adults and children from 2 years". The CMDh procedure was followed and completed without further agreement and therefore the procedure was referred to the CHMP on 24 September 2021, under Article 29(4) of Directive 2001/83/EC (EMA/190723/2022). The CHMP considered the provided information sufficient to approve the procedure. For details, reference is made to the public CHMP Assessment Report, dated 18 February 2022 (link; CHMP Assessment Report on Nasolam).

The member states, on the basis of the data submitted and the CHMP advice, considered that essential quality, efficacy and safety have been demonstrated for Nasolam, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 1 April 2022.

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-