EMADOC-1829012207-24310
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Tuzodi

International non-proprietary name: midazolam

Procedure No. EMEA/H/C/005658/0000

Note

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

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List of abbreviations

AUC	Area under curve
AEs	Adverse events
BID	two times a day
CHMP	Committee for Medicinal Products for Human Use
Cmax	Maximum concentration
CNS	Central nervous system
ENT	Ear nose throat
ERA	Environmental risk assessment
EU	European Union
FDA	Food Drug Administration
FPEN	Fraction of a population receiving the active substance
GABA	Gamma-aminobutyric acid
GCP	Good clinical practice
GLP	Good laboratory practice
GOF	Goodness-of-fit
H:	Hospital-based
HSV	herpes simplex virus
ICH	International Conference of Harmonisation
ID	intravenous diazepam
IM	Intranasal midazolam
INM	Intranasal midazolam
IV	Intravenous
IV-D	intravenous diazepam
Kow	Octanol/water partition coefficient
MDZ	midazolam
MedDRA	Medical Dictionary For Regulatory Activities
MRI	Magnetic resonance imaging
NCA	Non-compartmental analysis
NLME	Nonlinear mixed modelling effects
O	Open trial
OAA/SS	Observer's Assessment Of Alertness/Sedation Scale

OECD	Organisation for Economic Co-operation and Development
PBPK	Physiologically based pharmacokinetic
PBT/vPvB	Bio-accumulative toxic/very persistent very bio-accumulative
PD	Pharmacodynamics
PEC	Predicted environmental concentration
PECsw	Predicted environmental concentration for surface water
PH	Pre-hospital
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PopPK	Population pharmacokinetics
popPK/PD	Population Pharmacokinetic/Pharmacodynamic
RCT	Randomised controlled trial
RD	Rectal diazepam
SAEs	Serious adverse events
SmPC	Summary of product characteristics
SSS	Stanford Sleepiness Scale
TEAE	Treatment emerged adverse event
TTC	Threshold of toxicological concern
VPC	Visual predictive check

1. Rapporteur Recommendation

Based on the review of the data on quality, safety and efficacy, the generic/hybrid application for Tuzodi in the treatment of prolonged, acute, convulsive seizures in adults, adolescents, children and toddlers (from 2 years of age).

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (see section 5).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Quality aspects

Drug substance (applicant's part as provided by ASMF holder) – Module 3.2.S.3.2)

1. Nitrosamines – Drug Substance

   A nitrosamine risk assessment is missing. A full evaluation should be provided, covering all relevant sources (e.g. DMF use, nitrites/nitrates in water, EP impurity A).

Dug product

2. lack of information in the pharmaceutical development of the manufacturing process
3. Impurity Control – Drug Product

   The justification for the impurity specifications appears insufficient. A thorough and scientifically justified explanation should be provided.

4. ICH M7 Assessment

   A complete ICH M7 risk assessment should be submitted.

5. Nitrosamines – Drug Product

   The risk assessment for nitrosamines in the finished product should be expanded to consider risks from the drug substance, including carryover of DMF-related impurities and formation of nitroso derivatives. If any risk cannot be excluded, batch testing data should be submitted.

Deficiencies arising from concerns over the restricted part of the ASMF are mentioned in the appendix (this appendix is not supplied to the applicant). These concerns will be conveyed in confidence to the holder of the ASMF.

Clinical aspects

1. Both the population PK/PD and the PBPK model showed several critical deficiencies that render them presently unfit for purpose i.e. to support the claimed posology on all populations. At the current stage, the proposed posology for special populations and paediatric patients remains unconvincing. The existing population- and physiology-based pharmacokinetics models are not sufficiently developed and lack critical data from clinical studies necessary to support dose recommendations for these groups. Accordingly, additional clinical data and a more refined popPK is expected to ensure a robust extrapolation for these populations. In addition, to justify the similarity in exposure ranges, the applicant should place particular emphasis on both absorption and Cmax variability, and/or provide direct comparisons with Buccolam.

1.1. Questions to be posed to additional experts

None.

1.2. Proposal for inspection

1.2.1. GMP inspection(s)

Evidence of GMP compliance for all manufacturing and testing sites is available. A GMP inspection is not required.

1.2.2. GCP inspection(s)

GCP are documented in the PK analysis provided for this application. However, the applicant should provide information on inspection of sites by competent European health authorities – including dates and conclusion of inspections (OC). A GMP inspection is not required at this stage.

Co-Rapporteur Assessment
OC raised by Rapp is supported. The following OC have been raised by Co-Rap: In module 5, appendix 16-1-10, a GCP certificate from AIFA (Italian Drug Agency) provided (dated on 25 October 2018) to confirm suitability for clinical trials. The applicant should provide a summary of main GCP inspection outcomes and discuss if any major or critical findings have been detected. Information should be provided if any more recent GCP inspections by EU authorities have been carried out since the year 2018.

1.3. Similarity with authorised orphan medicinal products

Not applicable.

1.4. Derogation(s) from market exclusivity

Not applicable.

2. Executive summary

2.1. Problem statement

Epilepsy is a state of an enduring predisposition to recurrent epileptic seizures (Fisher et al., 2014). In population-based studies, incidence rates of epilepsy in childhood range from approximately 0.5 to 8 per 1,000 person-years (30-33 Hauser et al. 1991, Oka et al., 2006, Russ et al. 2012). The highest incidence of epilepsy occurs at the extremes of life [36 Annegers et al. 1995]. Incidence is lowest in young and middle adulthood and begins increasing in the 50s, with a dramatic increase after age 60; by age 70, the incidence exceeds that of infancy.

A seizure represents the clinical expression of abnormal, excessive or synchronous discharges of neurons residing primarily in the cerebral cortex. This abnormal paroxysmal activity is intermittent and usually self-limited, lasting seconds to a few minutes. According to the International League Against Epilepsy (ILAE) (Fisher, 2017), there are primarily three types of seizures: 1) generalised-onset seizures, 2) focal-onset seizures, and 3) unknown-onset seizures. The emergency treatment of

prolonged epileptic seizures, seizure clusters and status epilepticus (SE) is required to be rapid and efficient, as ongoing epileptic activity may lead to neuronal damage and result in increased morbidity and mortality (Kienitz, 2022)

The SE definition according to ILAE (Trinka, 2015) sets two time points (t1, t2), where t1 defines the semiological transition of a seizure to SE and t2 marks the point in time when neurological injury is likely to occur. Typically, the start of SE treatment is based on t1, with the time limit being 5 min for generalised convulsive (tonic–clonic) SE, 10 min for complex focal SE (focal SE with impaired consciousness), and 10–15 min for absence SE (Kienitz et al. 2022).

The emergency treatment of seizures is required to be rapid and efficient, as ongoing epileptic activity results in increased morbidity and mortality. Benzodiazepines (BZDs), such midazolam (MDZ) or diazepam (DZP) are established first-line drugs for the acute treatment of seizures.

Since 5 September 2011 midazolam has been authorised by the European Commission under the brand name Buccolam®, oromucosal solution, indicated for the treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years) and, in April 2022, as nasal spray solution (Nasolam) for the treatment of prolonged, acute, convulsive epileptic seizures in adults and children > 12 kg and aged 2 years and older.

The argument of the applicant is that in comparison to other delivery routes, intranasal midazolam may be a more favourable option as it can be administered in a significantly shorter interval and has been shown to be reliable and efficient. Furthermore, as compared with rectal diazepam, it is at least as effective in its anticonvulsive action and is preferred by caregivers. Additionally, intranasal midazolam can be easily administered, rendering drug delivery more convenient in cases where patients are cognitively impaired and gaining their cooperation is more difficult.

The proposed initial indication for Tuzodi is the treatment of prolonged, acute, convulsive seizures in adults, adolescents, children and toddlers (from 2 years of age).

2.2. About the product

Tuzodi (also referred to as MDZ-2.5) is a nasal spray solution containing 25mg/mL of midazolam in a bidose container, developed by a private pharmaceutical company, fully dedicated to the development and commercialisation of innovative nasal applications.

The nasal spray consists of a bi-dose device with the following features:

- Ready-to-use
- Administration of only 2 sprays (2 x 0.1 ml) – 1 spray per nostril
- One hand actuation
- Can be applied in any orientation (360° functionality).

The nasal spray device provides a technological innovation, which was the basis for the access to the European centralised procedure (Optional Scope following Article 3(2), eligibility request accepted by the European Medicines Agency).

Midazolam hydrochloride is the active substance of the nasal preparation containing the hydrochloride salt of midazolam, a short-acting benzodiazepine with an imidazole structure.

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 occurs. The mechanism of action behind the above-mentioned effects, which is similar to the

one of the other benzodiazepines, involves the enhancement of gamma-aminobutyric acid (GABA) neurotransmission in limbic, thalamic and hypothalamic regions of the central nervous system (CNS). On the other hand, 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.

Midazolam has anxiolytic and sedative properties and a more rapid onset of action and shorter duration of effect than diazepam.

Tuzodi is a 2.5 mg/spray nasal spray of midazolam (as hydrochloride) submitted under hybrid application. The medicinal product Tuzodi and its reference product Ipnovel are similar in terms of composition (active substance and excipients). Differences compared to the reference product are the pharmaceutical form, the strength, the route of administration and the therapeutic indication.

The applicant claims that, to support safety of Tuzodi, reference was made to safety data of the reference product Ipnovel while, the efficacy in the treatment of seizures was supported by reference to efficacy data of Buccolam, oromucosal solution authorised in EU for the treatment of prolonged, acute, convulsive seizures in infants from 3 months to adults.

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

The clinical development programme to support the marketing authorisation application of Tuzodi was initially presented and discussed with EMA in a Scientific Advice (EMEA/H/SA/4544/1/2020/SME/III) in October 2020 and in the subsequent Follow-up (EMA/SA/0000095512) in September 2022.

EMEA/H/SA/4544/1/2020/SME/III included questions on pre-clinical development and clinical development. The literature package was presented in this SA. It was confirmed that the literature cited could be a basis for a MAA provided the need for bridging is taken into account. The applicant was also made aware that he should be prepared to discuss / mitigate heterogeneity of the studies in critical aspects such as target population, endpoints, time of treatment after seizure start, dose and type of control. It is notable that no discussion is provided is the overview nor clinical summary for efficacy, which did not facilitate the assessment.

EMA/SA/0000095512 pertained to Quality (product stability testing, need for sub-visible particle testing Clinical), Non-Clinical (need for additional non-clinical study to evaluate pharmacokinetic and local adverse events of the proposed formulation) and Clinical aspects (Acceptability of clinical PK study design and adequacy of such study along with a PopPK study and published clinical efficacy and safety studies to support a MAA). It was highlighted that, while in a hybrid application the evidence of efficacy can be based on published literature, the suitability and adequacy of these studies to provide robust evidence of clinical efficacy in this indication across the proposed population will be part of the assessment of an MAA. The applicant should substantiate that their product can be bridged to the products used in the efficacy studies and that for their product, similar exposure levels are reached.

Modelling and simulation approach were agreed in the advices mentioned just above, but as the modelling is not yet appropriate, remodelling and / or another study may be needed (see **MO**).

2.4. General comments on compliance with GMP, GLP, GCP

Based on the review of quality data, CHMP did not identify the need for a GMP inspection.

GCP are documented in the PK analysis provided for this application. However, the applicant should provide information on inspection of sites by competent European health authorities – including dates and conclusion of inspections (OC). A GMP inspection is not required at this stage.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

- Article 10(3) of Directive 2001/83/EC, as amended– relating to applications for hybrid medicinal product.

The chosen reference product is:

Medicinal product authorised in the Union /Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Ipnovel Solution for injection 15 mg/ 3 mL
- Marketing authorisation holder: Cheplafarm Arzneimittel GmBh
- Date of authorisation: 15/11/1994
- Marketing authorisation granted by:
  - Member State (EEA): Germany

    - MRP/DCP: DE/H/3599/002
- Marketing authorisation number: 41119.01.00

2.5.2. Orphan designation

Not applicable.

2.5.3. Similarity with orphan medicinal products

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

2.5.4. Derogation(s) from orphan market exclusivity

Not applicable.

2.5.5. Information on paediatric requirements

Not applicable.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as an integral drug device combination composed of a vial containing the 2.5 mg/spray of midazolam (as HCl) in solution included in a nasal spray system (bi-dose delivery system (BDS)) able to deliver two (2) fixed sprays (puffs) of 100 µl. In order to release 2 x 100 µl (either 0.2 ml), an overfilling (0.24 ml) is applied to.

Other ingredients are: Sodium Chloride, hydrochloric acid and water for injection.

The product is available in a nasal spray system (BDS) containing a type I glass vial with a chlorobutyl plunger within a delivery device compounded to a container holder and the actuator.

3.1.2. Active Substance

General Information

The chemical name of midazolam Hydrochloride is 8-Chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5- a][1,4]benzodiazepine hydrochloride corresponding to the molecular formula $C_{18}H_{13}ClFN_3$.HCl. It has a relative molecular mass of 362.2 g/mol and the following structure:

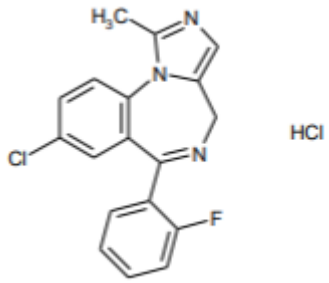


Figure 1: Active substance structure

The chemical structure of midazolam HCl was elucidated by a combination of IR, NMR and MS spectra.

The solid state properties of the active substance were measured by IR spectra, the DSC thermograms and the X-ray diffraction patterns.

The midazolam HCl is a pale yellow crystalline powder, hygroscopic, soluble in methanol (1:30), 0.1M HCl (1:100) and water (pH<4) No chiral centres are present in midazolam HCl.

Midazolam HCl has a non - chiral molecular structure.

Midazolam HCl corresponds to crystalline form.

Polymorphism is not relevant for the performance of the product as the drug product is a solution (water, pH acid) where the drug substance is completely soluble.

Manufacture, process controls and characterisation

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Midazolam HCl is synthesised in nine main steps using commercially available well defined starting material. See AR on Restricted part of the ASMF for additional details on specification of the SM.

A major objection has been raised for the control of possible genotoxic impurities. A risk assessment on nitrosamines has not been provided.

A Class 3 ICH M7 genotoxic impurity derived from the starting material is not controlled as the applicant claims Option 4 ICH M7 without providing sufficient justification thus a question has been raised.

See AR on the applicant's part of the ASMF for additional details.

The active substance packaging complies with EC 10/2011 as amended.

Specification (s)

The active substance specification includes tests for appearance, solubility (methanol), solubility (0.1M HCl), identification (IR, chlorides), colour (0.1M HCl), water, assay (volumetric analysis), impurity C (TLC), assay (HPLC), related substances (HPLC), residual solvents (GLC), Nickel and Palladium (ICP-MS) and potential genotoxic impurities by HPLC.

Specified impurities are controlled according to acceptable limits based on ICH Q3A and in line with EP monograph midazolam base except for one impurity. The applicant's should justify the difference in the control of this impurity between the CEP and the ASMF. In any case, based on these information, the level of impurity in the API should be limited. A qualification report has been provided for this impurity with genotoxic and toxicological evaluation. Limits for any unknown impurity at NMT 0.10% is acceptable. Limits for total impurities is not considered acceptable as in the EP midazolam base monograph the limit for total impurities is NMT 0.3%. Residual solvents are controlled according to the limits reported in ICH Q3C. Assay by HPLC range should be tightened. Justification should be provided for the absence of microbiological test.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. All in house methods have been adequately validated and described according to ICH Q2.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented in the ASMF. Updated data are required by the drug product manufacturer as CoA for midazolam HCl WS is not readable.

Batch analysis data of the active substance are provided. The results are within the specifications and consistent from batch to batch. However, results for lower scale batches should be provided.

See AR on the ASMF applicant's part for details.

Stability

Eighteen batches have been tested in long-term stability studies. Long-term stability studies have been conducted. The packaging has been optimised. The batches put under stability from 2019 are stored using the current packaging type and they are considered more representative for stability studies as they comply with real API container closure system. Data on batches put under stability from 2019 are available.

A batch prior to 2019 is out of specification at certain time points for KF value. All the other batches prior to 2019 comply with the limit. The results for KF value in the batch represent an isolated case of out of specification value compared to other batches prior to 2019 with the same packaging.

Furthermore, the actual packaging, including two desiccant packets, would assure better protection from humidity.

Accelerated stability studies have been conducted for 6 months. No significant degradation occurs after 6 months. Intermediate conditions stability studies have been conducted. No significant degradation occurs.

The following parameters were tested: appearance, solubility (methanol), colour, water, assay by HPLC, assay by volumetric analysis, impurity C by TLC, related substance by HPLC. The analytical methods used were the same as for release and were stability indicating.

Stress studies have been provided showing that midazolam HCl can lead to open midazolam analogue in acidic conditions. In alkaline and oxidative conditions, the possible increase of isomer and certain impurity have been noted respectively, these impurities are controlled in final API specification. No significant variations were observed for heat conditions and light exposure.

The applicant claims a retest period. Considering the issues for the limits on the impurity and total impurities (see S.4.1), a retest period cannot be granted yet. The applicant should revise the retest period based on the novel impurities' limits.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The drug product is a simple solution of midazolam (as HCl) containing well known isotonic agent and a pH adjuster and water for injection as solvent included in a nasal spray system (bi-dose delivery system (BDS)) able to deliver two (2) fixed sprays (puffs) of 100 µl (or 0.2 ml) for which the composition is presented.

No overage is deemed necessary nevertheless, an overfilling is applied to.

Excipients are those used in the reference product and have been already used in different products on the market administered by nasal route.

The BDS is classified as a class I medical device not reusable for which a statement of compliance with the relevant GSPRs of the MDR Annex I is provided.

However, several other concerns have been raised in terms of composition and nature of container closure system.

The formulation development was focused on an optimal acidic pH range in order to completely dissolve the drug substance, to avoid the use of a preservative and to obtain an isotonic solution in the nasal cavity. However, results of the experiment to assure midazolam hydrochloride solubilisation in water at different pH should be presented as well as all results allowing to justify/demonstrate the pH limits, iso-tonicity and the antimicrobial properties of the drug product.

An overall summary of the different clinical studies is presented in the document - INFORMATION FOR GENERIC, 'HYBRID' OR BIO-SIMILAR APPLICATIONS. However, a summary of clinical study is also expected in section 3.2.P.2. Moreover, the representativeness of clinical batches in comparison to the commercial batches should be addressed. In addition, the suitability of the nasal route of administration for local and systemic treatment with a particular paediatric medicinal product should be discussed and justified as well as the patient acceptability in relation to the palatability and sensation of the medicinal product on administration.

The drug product is a bi-dose delivery system that is an almost "double" single dose spray. Information on residence time after spraying, minimum fill, extractables and leachables, droplet size distribution, actuator deposition, cleaning, robustness, delivery device development notably the suitability for the patient age, spray pattern and plume geometry should be further addressed.

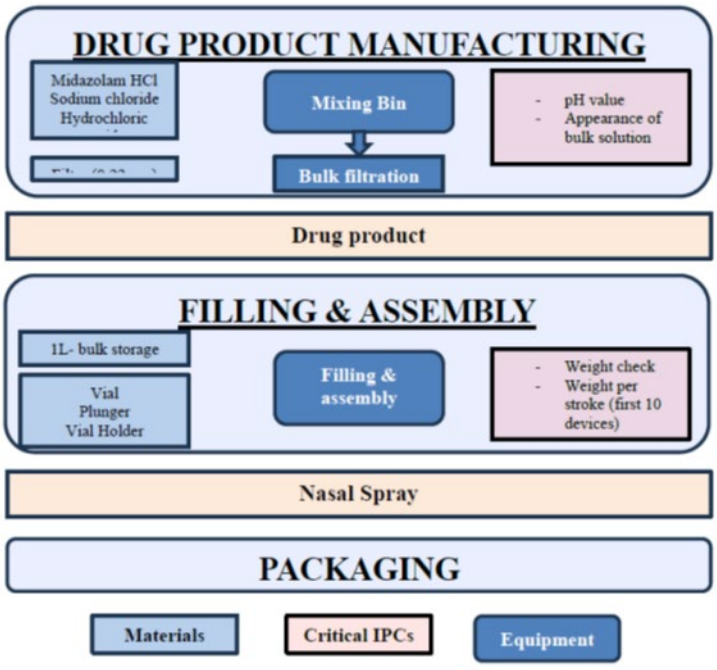
The container closure system consists of a glass vial containing the medicinal product and a delivery device (BDSL V3), constituting an integral drug-device combination product (iDDCP). Even though the results of uniformity of delivered mass complied with acceptance criteria, it should be addressed how the correspondence for dose indicator and the volume expelled has been carried out. Besides, the drug substance is a sedative substance. The applicant is asked to discuss the risk of misuse of the drug product and the impact on safety of the drug product.

The section pharmaceutical development was slightly detailed. Thus, several questions have been raised.

Manufacture of the product and process controls

The manufacturing process of the drug product consists of preparation of the bulk solution followed by a particle filtration and a filling before the device assembly (i.e. sealing of vials, transfer of vial into vial holder and assembly of actuator) as presented hereafter on Figure 2.

Figure 2: Finished product manufacturing process



The following points in terms of production areas on the flow chart, mixing speed limits, bulk storage container capacity, filter validation (at least extractable/leachable), pump setting, pump jet, sampling for assembly should be further discussed. In addition, a holding time of 60 days is stated for the bulk, nevertheless, the type of packaging and stability studies to validate this holding time should be provided.

Given the lack of information in the pharmaceutical development of the manufacturing process, the robustness of the manufacturing process is not considered as sufficiently demonstrated and the manufacturing site is not considered as sufficiently able to produce the drug product. Therefore, additional validation data should be provided on actual commercial batches stated in section 3.2.P.3.2.

Product specification (s)

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form according to ICHQ6A.

Nevertheless, regarding pH, droplet size and %droplet< 10 µm, mean delivered dose, extractable volume, impurities and total, limits should be added and/or further justified.

The analytical methods are adequately described; they include suitability tests with satisfactorily acceptable criteria and typical chromatograms. Nevertheless, for assay, degradation products, and droplet size distribution, microbiological testing, the full reports including raw data should be provided. Moreover, the stability indicating character of the assay method should be shown. In addition, the provided Certificate of Analysis for midazolam LGC standard is illegible. A clear and complete version of the certificate is required to allow appropriate evaluation of the data and for the impurity standards, only results are provided, including identification, chromatographic purity, and/or assay. Certificates of Analysis for these standards are requested to ensure full documentation and appropriate evaluation of the data.

The overall control strategy for impurities lacks consistency. The applicant is requested to provide a scientifically justified rationale for the selection of impurities included in the specifications. In particular, the omission of a limit for impurity D requires clarification, as does the absence of testing for impurity F in the finished product. A comprehensive discussion of each impurity's origin, potential presence, and toxicological relevance should be included to support the proposed specification limits. This constitutes a major objection.

Furthermore, the applicant is reminded to provide a complete risk assessment following the concepts of the ICH M7 guidance including all the potential and likely impurities of midazolam DP. All these compounds should be evaluated for their mutagenic potential using two complementary methodologies. The results of ICHM7 assessment should be provided as well as details on the methodologies used. This is also raised a major objection.

Regarding elemental impurities, the complete risk assessment following the concepts of the ICH Q3D guidance should be provided.

A Nitrosamine risk assessment has been submitted for the finished product; however, it should be supplemented to cover risks identified at the API level, including possible carryover from solvent use, nitrites/nitrates in process water, and potential formation of N-nitroso derivatives such as EP impurity A. The residual risk in the finished product should be discussed. If the risk cannot be excluded, batch testing data using validated methods should be provided. This is identified as a major objection.

Batch analysis results are provided for three validation batches manufactured according to the process described in Section 3.2.P.3.3. Results comply with the proposed specifications except for pH.

Stability of the product

The primary packaging of drug product consists of a bi-dose delivery system (BDSI) composed of glass vial containing the medicinal product and a delivery device. Nevertheless, several points have been raised in terms of incoming control of packaging materials, attestation from the suppliers of primary packaging materials comply with Ph. Eur. quality standard and with EU regulation for plastics material in contact with food, justification for the absence of actuation force data.

Stability studies for three validation drug product batches were performed under long-term (25°C/60% RH) storage conditions for up to 24 months, intermediate (30°C/65% RH) storage conditions for up to

12 months and under accelerated (40°C/75% RH) storage conditions for up to 6 months (solely for two batches).

All quality attributes remained within specification, except for pH. This systematic out-of-specification trend, observed from t=0 and remaining stable over time, does not reflect product degradation but rather a misalignment between the specification and the formulation's actual behaviour. The applicant was requested to justify or revise the pH specification accordingly. A shelf-life of 24 months under long-term conditions could be granted once the issue is resolved.

Neither photostability studies nor stress condition studies are reported or described in the submitted documentation and results should be provided.

Post approval change management protocol

N/A

Adventitious agents

N/A

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Insufficient information in quality sections of the dossier covers the general and specific attributes of the proposed drug substance and drug product. Therefore, there are 5 major objections and several other concerns which need to be appropriately addressed prior to an approval.

3.1.5. Recommendation(s) for future quality development

N/A

3.2. Non clinical aspects

Non-clinical overview is based on literature and data issued from the public assessment reports of other midazolam-containing products. The applicant has not provided additional non-clinical studies to support Tuzodi's development, for the treatment of prolonged, acute, convulsive seizures in adults, adolescents, children and toddlers (from 2 years of age), as the pharmacodynamic, pharmacokinetic and toxicological properties of midazolam are well known. The submitted non-clinical package relies on data of the active ingredient midazolam from older publicly available data, and such studies were not often conducted in compliance with current OECD protocols and GLP compliance. Considering these experimental studies and results cited in Modules 2.4 and 2.6 have previously been reviewed in support to previous FDA- or EMA-approved midazolam-containing products from the 1980's up to 2020's, these data would be considered supportive to grant marketing authorisation of Tuzodi. To this view, there is no reason to further investigate for GLP compliance and reconsider established knowledge.

Moreover midazolam is a widely used and well-known active substance described in the European Pharmacopoeia, in particular for use in the context of epilepsy and sedation, including in infants, toddlers, children and adolescents (from 3 months to < 18 years) as well as in adults, making non clinical data would add no significant knowledge for the age population and indication relative to the clinical established knowledge.

Given route, strength and formulation are different to the reference product, Ipnovel 15 mg/3 ml infusion for injections, specific non-clinical studies would have been conducted. In this way, applicant has been advised (EMA/SA/0000095512) that a bridging pharmacokinetic study should be performed with Tuzodi in animals and that local adverse events should be investigated. Instead, new clinical (PK and local tolerability) and modelling (popPK/PD and PBPK models) data were submitted to support the Hybrid Application, as an alternative option left open during the Scientific Advice.

The formulation, strength and routes for Tuzodi are different from the references products (Ipnovel, for dose and PK comparison/models; Buccolam granted for treatment of prolonged, acute, convulsive seizures in infants from 3 months to adults support the indication of Tuzodi), and the non-clinical overview did not comprise a sufficient discussion on adequacy of clinical data to overcome non-clinical studies recommended at time of Scientific Advice EMEA/H/SA/4544/1/2020/SME/III: whether exposure and local tolerance in MDZ-NS-22 clinical study with Tuzodi, and pharmacokinetic modelling studies supersede the lack of pharmacokinetic bridging and local tolerance studies in animals should be discussed. In addition, the non-clinical overview did not comprise a position on the risk assessment of impurities, and one has to refer to Module 3.

The applicant provided the environmental risk assessment (as per EMEA/CHMP/SWP/4447/00 Rev. 1) in the EU resulting from the use of midazolam hydrochloride spray for the treatment of prolonged, acute, convulsive seizures in adults, adolescents, children and toddlers (from 2 years of age).

3.2.1. Pharmacology

3.2.1.1. Primary pharmacodynamic studies

In line with the CHMP scientific advice, no new studies have been conducted in support of this application. midazolam has an anticonvulsant effect, a hypno-sedative effect, and an anxiolytic and muscle-relaxant effect. The applicant has not performed dedicated *in vivo* pharmacodynamic studies to support the intranasal administration, which is considered acceptable in view of the well-established clinical experience with midazolam, including the clinical experience with the intranasal dosage form.

3.2.1.2. Secondary pharmacodynamic studies

In line with the CHMP scientific advice, no new studies have been conducted in support of this application.

3.2.1.3. Safety pharmacology programme

In line with the CHMP scientific advice, no new studies have been conducted in support of this application. The applicant has only provided safety data on the cardiovascular effects of midazolam. These data suggest that midazolam exerts mild haemodynamic effects in conscious dogs at systemic exposures estimated to be several folds above human therapeutic exposures. In view of the lack of a clinical concern regarding the safety pharmacology of midazolam and the extensive clinical experience with midazolam, the paucity of non-clinical safety pharmacology data was not considered to be a concern.

3.2.1.4. Pharmacodynamic drug interactions

In line with the CHMP scientific advice, no new studies have been conducted in support of this application. Only the pharmacodynamic drug interaction between dexmedetomidine and midazolam is included in the non-clinical overview based on rodent studies. Considering that midazolam is a well-known active substance, and that the pharmacodynamic drug interaction described in the SmPC for

Tuzodi relates to clinical data, this is sufficient.

3.2.2. Pharmacokinetics

In line with the CHMP scientific advice, there is exhaustive knowledge: rapid absorption with an absolute bioavailability of approximately 45% after oral dosing, high binding to plasma proteins (94-98%), extensive distribution due to high lipophilicity. Metabolism is mainly through CYP3A4, and the principal metabolite is 1-OH-midazolam, which is rapidly conjugated with glucuronic acid. Clearance is mediated through liver metabolism and mainly the renal route with less than 1% of midazolam excreted unchanged in the urine. Elimination half-life was < 1h in all species.

No bridging PK studies have been conducted in animals. The applicant did not include in the non-clinical overview a summary of new PK clinical data or a discussion regarding the adequacy of the data to supersede the requirement for non-clinical PK bridging studies. During MDZ-NS-22 phase I trial, monocentre, open label, randomised, 5-single-dose cross-over study to assess the PK and safety profile, the mean (SD) maximum concentrations (Cmax) were 25.52 (7.181) ng/mL, 49.49 (15.975) ng/mL, 85.79 (27.745) ng/mL, 119.24 (39.640) ng/mL and 179.40 (125.517) ng/mL for MDZ-1 1 mg, MDZ-1 2 mg, MDZ-1 4 mg, MDZ-2.5 5 mg and Ipnovel 2.5 mg, respectively. A modelling approach was developed based on data from the MDZ-NS-22 clinical study, to derive PK/PD properties of midazolam by describing the observed response in terms of sedation in healthy volunteers. Furthermore, a PBPK model was developed based on both literature and MDZ-NS-22 study collected data, to translate and predict drug exposure, thus supporting posology of Tuzodi in paediatric and special (elderly, obese, liver impaired and renal impaired subjects) populations. A modelling approach was developed based on data from the MDZ-NS-22 clinical study, to derive PK/PD properties of midazolam by describing the observed response in terms of sedation in healthy volunteers.

3.2.3. Toxicology

3.2.3.1. Single dose toxicity

In line with the CHMP scientific advice, no new studies have been conducted in support of this application.

3.2.3.2. Repeat dose toxicity

In line with the CHMP scientific advice, no new studies have been conducted in support of this application. Liver had been identified a target organ in repeated dose IV and oral toxicity studies in non-clinical species; other adverse effects are 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.

3.2.3.3. Genotoxicity

In line with the CHMP scientific advice, no new studies have been conducted in support of this application. midazolam was concluded negative for genotoxicity potential.

3.2.3.4. Carcinogenicity

In line with the CHMP scientific advice, no new studies have been conducted in support of this application. No conclusive evidence emerged from in a 2-year oral studies in rodents.

3.2.3.5. Reproductive and developmental toxicity

In line with the CHMP scientific advice, no new studies have been conducted in support of this application. 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 usually recommended.

3.2.3.6. Toxicokinetic data

In line with the CHMP scientific advice, no new studies have been conducted in support of this application.

3.2.3.7. Local tolerance

No non-clinical studies have been conducted to evaluate the local tolerance of the intranasal route of Tuzodi formulation. Local adverse events were reviewed within MDZ-NS-22 clinical study.

3.2.3.8. Other toxicity studies

The non-clinical overview did not include toxicological studies in juvenile species.

The applicant stated in the non-clinical overview that Tuzodi contains the same excipients as the reference product. Midazolam hydrochloride drug substance (2.2mg) is formulated in water for injection (197.2 mg) as solvent, sodium chloride (1.5 mg) as isotonic agent, and hydrochloric acid (0.5 mg) as pH adjuster. As a remark, Ipnovel (as Buccolam) also contains sodium hydroxide which is not present in the midazolam spray.

No non-clinical studies on impurities have been conducted, and the risk assessment has not been elaborated on in either the non-clinical overview or the toxicology summary. The risk assessment has been elaborated in Module 3 documents.

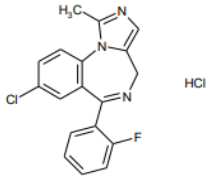
The potential degradation impurities in the drug product are those reported for the drug substance and are reported in the European Pharmacopoeia. Elemental impurities are within the limits of ICH Q3D. In the drug substance, residual solvent benzene that is class 1 (mutagenic impurities with positive carcinogenicity data) is below the defined ICHQ3C limit, and other potential genotoxic impurity para-chloroaniline belonging to class 1 is below the less-than-lifetime exposure according to ICHM7. Two other potential alerting structures were classified class 3 according to ICHM7, benzophenone- and bromoacetyl fluoro-related impurities, and are both controlled below TTC limit. As a remark, batch analysis showed these latter impurities were always below the limit of detection corresponding to a level 20-fold lower than the TTC-based acceptable intakes.

3.2.4. Ecotoxicity/environmental risk assessment

According to "Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1)", the applicant has to perform phase I environmental risk assessment and PBT/vPvB assessment (Table 1). Taking into account the refined FPEN value applied to the PECSW calculation reported above, the result is 0.0000411 µg/L, which is below the limit of 0.01 µg/L. Therefore, the risk assessment for midazolam can be concluded in Phase I, since it is confirmed not to pose a risk to the environment. A PBT/vPvB screening assessment has been performed based on the octanol-water partition coefficient. Nasolam Public Assessment Report 2023 (NL/H/5089/001-

003/DC) was provided as a support for the published value at 2.73, which is below the action limit (log Kow = 4.5). According to "Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1)", drug substances with a log Kow < 4.5 should not be screened additionally.

Table 1. Summary of main study results

Substance (INN/Invented Name): midazolam hydrochloride **IUPAC name:** 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a] [1,4]benzodiazepine; hydrochloride **Structure:** 			
CAS-number (if available): 59467-96-8			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	2.73	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.73	not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB ~~The compound is considered as vPvB~~ ~~The compound is considered as PBT~~		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$ (refined)	0.0000411	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(Y/N)

3.2.5. Discussion on non-clinical aspects

Given that the strength, formulation and routes are different to the reference product, the applicant was advised by CHMP that a pharmacokinetic bridging study should usually be performed with the new formulation at the intended doses in animals, and local adverse events should be investigated (EMA/SA/0000095512). Instead, new clinical data and modelling studies were conducted to address these concerns at human level.

(i) Pharmacokinetic results of MDZ-NS-22 study indicated rapid uptake across the nasal mucosa with near-complete absorption of Tuzodi and with an absolute IN bioavailability ranging from 91 to 100%. Notably, interindividual variability in Cmax was markedly lower than that seen with the IV formulation. Systemic exposure to midazolam after intranasal administration increased with increasing dose, suggesting absence of any saturation of absorption of midazolam across the nasal mucosa. There was a similar AUC metabolite/parent ratio after intravenous and intranasal administration. Based on the direct absorption into the circulation, elimination of midazolam was similar following both administrations. During MDZ-NS-22 phase trial mean Cmax MDZ-2.5 5 mg were lower than Ipnovel 2.5 mg. From PK modelling

studies presented in the clinical overview, Forest plot predicted Cmax distribution after BID administration of Tuzodi (2.5+2.5 mg) would remain within median and the 10th to 90th percentiles range of Buccolam, below the safety threshold, including for the paediatric patients. Exposure to the main metabolite α-hydroxy-midazolam is not increased compared to the reference. This information is considered more relevant than conducting non-clinical studies as pharmacokinetics derived from intranasal administration in animals are not expected to be completely translatable to humans due to differences in nasal anatomy. From a non-clinical view, there is no need to conduct new animal pharmacokinetic studies with the spray formulation. With the lack of increased human systemic exposure compared to approved products, this renders not useful the conduct of new standard toxicology studies, excepted investigation of local tolerance effects given the new route and formulation compared to the reference product.

(ii) The applicant did not address local tolerance of Tuzodi by intranasal route of delivery in animal studies, but from MDZ-NS-22 trial enrolling human adults, which data are considered of higher relevance. This is considered not of non-clinical concern given another nasal spray has been previously approved as Decentralised Procedure (Nasolam, NL/H/5089/001-003/DC) from age of 2 years and older with the same dose, and as Tuzodi's formulation (sodium chloride water, hydrochloride acid) is safe than hypertonic formulation of Nasolam (water, propylene glycol and ethanol). There are many significant differences in the anatomy of nasal cavities of man and laboratory animals (Chamanza and Wright, 2015), making animal studies uncertain for human translation, and age specific studies. There are many significant differences in the structural and functional anatomy of the nasal cavity of man and laboratory animals. Some of the differences may be responsible for the species-specific nasal lesions that are often observed in response to inhaled toxicants. Gross anatomical variations such as turbinate structure, folds or grooves on nasal walls, or presence or absence of accessory structures, may influence nasal airflow and species-specific uptake and deposition of inhaled material. In addition, interspecies variations in the morphological and biochemical composition and distribution of the nasal epithelium may affect the local tissue susceptibility and play a role in the development of species-specific nasal lesions and toxicities. Nasal irritation or itching and nasal pain or discomfort were more reported in the treatment groups where the administration required of the nasal sprays into both nostrils. Nasal congestion was generally mild and significant respect to pre-dose only at the first time-point of 5 minutes; runny nose was generally absent or mild until 30 minutes. No alteration in the sense of smell was perceived by the subjects. Nasal examination evidenced few, mild and transient abnormalities, completely resolved within 6 hours from dosing, with an incidence equal among treatment groups. The main PK parameters of midazolam and α-hydroxy-midazolam along with dosages of Tuzodi confirmed humans were systemically exposed at similar level of that of reference Ipnovel. Not addressed, was whether a direct delivery to the brain via the nasal cribriform would increase brain concentration of midazolam and α-hydroxy-midazolam compared to other routes and formulations, and local tolerance among ages. Alternatively, MDZ-NS-22 clinical study showed TEAEs relative to Nervous System Disorders and Psychiatric Disorders were anterograde amnesia, headache, insomnia, graded mild to moderate and these effects were reversible, and these effects are not new. Finally, it is concluded non-clinical data can be waived. Section 5.3 proposed for the SmPC, must be deleted of the sentence 'During local tolerance studies in animals, midazolam was well tolerated after intranasal administration' as the information on local effects by intranasal route with the drug product was issued from a human study **(OC**).

The non-clinical overview did not include toxicological studies in juvenile species. Given the extensive experience with approved midazolam products in infants and children, this lack of data is accepted.

The components of the intranasal spray formulation are well-known and safe excipients, complying with Ph. Eur. requirements, and already used in other intranasal formulations. No further safety data are mandatory from a non-clinical view. No dedicated non-clinical studies on impurities have been conducted and risk assessment has been elaborated in the Module 3 documents. The impurity profile in the final product is not deemed to raise concern from a non-clinical view as impurity levels are within limits of relevant guidelines and controlled below TTC limit for genotoxic impurities identified *in silico*. Although the impurity profile of the finished product does not raise concerns, the applicant's non-clinical overview should also include a discussion of impurities according to Directive 2001/83/EC Annex I, Part I and the Notice to applicants, Volume 2B **(OC**).

In line with the "Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1)", the applicant has performed a phase I environmental risk and a PBT/vPvB assessment. Although the prevalence of 6 per 1000 referred to an old review of epidemiology of epilepsy in Europe dated 2005, World Health Organization's website estimated that in the general population, the proportion of people with progressive epilepsy (i.e. having chronic seizures or requiring treatment) at any given time is between 4 and 10 per 1000 people, with higher rates of people diagnosed with epilepsy in low- and middle-income countries. The proposed prevalence value in EU may be acceptable and it refers to both paediatric and adults that coincides with the target population for Tuzodi. For Phase I ERA, considering refined FPEN value based on this prevalence value, the refined PECSW was calculated 0.0000411 µg/L, which is below the limit of 0.01 µg/L.

The applicant provided several values of octanol/water partition coefficient (log Kow), the parameter for predicting the distribution of a substance in the environment, as starting point for PBT/vPvB assessment. Predicted approach provided is not acceptable *as per* the relevant Guideline (EMEA/CHMP/SWP/4447/00 Rev. 1), and other published values are issued from scientific literature, which GLP and OCDE protocol compliance cannot be verified, and a Public Assessment Report. The most up-to-date value is from the nasal spray Nasolam 5 mg Public Assessment Report (2023), which has been established through the OECD protocol of Shake-flask method. In the procedure, midazolam has been not considered persistent bio-accumulative toxic as the log Kow does not exceed 4.5., and this is agreed according to Figure 3 - PBT/vPvB Screening Decision tree of 'Guideline on the environmental risk assessment of medicinal products for human use' (EMEA/CHMP/SWP/4447/00 Rev. 1). When the trigger value of log Kow >4.5 is no met, a definitive PBT/vPvB assessment is not needed, should be performed.

To conclude, the PECsw for midazolam hydrochloride is below the action limit of 0.01 µg/l and the substance is not persistent bio-accumulative toxic as the log Kow does not exceed 4.5. Therefore, no Phase II ERA and no further PBT/vPvB assessment are required. Although there are several sources of information on log Kow values for midazolam, it is considered that the most up-to-date and acceptable information provided by the applicant to support the octanol/water partition coefficient value was from the Nasolam Public Assessment Report. Public Assessment Reports and reviews or summary data from other regulatory frameworks cannot be used as data in the ERA dossier. Data from Nasolam procedure are owned by the company who submitted them in the original procedure and cannot be used by other applicants without a letter of access (section 6.1, EMEA/CHMP/SWP/4447/00 Rev. 1). Therefore, the Risk assessment for intranasal midazolam hydrochloride could be concluded sufficient and not to pose a risk to the environment only if the applicant would provide a letter of access, with the study reports from the other MAH about recent determination of octanol/water partition coefficient (**OC**). If cross-reference to experimental determination of log K_{OW} from this original study reports is not feasible, the applicant is requested to provide its own studies.

3.2.6. Conclusion on non-clinical aspects

This hybrid application relies in part on the results of publicly available preclinical data for approved midazolam-containing products usable for infants, toddlers, children and adolescents as well as in adults, and clinical data for the reference product and others obtained with Tuzodi. There was a well-established clinical use of midazolam, including in the epilepsy context, an extensive knowledge on non-clinical pharmacology, pharmacokinetics and toxicology of midazolam, making not useful the conduct of the full usual non-clinical programme. Non-clinical data therefore would not add to the wealth of efficacy and safety data available from clinical use. However, since the route of administration, concentration and formulation are different from those of the reference product, specific non-clinical studies may be necessary unless clinical knowledge surpasses them. Excipients of the intranasal spray formulation are well-known and safe. The safety risk for impurities can be considered low from a non-clinical view and appropriate control strategy were defined when required, however the applicant's non-clinical overview should also include a discussion of impurities to comply with the Directive 2001/83/EC Annex I, Part I and the Notice to applicants, Volume 2B (**OC**).

PB/PK-Pop/PK modelling studies, pharmacokinetic and safety human data collected from a clinical study with Tuzodi, supporting midazolam systemic exposure not higher than the reference product, and human acceptable local tolerability with Tuzodi, overcome the need of bridging non-clinical pharmacokinetic and local tolerance studies with Tuzodi in animals, which relevance would be limited, as well as other non-clinical requirement. All together this information justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data, including non-clinical studies on a local tolerance of the intranasal use in light of the clinical studies that have been conducted.

While the applicant has provided the public assessment report of Nasolam to justify the value of octanol/water partition coefficient, the applicant is reminded that public assessment reports and reviews or summary data from other regulatory frameworks cannot be used as data in the ERA dossier without providing both a letter of access and initial study reports (section 6.1, EMEA/CHMP/SWP/4447/00 Rev. 1). Therefore, the risk assessment for intranasal midazolam hydrochloride could be concluded as sufficient and not to pose a risk to the environment only if the applicant would provide a letter of access as well as study reports from the original MAH. If cross-reference to experimental determination of log KOW based on original reports is not feasible, the applicant must provide its own studies (**OC**).

SmPC 5.3 must only refer to non-human data. In the non-clinical overview, as well as section 2.6.6.7 Local tolerance of the toxicology written summary, the information on local effects by intranasal route with the drug product was issued from a human study (MDZ-NS-22 trial). Consequently, the sentence 'During local tolerance studies in animals midazolam was well tolerated after intranasal administration' must be deleted from the proposed section 5.3 of the SmPC (**OC**).

The application could be approved from a non-clinical side but as stated above, there are issues that need to be clarified. See list of questions.

3.3. Clinical aspects

This application is a hybrid application with Ipnovel 15 mg/3 ml solution for injection (marketing authorisation holder Cheplapharm Arzneimittel GmbH) as reference product.

The SmPC for Tuzodi is largely taken from Hypnovel, wording on advice of healthcare professional regarding the second dose is also to be discussed, please see safety section.

To support the Article 10(3) marketing authorisation application of Tuzodi, the clinical development programme included:

- a clinical PK study (MDZ-NS-22) to assess pharmacokinetics, pharmacodynamics, safety and local tolerance of single doses of midazolam nasal spray (MDZ) respect to the reference product (Ipnovel).
- a population pharmacokinetic/pharmacodynamic (popPK/PD) model that was developed based on the data collected in MDZ-NS-22 study to derive PK/PD properties of midazolam by describing the observed response in terms of sedation in healthy volunteers.
- a Physiologically Based Pharmacokinetic (PBPK) model that was developed based on both literature data and data collected in MDZ-NS-22 study, and predictions were performed for sedation posology in adults, paediatrics and special populations.

3.3.1. Exemption

NA

3.3.2. Clinical pharmacology

Pharmacokinetics

Study MDZ-NS-22

- **Study design**

This was a phase I, monocentre, open label, randomised, 5-single-dose (5 treatment sessions per volunteer) cross-over study to assess the PK and safety profile of:

• MDZ-1 (10 mg/mL) 1 mg (100 µL) as one puff into a nostril

• MDZ-1 (10 mg/mL) 2 mg (200 µL) as one puff per nostril

• MDZ-1 (1 0mg/mL) 4 mg (400 µL) as four puffs into both nostrils (two puffs per nostril)

• MDZ-2.5 (25 mg/mL) 5 mg (200 µL) as one puff per nostril versus

• Ipnovel (15 mg/3 mL solution for injection) as 2.5 mg diluted in 2.5 mL injected over 2 min. (Reference Product).

With a predicted elimination half-life of 3h for midazolam, a wash out of 3 days and 12h PK sample collections are appropriate. Study design is well described and follows the scientific advice – except that it also called for Ipnovel (15mg/3mL solution for injection) as 5 mg (1mL) dropped into both nostrils (0.5 mL per nostril in a slow stream over 15 sec. via a needleless syringe). SAG commented that "The applicant's proposal to establish bioequivalence between the new formulation against Ipnovel given IN (15mg/3ml solution for injection) would suggest some literature studies were performed with/against Ipnovel given IN. If not, evaluation of similar exposure versus Ipnovel I.V may be more appropriate." Discussion for the removal of this arm could not be found, the applicant should comment, taking into account the comment from the SAG. (OC)

- **Test and reference products**

Certificates of analysis for the study drugs were mentioned in the study report but could not be found; the applicant should provide them. (**OC**)

- **Population(s) studied**

28 subjects were studied. Justification for number of subjects sufficient could not be found, the applicant should detail (OC).

- **Analytical methods**

Reports were provided. Stability and ISR were acceptable. However, the applicant should detail the "re-analysis for PK reasons" since this is generally not acceptable (**OC**).

- **Pharmacokinetic Variables**

PK variables calculated are appropriate.

- **Statistical methods**

Statistical methods are consistent with the objectives and acceptable.

- **Results**

The applicant states that

- Following single nasal administration of midazolam at doses of 1 mg to 5 mg, drug absorption was rapid, and maximum concentrations were reached after 10-15 minutes with an absolute IN bioavailability ranging from 91 to 100%. Notably, interindividual variability in Cmax was markedly lower than that seen with the IV formulation.
- Systemic exposure to midazolam after intranasal administration increased with increasing dose, suggesting absence of any saturation of absorption of midazolam across the nasal mucosa.
- No second absorption peaks were observed after IN administration, which indicates absence of absorption of orally ingested midazolam. This is further supported by the similar AUC metabolite/parent ratio after IV and IN administration
- As expected, based on the direct absorption into the circulation, elimination of midazolam was similar following IV and IN administration.

Plots and tables of section 14 were in document 16.1.13_TLF, making the application harder to analyse.

Intranasal pathway leads to a rapid absorption around 15 minutes, terminal half-lives similar to IV, and apparently no second peak showing oral ingestion. PK appears also linear.

Study ACS-2024-0007 Population PK PD analysis

A population pharmacokinetic/pharmacodynamic (popPK/PD) model has been developed based on the data collected in MDZ-NS-22 study to derive PK/PD properties of midazolam by describing the observed response in terms of sedation in healthy volunteers.

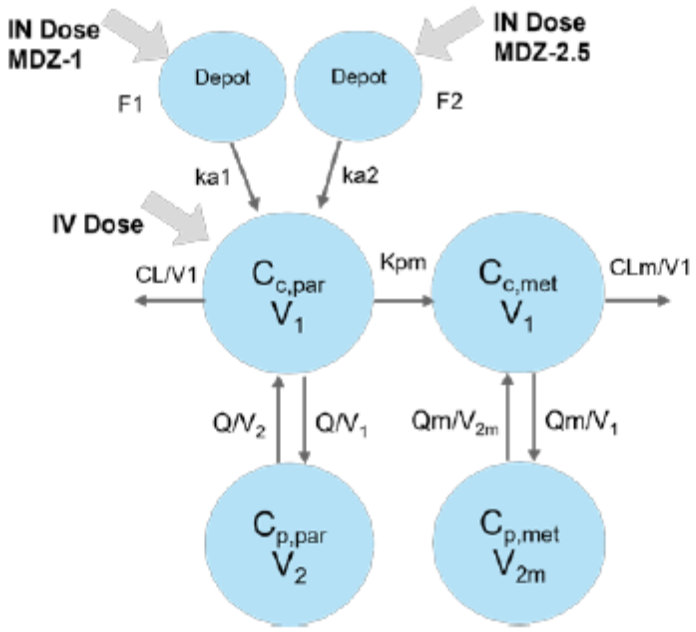


Figure 3: Population PK model scheme

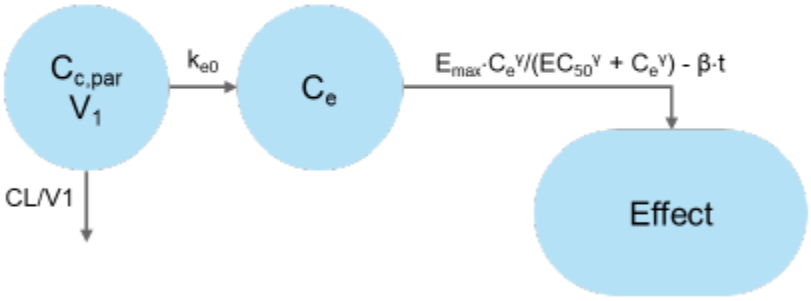


Figure 4: Population PD model scheme

PK model parameters and PD model parameters are presented below.

Table 2: midazolam PK model parameters

Parameter	Distribution	Estimate (CV%)	SE	RSE (%)
Fixed Effects				
F1_pop (-)	Logitnormal	0.95	0.02	2.1
F2_pop (-)	Logitnormal	0.99	0.00082	0.08
ka1_pop (1/h)	Lognormal	5.40	0.65	12.1
ka2_pop (1/h)	Lognormal	5.55	0.62	11.2
V1_pop (L)	Lognormal	14.37	2.67	18.6
Cl_pop (L/h)	Lognormal	19.99	1.82	9.1
Q_pop (L/h)	Lognormal	63.90	11.65	18.2
V2_pop (L)	Lognormal	30.29	2.10	6.9
Clm_pop (L/h)	Lognormal	20.59	4.92	23.9
Qm_pop (L/h)	Lognormal	4.28	0.43	10.1
V2m_pop (L)	Lognormal	10.40	2.65	25.4
Kpm_pop (1/h)	Lognormal	0.62	0.20	31.7
beta_Kpm_WEIGHT		-0.017	0.0046	27.1
Standard Deviation of the Random Effects (ω)				
omega_F1		1.64 (16.6%)	0.35	21.3
omega_F2		4.4 (17.3%)	1.28	29.2
omega_ka1		0.61 (67.2%)	0.09	14.9
omega_ka2		0.57 (62.3%)	0.08	14.2
omega_V1		0.94 (118.4%)	0.13	14.0
omega_Cl		0.45 (47.6%)	0.07	14.9
omega_Q		0.84 (101.1%)	0.19	22.3
omega_V2		0.3 (30.3%)	0.05	17.8
omega_Clm		1.18 (174.7%)	0.18	14.9
omega_Kpm		0.28 (28.3%)	0.04	15.1

Parameter	Distribution	Estimate (CV%)	SE	RSE (%)
Error Model Parameters				
a1		9.37	0.17	1.77
a2		0.68	0.012	1.81

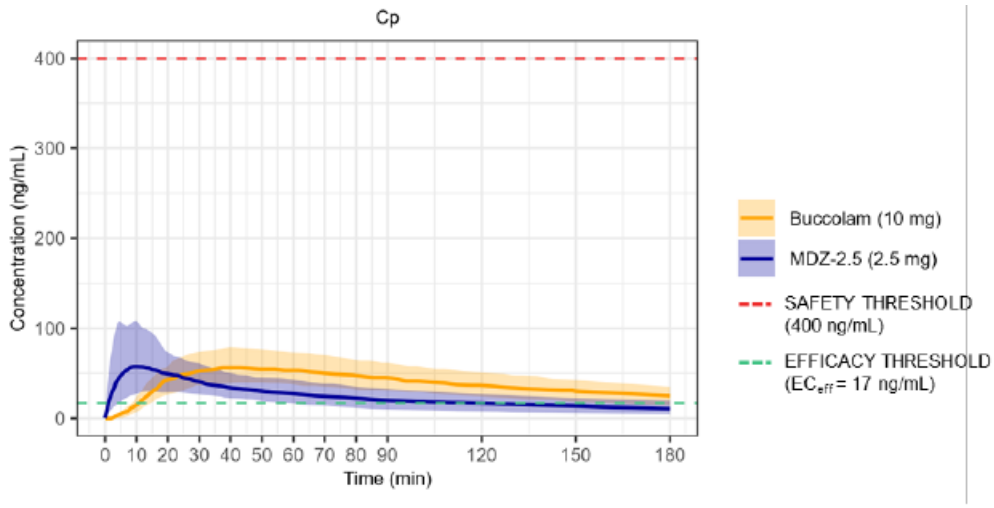
RSE: Percentage of relative standard error (100%·SE/Estimate).
ω Represents the standard deviation of the interindividual variability parameter.
The parameter b is the proportional component of the residual error of the model.

Table 3: midazolam PD model parameters

Parameter	Distribution	Estimate (CV%)	SE	RSE (%)
Fixed Effects				
theta1sss_pop (-)	Normal	1.74	0.24	14.0
theta2sss_pop (-)	Lognormal	3.93	0.17	4.2
theta3sss_pop (-)	Lognormal	2.78	0.15	5.4
theta4sss_pop (-)	Lognormal	1.84	0.14	7.7
theta5sss_pop (-)	Lognormal	1.52	0.15	10.1
theta6sss_pop (-)	Lognormal	2.13	0.23	10.9
theta2oaass_pop (-)	Normal	9.48	0.34	3.6
theta3oaass_pop (-)	Lognormal	3.69	0.25	6.8
theta4oaass_pop (-)	Lognormal	3.11	0.48	15.4
theta5oaass_pop (-)	Lognormal	3.00	1.09	36.4
Emax_pop (-)	Lognormal	16.11	1.07	6.6
EC50_pop (ng/mL)	Lognormal	12.34	1.99	16.2
gamma_pop (-)	Lognormal	0.71	0.07	9.3
ke0_pop (1/h)	Lognormal	1.02	0.17	17.0
bt_pop (-)	Lognormal	2.62	0.27	10.1
Standard Deviation of the Random Effects (ω)				
omega_theta1sss		1.77 (102.15%)	0.26	14.5
omega_ theta2oaass		2.03 (21.41%)	0.34	16.9
omega_Emax		0.21 (21.25%)	0.04	21.4
omega_EC50		0.44 (45.88%)	0.13	30.5
omega_gamma		0.54 (58.75%)	0.09	17.7
omega_ke0		0.71 (81.35%)	0.10	13.7
omega_bt		0.78 (92.13%)	0.072	9.13
RSE: Percentage of relative standard error (100%·SE/Estimate). ω Represents the standard deviation of the interindividual variability parameter.				

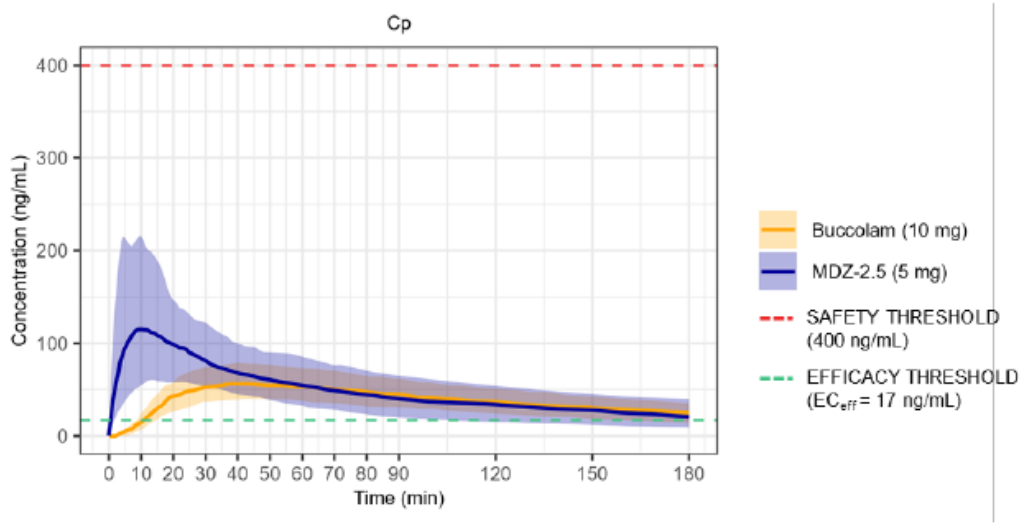
Simulated profiles vs. Buccolam for several doses – 2.5mg, 5 mg, twice 2.5 mg and twice 5 mg in the adult population are presented below.

Simulations for Nasolam come from the Nasolam public assessment report.



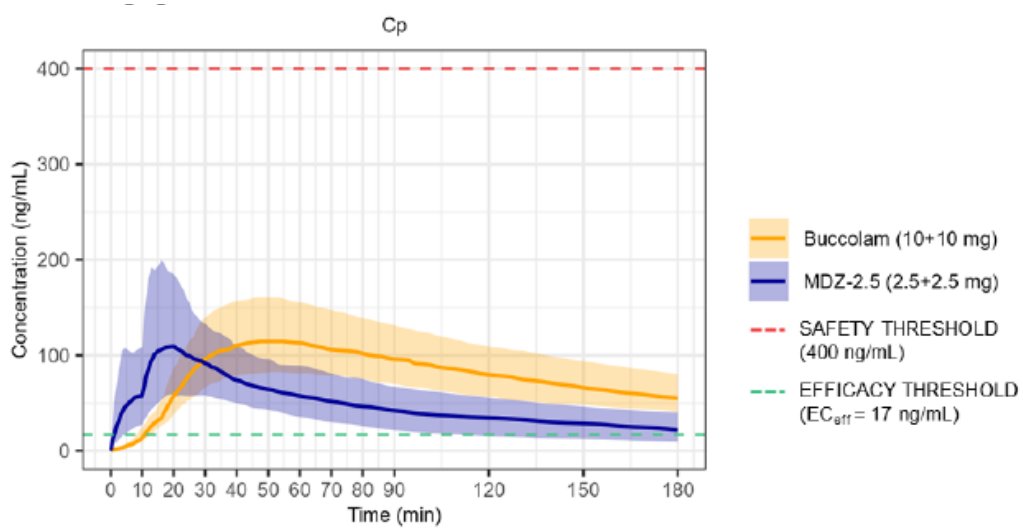
*Simulated Buccolam (10 mg) data were gathered from Nasolam public assessment report (EMEA/H/A-29(4)/1511).

Figure 5: Simulated PK profiles with Tuzodi 2.5 mg vs. Buccolam 10 mg in adult population



*Simulated Buccolam (10 mg) data were gathered from Nasolam public assessment report (EMEA/H/A-29(4)/1511).

Figure 6: Simulated PK profiles with Tuzodi 5 mg vs. Buccolam 10 mg in adult population



*Simulated Buccolam (10 mg) data were gathered from Nasolam public assessment report (EMEA/H/A-29(4)/1511).

Figure 7: Simulated PK profiles with Tuzodi 2.5 mg twice with 15 mins between dosing vs. Buccolam 10 mg twice with 15 mins between dosing in adult population

Study ACS-2024-0007: PBPK Modelling to Support Sedation and Anti-epileptic Posology in Adults, Special Populations and Children

In this application, a high impact PBPK modelling approach was used using GastroPlus (Simulation Plus, v9.8.3002) to predict midazolam PK in paediatric population from 2 years old and above and in special population such as elderly, obese patients, renally and hepatic impaired patients. The applicant built a PBPK model using in vitro and in vivo parameters to describe midazolam PK in healthy adults following IV and oral administrations. To describe midazolam absorption following IN administration, nasal parameters of absorption rate, permeability and mucus binding were calibrated using "the experimental profile of MDZ-1".

Model verification

The model was evaluated against published plasma profiles after intravenous (IV), oral (PO) and inhaled (IN) administrations in healthy human adults, paediatric, and special populations (i.e. elderly, obese, patients with respectively hepatic and renal impairment) from literature mainly.

Model prediction/simulation

Ultimately, the model was used to predict midazolam PK following IN administration in special and paediatric populations (<19 kg; 19-44 kg; > 44 kg) to support posology in target population.

Fraction unbound and blood to plasma ratio were automatically scaled by the PBPK model.. For each subpopulation, a unique subject was simulated representing the average physiology and PK exposure predicted with GastroPlus.

Midazolam IN PK was simulated in each sub population group following 1 mg, 2 mg, 3 mg, 4 mg, 2.5 mg, 5 mg, both QD and BID.

Midazolam IV PK in adult special population was simulated following an IV infusion during the t = 0-2 min interval of 1 mg, whereas, in paediatric populations an IV infusion during the t = 0-2 min interval, with either low or high dose amounts depending on the age range as per posology reported in the

Ipnovel SmPC: 0.05-0.1 mg/kg in 2 to 6 years, 0.025-0.05 mg/kg in >6 and ≤12 years, 2-2.5 mg in >12 and ≤18 years.

Pharmacodynamics

NA

3.3.3. Discussion and conclusion on clinical pharmacology

To characterise midazolam PK following TUZODI intra nasal administrations from 1 up to 5 mg, the applicant conducted Study-MDZ NS-22 in healthy volunteers (n=28) to assess TUZODI PK in healthy adult populations. At the tested doses, midazolam was rapidly well absorbed with lower interindividual variability in Cmax than IV formulations. Tmax reached within 15 min with bioavailability ranging from 91 to 100%. However, there are several points to be clarified on the PK study provided. (OC)

To further support TUZODI posology in the target populations modelling in simulation approaches. A PK/PD model was developed to support the dose in healthy adults whereas PBPK model was used to predict midazolam PK following Tuzodi IN administration in special and paediatric populations.

POP PK/PD modelling

Overall, the results of this modelling is not satisfactory. Little discussion was provided on how to model properly IN absorption.

In particular, the applicant did not discuss how absorption may be changed in case of nasal irritation or inflammation, this point should be discussed.(OC)

Regarding the modelling, several points are of concern. As the whole modelling is called into discussion, they will all be considered major points.

Absorption is barely discussed though as we deal with a new administration form that it is a crucial point. More attention should have be given and reported to test different absorption models and discrimination between them. Observation of VpC plots clearly suggests that Cmax is highly variable, and missed; this could be due a poor modelling of absorption. A better modelling of absorption might yield a better modelling and thus estimation of Cmax. (MO)

Initial parameters are not clearly displayed in the reports and should be clearly reported in the answer to the LoQ. (OM)

It is also difficult to read and interpret the VPCs for PD without the individual observations, the applicant should update the plots to include observations. (OM)

Additionally, it can be commented that the issues with Cmax is mainly about the variability, making the use of these simulations problematic for efficacy, but not so for preclinical discussion.

Finally, paediatric and special populations are more precisely discussed in the PBPK model discussion below.

PBPK modelling to support TUZODI posologies in paediatric and special populations

The structural model, the important related parameters used, and the model assumptions were not described nor presented (preferably in a figure whenever possible) which does not allow the understanding of the model mechanistic aspects, e.g. how the different route of administrations are related within the model. More importantly, it does not allow to clearly identify critical parameters in PK predictions. The main equations involving critical parameters, or equations describing the routes of administration were also not presented, which does not allow to understand how the parameters could

be correlated. Given the high impact of the model in this application, the model is not acceptable in the present state. (MO)

Model verifications

The PBPK model predictions was verified in healthy adults following IV, IN, and oral administrations using several publications (IV n=8: PO n=4; IN n=3) whereas model predictions in paediatric and special populations were verified using limited number of publications for each subpopulation, especially following IN administrations, the route of administration of interest. Literature data were only available in paediatric – based on Walberg et al., 1991 study which included 19 subjects comprised between 14 months old and 5 year old subject – and in the elderly – based on Berg et al., 2017 study which included 18 geriatric subjects with a mean age of 69.6 (ranging from 65 up to 78 years old).

In healthy adults midazolam PK predictions following IV administrations were reasonable. By contrast predictions of oral and IN absorption (Cmax %PE 137%, and 118%) were not convincing.

Among the subpopulations to be predicted, only paediatric (Walbergh et al 1991) and geriatric (Berg et al. 2017) populations were verified following IN administration. There were no verifications of the model predictive capacity on renal, hepatic or obese patients PK.

In the paediatric population, despite a small under prediction (%PE 4%) of mean Cmax from Walbergh et al. 1991, the model also predicted a delayed absorption as compared to observed data which could question the actual model capacity to predict TUZODI PK following IN administration.

Indeed while the PBPK models failed to capture the IN absorption in healthy adults, it is not clear how the model could reliably predict midazolam PK in children. Additionally, the model was only verified using children data ranging from 2 to 5 yo (Walbergh et al 1991) but was subsequently used to predict midazolam PK in children from 6 and above.

Furthermore, given the high impact of the PBPK model, in its use to support in subpopulations lacking clinical PK data following TUZODI administration in the target population, the variability in the PK predictions is critical. Therefore, the predicted mean PK is not considered acceptable.

In special populations, simulations were performed using only a single virtual subject per subgroups, and in paediatric population some variability is provided but it does not account for the uncertainty on the critical parameters used in the model, nor does the used virtual populations reflect in vivo variability (i.e. only one subject per age).

Overall, the provided PBPK model at D80 to support TUZODI PK in special and paediatric populations is not considered qualified to support the proposed posologies in special and paediatric population and population PK approach is considered more suitable for this purpose.

To conclude, an update of the population PK/PD is requested. It will have to demonstrate higher predictive performance of both PK/PD modelling approaches. This includes providing satisfactory responses to all questions listed below. In addition, to justify the similarity in exposure ranges, the applicant should place particular emphasis on both absorption and Cmax variability, and/or provide direct comparisons with Buccolam. (see MO)

Co-Rapporteur discussion on the clinical pharmacology

Tuzodi (also referred to as MDZ-2.5) is an innovative nasal spray solution containing 25mg/mL of midazolam in a bi-dose container, with proposed indication for the treatment of prolonged, acute, convulsive seizures in adults and children > 12 kg and aged 2 years and older.

The legal basis of this marketing authorisation application for Tuzodi 2.5 mg/spray is Article 10(3) of Directive 2001/83/EC, a so-called "hybrid" application to the reference medicinal product Ipnovel 15 mg/3 ml IV solution.

Ipnovel 15 mg/3 ml IV solution has been authorised for sedation and premedication related to procedures or anaesthesia in the EU on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC. Tuzodi formulation is similar to the reference product, considering that they are both simple aqueous solutions containing the same excipients (except for the sodium hydroxide). Differences compared to the reference product are the pharmaceutical form, the strength, the route of administration and the therapeutic indication.

In the EU, midazolam (Buccolam) has been available as an oromucosal solution in doses of 2.5 mg, 5 mg, 7.5 mg, and 10 mg since September 2011. It is used to treat prolonged, acute, convulsive seizures in children from 3 months to under 18 years old. Since April 2022, midazolam is also available as a nasal spray (Nasolam) in doses of 2.5 mg, 3.75 mg, and 5 mg for treating similar seizures in adults and children over 12 kg and aged 2 years and older.

For this application, to support safety of Tuzodi, reference is made to safety data of the reference product Ipnovel while, the efficacy in the treatment of seizures is supported by reference to efficacy data of Buccolam.

The clinical development programme includes:

- a clinical PK study (MDZ-NS-22) to assess pharmacokinetics, pharmacodynamics, safety and local tolerance of single doses of midazolam nasal spray (MDZ) respect to the reference product (Ipnovel)

- a population pharmacokinetic/pharmacodynamic (popPK/PD) model that was developed based on the data collected in MDZ-NS-22 study to derive PK/PD properties of midazolam by describing the observed response in terms of sedation in healthy volunteers

- a Physiologically Based Pharmacokinetic (PBPK) model that was developed based on both literature data and data collected in MDZ-NS-22 study, and predictions were performed for sedation posology in adults, paediatrics and special populations (i.e. renal impaired population, hepatic impaired population, elderly population, and obese population).

The applicant received CHMP Scientific Advice pertinent to the clinical investigation ((EMEA/H/SA/4544/1/2020/SME/III) in October 2020 and in the subsequent Follow-up (EMA/SA/0000095512) in September 2022). This advice concerned the adequateness of the nonclinical and clinical package in support of a Marketing Authorisation Application (MAA) according to the intended legal basis. Overall, the applicant has largely adhered to the provided recommendations; however, several identified concerns remain especially in respect of PK extrapolation to paediatric population.

A GCP certificate from AIFA (Italy), dated 25 October 2018, confirms suitability for clinical trials. A summary of key inspection outcomes, including any major or critical findings, is requested (**LoQ)**.

Study MDZ-NS-22

Comparative bioequivalence (BE) studies were not performed considering the different pharmaceutical forms of Tuzodi (nasal spray solution, 2.5 mg/spray) and the reference product Ipnovel (intravenous solution, a.k.a. Hypnovel/Dormicum, typically 1 mg/ml and 5 mg/ml).

A characterisation of the bioavailability of Tuzodi in healthy volunteers has been evaluated in MDZ-NS-22 PK study a phase I, monocentre, open label, randomised, 5-single-dose (5 treatment sessions per volunteer) cross-over study.

A total of 34 volunteers were screened, with six deemed ineligible and not randomised. Of the 28 enrolled, 26 completed the study, as two withdrew before the final dosing session. Justification for the sample size estimation is requested. (**See LoQ**) Each subject received five administrations in a randomised order. Blinding was applied only to the investigator during sedation status assessments. The study population comprised healthy males (n=16) and females (n=18), aged 18 to 50 years, with a BMI range of 18.4–27.8 kg/m². Inclusion and exclusion criteria, as well as subject medical and surgical histories, were well documented. Reasons for subject discontinuation and exclusion were sufficiently justified. Overall, the study design and chosen population is acceptable and in line with SA recommendations.

Primary objective of MDZ-NS-22 study was to assess the pharmacokinetic profiles of midazolam and its active metabolite α-hydroxymidazolam from the test product Tuzodi (as forms MDZ-1 (10 mg/mL) or MDZ-2.5 (25 mg/mL) to administer 1 mg, 2 mg or 5 mg as one puff per nostril, or 4 mg as two puffs per nostril), versus the reference formulation Ipnovel (15 mg/3 mL solution for injection, as 2.5 mg diluted in 2.5 mL injected over 2 min). Secondary objectives were to evaluate the general safety, local tolerance, of the test drug administered intranasally, compared to intravenous comparator administration, in male and female healthy subjects, and to evaluate the sedation level reached with the test drug compared to the reference drug.

The pharmacokinetic parameters were determined from the plasma concentration vs. time data and derived from individual measured concentrations using non-compartmental analysis (NCA). The parameter choice is adequate (C_{max}, t_{max}, $t_{1/2}$, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$). The final study report, initially absent from module 5, is requested to complete the assessment. **(See LoQ)** Additional data on the individual subject results is anticipated with the final report, such as individual subject concentration data, pre-dose concentrations. Protocol deviations (appendix 16.2.2), such as sample storage inconsistencies and missing PK blood samples, should be discussed and justified by the applicant regarding their impact on study results. (**See LoQ**)

For statistical analysis, a mixed-effect model with fixed effects (treatment, sequence, period, and subject within sequence) is applied, with log-transformed AUC and C_{max} used to derive geometric least-squares means (GLSM). Relative bioavailability is explored via GLSM ratios and 90% confidence intervals, including analysis of midazolam's metabolite, observing the ratio of $AUC_{(0-\infty)}$ and the relative 90% confidence interval.

The pharmacokinetic parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $T_{1/2}$, CL, and Vz demonstrate comparable values between Tuzodi (IN) and reference Ipnovel (IV), indicating similar overall exposure and elimination. However, Tuzodi exhibits lower Cmax values and a delayed Tmax relative to the reference Ipnovel. Given that efficacy is supported by data from Buccolam (IB), no further justification for these differences is required.

Notably, interindividual variability in Cmax for Tuzodi is significantly lower than observed with IV administration, suggesting a more consistent absorption profile. Additionally, systemic exposure to midazolam increases proportionally with dose following intranasal administration.

Sedation effect as secondary endpoint was assessed by: Evaluation of score of the Stanford Sleepiness Scale (SSS); Evaluation of the Observer's Assessment of Alertness/Sedation Scale (OAA/SS). Subjective sedation increased in a dose-dependent fashion, with statistically significant effects at all dose levels. Sedation had a duration of approximately 4h at all dose levels. The degree of sedation following Ipnovel 2.5 mg was comparable to that seen after 2 mg Tuzodi IN administration. Similarly, the OAA/SS showed a dose-dependent effect, which coincided with the subjective scoring. Rationale is requested about several subjects excluded from the sedation analysis (appendix 16-2-3; **See LoQ**).

Additionally, please see the discussion on safety below.

No second absorption peaks were observed after Tuzodi administration, suggesting the absence of orally ingested midazolam absorption. According to the applicant this is further supported by the similar AUC metabolite/parent ratio after IV and IN administration; however, comparative data visualisation or ratio estimates are only partially provided (**See LoQ**).

Pharmacokinetic (PK) results indicate rapid absorption across the nasal mucosa, with an absolute IN bioavailability ranging from 91% to 100%. Bioavailability comparisons use a 5 mg Tuzodi dose, while the proposed initial posology for adults is 2.5 mg. Data supporting comparisons between Ipnovel 2.5 mg and Tuzodi 2.5 mg should be provided. (**See LoQ**)

Based on the applicant, insufficient IV sampling frequency for Ipnovel could have occurred, potentially underestimating IV exposure. Further discussion and justification is needed to confirm that this underestimation does not compromise result reliability (**See LoQ**).

Distribution, metabolism and elimination of midazolam is expected to be comparable between IN administration and IV administration of midazolam; therefore, no additional studies were performed by applicant. No new drug interaction studies with Tuzodi were performed. It is known from previous studies that midazolam is metabolised into an active metabolite 1-hydroxymidazolam and 2 minor inactive metabolites: 4-hydroxy metabolite and 1,4 -hydroxy metabolite. Study MDZ-NS-22 shows that Tuzodi appears to have an extensive distribution (apparent terminal volume distribution range of 104 L) reflecting its high lipid solubility; plasma clearance of Tuzodi was 24.06 L/h and the elimination half-life was 3 hours.

Demonstrating the bioavailability of MDZ under various physiological conditions is of paramount importance. In this regard, it is essential to consider that the unique nasal anatomy of children and the frequent occurrence of respiratory viral infections—which often lead to rhinorrhoea—may adversely affect MDZ absorption. Furthermore, the impact of possible rhinorrhoea has not been adequately studied in the adult population, and the exclusion of such investigations is not justified; therefore, additional studies or a clear rationale addressing this issue in the respective populations is expected (**See LoQ**).

Pharmacodynamics of midazolam delivered by the authorised routes of administration are well-known. Data is provided from scientific literature. No pharmacodynamic studies were conducted in support of the proposed indication for the treatment of prolonged, acute convulsive seizures. The provided pharmacodynamic information of midazolam is deemed adequate to support the therapeutic use of Tuzodi.

Population pharmacokinetic/pharmacodynamic (popPK/PD) model

The popPK/PD modelling was developed based on data from the MDZ NS 22 clinical study, to derive PK/PD properties of midazolam by describing the observed response in terms of sedation in healthy volunteers. Specifically, PK data of midazolam and its metabolite (1-OH midazolam) and sedation data (assessed using Stanford Sleepiness Scale and Observer's Assessment of Alertness/Sedation Scale) were used to develop a PK/PD modelling using Nonlinear Mixed Modelling Effects (NLME).

This model compared the pharmacokinetic profiles of the investigational intranasal product in four strengths (1mg, 2mg, 4 mg and 5 mg) with two IN midazolam formulations (MDZ-1 and MDZ-2.5) against the reference product, Ipnovel. While popPK/PD analysis was aimed to describe the observed response in terms of sedation in healthy volunteers, the respective analysis compared MDZ-1, MDZ-2 and Ipnovel exposure, providing insights relevant to safety assessments. Both IN formulations and reference product demonstrated comparable AUC. Moreover, the IN formulation of MDZ-2.5 was below the established safety threshold of 400 ng/mL in both QD and BID dosing regimens.

Once the optimal popPK/PD model was established, the estimated population parameters (both fixed and random effects) were used to generate an in silico cohort of 100 adult subjects, each one represented by an individual combination of model parameters. The model parameters estimate of fixed and random effects with their corresponding relative standard error (RSE; %) for the final PK/PD model are reported in Section 2.7.2. Each in silico subject underwent a series of simulations testing different treatment regimens of single dose (QD) of Tuzodi (2.5 mg and 5 mg). Additionally, a series of simulations were performed testing the second dose (BID) of Tuzodi administered after 10 minutes.

The results of the popPK/PD analysis suggest that the investigational intranasal product is comparable to the reference product, Ipnovel, thereby overall supporting an acceptable safety profile for the developed intranasal formulation in healthy individuals. However, there are few uncertainties that should be addressed by the applicant before final conclusions. The clinical study *MDZ-NS-22*, used for the popPK analysis, included a study population of 28 healthy individuals (16 males and 12 females) aged 18 to 50 years, with a BMI range of 18.4–27.8 kg/m². The applicant is required to comment on any covariate analysis conducted as part of the popPK modelling. Given that posology for special populations has not been established, a thorough covariate analysis could prove instrumental in assuring appropriate dosing in elderly, obese, liver-impaired, and renal-impaired individuals. However, the homogeneity of the population studied in MDZ-NS-22 is noted, and it is likely that the inclusion of patients representing these special populations, along with an extended covariate analysis, would be necessary to adequately address the concern. **(OC)**

The applicant should provide a table summarizing the physiological characteristics and pharmacokinetic parameters of the patients used in the popPK analysis, thereby clarifying the general dataset included in the final popPK model. **(OC)**

The Visual Predictive Check (VPC) plot for the midazolam intranasal dosage form indicates underprediction at early sampling points. The potential impact of this underprediction on the evaluation of the model's robustness and sensitivity should be discussed. Furthermore, the exclusion of potential covariates that may affect absorption should also be addressed. **(OC)**

In summary, provided popPK was established in appropriate manner and provides adequate estimates for studied adults' population. However, since clinical PK data for the paediatric population is unavailable, the popPK model is not applicable for posology extrapolation to paediatric patients. It is noted that the applicant has provided PBPK-based simulations, however these alone are insufficient to support paediatric dosing recommendations due to the inherent limitations of model-based extrapolation in the absence of clinical pharmacokinetic data. (**See LoQ, MO**). Posology extrapolation through popPK modelling is the preferred approach and should be considered when clinical pharmacokinetic data becomes available.

Physiologically Based Pharmacokinetic (PBPK) model

In addition, to identify suitable posology and support the clinical efficacy of Tuzodi for treatment of prolonged, acute, convulsive seizures in adult and children population and respective subgroups (elderly, hepatically or renally impaired patients) the applicant developed a physiologically based pharmacokinetic (PBPK) model based on literature and MZD-NS-22 study to describe the exposures of both MDZ-1 and MDZ-2.5 in the target populations and to assess these exposures against available comparator formulations (primarily Ipnovel for safety and Buccolam for efficacy).

In the PBPK model, for each population, the optimal Tuzodi dose regimen for anti-epileptic indication was selected, among all trials, based on the comparison with intrabuccal (IB) midazolam (Buccolam) exposure and efficacy threshold for effective seizure control. It has been noted, that Buccolam data were gathered from Nasolam public assessment report (EMEA/H/A-29(4)/1511), The applicant is expected to clarify why Buccolam ePAR was not utilised as the reference source data. (**OC**)

While simulated intranasal doses of Tuzodi produced systemic exposures comparable to IB midazolam Buccolam in the healthy adult population evaluated within the MDZ-NS-22 study and the PK-bridging process for midazolam IN formulation against IV and IB formulations is generally supported, further extrapolation of these findings to special and paediatric populations via PBPK modelling is not supported by the available evidence. Presented PBPK modelling is not enough qualified to support dose recommendations in these populations due to critical limitations in the model structure and lack on available clinical data **(See LoQ, OCs).** Posology recommendations for children that rely heavily on PBPK modelling, especially when supported by only limited or no clinical exposure data, are regarded as applications with significant regulatory impact and requires more sophisticated modelling approach (see the Guideline on the Reporting of Physiologically Based Pharmacokinetic (PBPK) Modelling and Simulation [EMA/CHMP/458101/2016]). The available data for the paediatric population from literature is very sparse and does not correspond to the respective formulation.

Based on PBPK results, a 2.5 mg dose of MDZ-2.5 achieves comparable C_{max} exposure to Buccolam (10 mg) in elderly subjects, whereas a 5 mg dose is required for similar exposure in obese and liver- and renal-impaired populations. This results in a posology recommendation of 5 mg, which does not align with IV or IB midazolam formulations—where prolonged action and reduced clearance are typically expected. Moreover, the absence of PK data for special populations in the literature highlights the need for at least sparse pharmacokinetic data for the newly developed intranasal dosage form. **(See LoQ, MO)** In addition, further clarification and justification is expected regarding established efficacy threshold (17 ng/mL). **(OC)**

At current stage, the proposed posology for special populations and paediatric patients remains unconvincing. Accordingly, additional clinical data and refined popPK and PBPK analysis are expected **(See LoQ, MO)**.

For further comments, please see the SmPC.

3.3.4. Clinical efficacy

3.3.4.1. Dose response study(ies)

No dose response study was provided.

Main studies

The applicant did not perform any efficacy study but provided published clinical studies to support the efficacy of Tuzodi in the intended indication:

> Tuzodi is indicated for the treatment of prolonged, acute, convulsive seizures in adults, adolescents, children and toddlers (from 2 years of age).

Published data from clinical efficacy studies with midazolam hydrochloride administered by the proposed route of administration (intranasal) for the treatment of acute and prolonged seizures in the target population (adults and children) were provided. The efficacy dataset defined from the literature search comprises a total of 17 efficacy studies in the target population treated with the midazolam aqueous solution currently marketed for intravenous use in adults and children ('Ipnovel') by intranasal route as follows:

- 8 non-controlled studies.

- 9 comparative controlled studies (4 vs intravenous diazepam, 5 vs rectal diazepam).

Comparative studies

Table 4: published clinical studies

Author	Study, Design, Setting, Indication	Endpoint: proportion of subjects with seizure cessation defined as:	Age range	Treatment arms N of subjects /Dose
Fisgin et al., 2002 (Turkey)	Comparative controlled, RCT, H, Acute	< 10 min	1-18 years	IM: 22 Dose: 0.2-mg/Kg RD: 23 Dose: 0.3 mg/kg
Mahmoudian and Zadeh, 2004 (Iran)	Comparative controlled, RCT, H, Acute	< 10 min Mann-Whitney (means), χ2	2 months-15 years	IM: 35 Dose: 0.2 mg/Kg ID: 35 Dose: 0.2 mg/kg
Bhattacharyya et al., 2005 (India)	Comparative controlled, RCT, H, Prolonged	< 10 min Student t-test, Fisher, Mann-Whitney, χ2, *U* Wilcoxon	3 months-12 years	IM: 23 Dose: 0.2 mg/Kg RD: 23 Dose: 0.3 mg/kg
Mittal et al., 2006 (Indian)	Comparative controlled , RCT, H	Not specified	< 18 years	IM: 24 Dose: 0.2 mg/Kg ID: 25 Dose: 0.3 mg/kg
Holsti et al., 2007 (USA)	Comparative controlled	< 5 min	8 months-16 years	IM: 39 Dose: 0.2 mg/Kg RD: 18 Dose: 0.3-05 mg/kg
Holsti et al., 2010 (USA)	Comparative controlled, RCT, PH, Prolonged	< 10 min Mann-Whitney, χ2 , *U* Wilcoxon	<18 years	IM: 50 Dose: 0.2 mg/Kg RD: 42 Dose: 0.3-0.5 mg/kg
De Haan et al., 2010 (Netherlands)	Comparative controlled, PH	Not specified	25-69 years	IM: 21 Dose: 10 mg RD: 21 Dose: 10 mg
Javadzadeh et al., 2012 (Iran)	Comparative controlled , H	< 5 min	2 months-15 years	IM: 30 Dose: 0.2 mg/Kg ID: 30 Dose: 0.3 mg/kg

Thakker and Shanbang, 2013 (India)	Comparative controlled, RCT, H, Acute	< 5 min Student t-test or Fisher	1 month-12 years	IM: 27 Dose: 0.2 mg/Kg ID: 23 Dose: 0.3 mg/kg

Prolonged>5min, Status >10 min. IM: intranasal midazolam, ID: Intravenous Diazepam, RD: Rectal Diazepam, H: hospitalised based, PH: prehospital, RCT: randomised controlled trial.

Across the eight publications, most did not report a formal sample size calculation. Randomisation was variably reported; where described, the method was often simple and lacked detail on allocation concealment. Statistical methods were mostly basic and did not account for repeated measures. No publication reported a method for handling missing data. None described adjustment for multiple comparisons or alpha control.

Only Brigo et al. 2015 (meta-analysis) and Holsti 2010 achieve a Moderate level of evidence according to GRADE. Other studies were classified as Low or Very Low due to significant risks of bias, imprecision from small sample sizes, incomplete reporting of methodological elements, and limitations inherent to non-randomised or poorly reported designs.

Methods

- **Study Participants**

One study on the 9 presented included adult participants while 8/9 studies included children ranging from 1 month to 18 years. Eight studies included patients with all type of seizures, while no information is retrieved from. Four studies included patients with a seizure duration of at least 10 minutes and 3 studies of at least 5 minutes (not specified in 2 publications). Thus, most of the studies included patients with at least 5 minutes' duration of seizure but no discussion whether it was the most relevant considering to the heterogeneity in the type of seizure authorised to be included in the different publications is provided. (**OC**)

- **Treatments**

In the provided publications, intranasal midazolam (IM) was compared to either intravenous diazepam (ID) in 4 studies or rectal diazepam (RD). Doses were 0.2mg/kg in children, 10 mg in adults for IM (thus 4 time the proposed dose of 2.5 mg), 0.2mg/kg to 0.3 mg/kg for ID, and 0.3 mg/kg to 0.5 mg/kg in children, 10 mg in adults for RD

Intranasal administration was by the means of an injector, nasal dropper, nasal spray, dropped by syringe, drops, Mucosal Atomisation Device, therefore different from the intended device.

- **Objectives**

Overall, most of the studies described efficacy and safety as objectives without hierarchical specification. All studies compared intranasal midazolam versus intravenous or rectal diazepam in the treatment of acute seizure in paediatric or adult patients (1 study, De Haan et al.).

Only Holsti et al., 2010 described clearly efficacy as primary endpoint.

- **Outcomes/endpoints**

Primary outcomes varied among publications, and whether it was primary or secondary was not always specified when several outcomes were planned.

The most frequent primary outcome for efficacy was the proportion of subjects with seizure cessation < 10 minutes or < 5 minutes (Holsti et al., 2007, Javadzadeh et al., 2012, Thakker and Shanbang, 2013)

"*Time to cessation of seizure after giving drug*" was also analysed in some studies, as well as "*Time to cessation of seizure after arrival at hospital*", and "*time from seizure to start of treatment*", "*total seizure time*".

Safety Outcomes (Vital signs or side effects) were also reported

Some of the publications collected also data on recurrences (Bhattacharyya et al, 2006, De Hann, 2010, Thakker and Shanbang, 2013, Holsti et al., 2007.

Results

- **Participant flow and numbers analysed**

The number of participants and assignment are included in above Table 4, and information on the recruitment are provided in Table 5 below.

Table 5: recruitment periods

Authors	Year	Recruitment Period
Bhattacharyya et al.	2006	Not specified
De Haan et al.	2010	Not specified
Fisgin et al.	2002	Nov. 1997 – Jan. 1999
Holsti et al. (2007)	2007	18 months before/after July 2003
Holsti et al. (2010)	2010	July 2006 – Sept. 2008
Javadzadeh et al.	2012	Oct. 2008 – June 2009
Mahmoudian et al.	2004	Sept. 1998 – Oct. 1999
Mittal et al.	2006	July 2003 – Aug. 2004
Thakker et al.	2012	Jan. 2006 – Dec. 2006

- **Baseline data**

Table 6: Age at baseline in midazolam and comparator group

Reference	Population	Unit	Midazolam	Comparator Diazepam IV or R	P Value
Bhattacharyya et al., 2006		Months, mean (SD)	60.47 (45.38)	74.53 (38.29)	0.29
De Haan et al., 2010	21 adult epileptic patients	Years, mean	40.2		-

Fisgin et al., 2002	45 children (1 month - 13 years)	0-24 months (%)	16 (72.7)	12 (52.1)	-
		25 months to 7 yrs (%)	4 (18.1)	7 (30.4)	
		7+ years (%)	2 (9)	4 (17.3)	
Holsti et al., 2007	124 children in prehospital care	Years, median (range)	4.5 (8 mo-16 years)	2.9 (1-17)	0.27
Holsti et al., 2010	358 epileptic children	Years, median (IQR)	5.6 (2.5-0.7*)	6.9 (3.8-10.8)	-
Javadzadeh et al., 2012	60 children (2 months - 15 years)	Years, median (IQR)	2.3 (1,5)	2.5 (1.2,6)	-
Mahmoudian et al., 2004	70 children (2 months - 15 years)				-
Mittal et al., 2006	125 children (youngest was 11 days old)				>0.05
Thakker et al., 2012	50 children (1 month - 12 years)	Years, mean (±SD)	3.84 (±2.93)	3.97 (±3.33)	-

* As reported in the publication

Table 7: sex in midazolam and comparator group when available

Reference	Treatment Group	N	Males (n, %)	Females (n, %)
Fisgin et al., 2002	Midazolam	24	8 (34.0%)	15 (65.2%)
	Diazepam (R)	22	11 (50.0%)	11 (50.0%)
Thakker et al., 2012	Midazolam	27	15 (55.6%)	12 (44.4%)
	Diazepam (IV)	23	12 (52.2%)	11 (47.8%)
Javadzadeh et al., 2012	Midazolam	30	16 (53.3%)	14 (46.7%)
	Diazepam (IV)	30	17 (56.7%)	13 (43.3%)
Holsti et al., 2007	Midazolam	39	18 (46.2%)	21 (53.8%)
	Diazepam (R)	18	10 (55.6%)	8 (44.4%)
Holsti et al., 2010	Midazolam	50	24 (48%)	26 (52%)
	Diazepam (R)	42	22 (52%)	20 (48%)
Bhattacharyya et al., 2006	Midazolam	46	55.6%	44.4%
	Diazepam (R)		67.9%	32.1%
Mittal et al., 2006	Midazolam	27		
	Diazepam (IV)	22		

De Haan et al., 2010		21	13	8
Mahmoudian, 2004				

Table 8: Type of seizure in midazolam and comparator group when available as described in the publications

Reference	Treatment Group	Type
Bhattacharyya et al., 2006		Number of Episodes (%) (n =188) 1 Simple partial seizures 92 (48.9%) 2 Generalised tonic clonic seizures 70 (37%) 3 Myoclonic seizures 19 (10.1%) 4 Others, e.g., absence, atonic seizures 7 (3.8%)
De Haan et al., 2010		long-lasting tonic–clonic seizures in 11 patients; long lasting tonic, complex partial, or tonic–clonic seizures in six patients; two patients had long lasting tonic–clonic seizures and seizure flurries, two patients had seizure flurries exclusively
Fisgin et al., 2002	Midazolam	simple focal episodes (7), after focal secondarily generalised episode (1), generalised tonic-clonic episodes (14), myoclonic episode (1).
	Diazepam	simple focal episodes (3), after focal secondarily generalised episodes (3), generalised tonic-clonic episodes (14), generalised tonic episode(1), myoclonic episode (1).
Holsti et al., 2007	Midazolam	Seizure NOS (18%), Febrile (10%), Generalised (33%), Complex partial (10%), Metabolic (3%), Status epilepticus (25%)
	Diazepam	Febrile (6%), Generalised (33%), Complex partial (11%), Status epilepticus (50%)
Holsti et al., 2010		No information
Javadzadeh et al., 2012	Midazolam	Simple febrile seizures (17), complex febrile seizures (3), generalised tonic-clonic epilepsy (3), partial seizures with secondary generalisation (2), Lennox-Gastaut syndrome (2), cases of infantile spasms (2), and undetermined case (1)
	Diazepam	Simple febrile seizures (19), complex febrile seizures (3), generalised tonic-clonic epilepsy (4), partial seizures with secondary generalisation (2), Lennox-Gastaut syndrome (1), infantile spasm (1), and no undetermined cases.
Mahmoudian et al., 2004	Midazolam	Generalised tonic-clonic seizures (25), simple partial seizures (3), complex partial seizures (4), and myoclonic seizures (3).
	Diazepam	Generalised tonic-clonic seizures (25), simple partial seizures (3), complex partial seizures (8) and myoclonic seizures (2).

Mittal et al., 2006		Not reported
Thakker et al., 2012		Midazolam: Generalised tonic–clonic (14), Simple partial seizure (6), Complex partial seizure (4), Subtle convulsion (3) Diazepam: Generalised tonic–clonic (16), Simple partial seizure (5), Complex partial seizure (1), Subtle convulsion (1)

*As described in the publication

Table 9: etiology in midazolam and comparator group when available

Reference	Group	Mentioned etiology
Holsti et al., 2007	IN midazolam (n=39)	Seizure NOS (18%), Febrile (10%), Generalised (33%), Complex partial (10%), Metabolic (3%), Status epilepticus (25%)
	PR Diazepam (n=18)	Febrile (6%), Generalised (33%), Complex partial (11%), Status epilepticus (50%)
Mahmoudian et al., 2004	Midazolam (n=35)	Hypocalcaemia (2), Febrile convulsions (14), Epilepsy (14), CNS infection (4), Hyponatremia (1)
	Diazepam (n=35)	Hypocalcaemia (8), Hypoglycaemia (2), Febrile (1), Epilepsy (13), CNS infection (10), Head trauma (1)
Thakker et al., 2012	Midazolam (n=27)	Febrile convulsion (3), Seizure disorder (7), CNS infection (7), Hypocalcaemia (3), Cerebral palsy (4), Hydrocephalus (3)
	Diazepam (n=23)	Febrile convulsion (2), Seizure disorder (6), CNS infection (6), Hypocalcaemia (2), Cerebral palsy (5), Hydrocephalus (2)
De Haan et al., 2010	Adult Patients (n=21)	Cryptogenic (16), Vascular (1), Hereditary dementia (1), Frontotemp dementia (1), Encephalitis (1), Sturge-Weber syndrome (1)
Bhattacharyya et al., 2006	Enfants (n=46)	Epilepsy (39.1%), Degenerative brain disease (21.7%), Neurocysticercosis (15.2%), Others CNS (rest)

- **Outcomes and estimation**

Reference	Comparator	Endpoint	Results	*p*
Proportion of seizure cessation within 5 or 10 minutes				
Fisgin 2002	Rectal diazepam	Proportion of subjects with seizure cessation <10 min	Intranasal midazolam : 87% (20/23) Rectal diazepam group: 60 % (13/22)	p<0,05
Mahmoudian 2004	**Intravenous diazepam**	Proportion of subjects with seizure cessation <10 min	All patients in both groups	p>0.05
Bhattacharyya 2006	Rectal diazepam	Proportion of episodes with seizure cessation <10 min	Intranasal midazolam : 96.7 % (89/92) Rectal midazolam : 88.5% (85/96)	p=0.06
Thakker 2012	**Intravenous diazepam**	Proportion of subjects with seizure cessation <5 min	Intranasal midazolam: 18/27 Intravenous diazepam : 15/23	Not specified
De Haan 2010	Rectal diazepam	Proportion of episodes with seizure cessation (duration not specified)	Intranasal midazolam: 50/61 episode Rectal diazepam group: 56/63 episodes	Not specified
Time to seizure cessation after giving the treatment				
Holsti 2010	Rectal diazepam	Time to seizure cessation (median)	Intranasal midazolam :3.0 min (IQR: 1.0-10.0) Rectal diazepam : 4.3 minutes (IQR: 2.0-14.5)	p=0.09
Javadzadeh 2012	Intravenous diazepam	Time to seizure cessation (mean)	Intranasal midazolam : 3.16 min (SD: 1.24) Intravenous diazepam : 2,16 min (SD:1,02) *Taking into account time to insert IV line* Intranasal midazolam :3.16 min (SD: 1.24) Intravenous diazepam : 6.42 min (SD:2.59)	p= 0.01 p<0.001
Mahmoudian 2004	Intravenous diazepam	Time to seizure cessation (mean)	Intranasal midazolam: 3.58 min (SD 1.68) Intravenous diazepam: 2.94 min (SD 2.62)	p=0.007
Mittal 2006	Intravenous diazepam	Time to seizure cessation (mean)	Intranasal midazolam: 2.97 min (SD 0.53) Intravenous diazepam : 1.92 min (SD 0.45) *After arrival at hospital* Intranasal midazolam: 5.25 min (SD 0.86) Intravenous diazepam : 6.51 min (SD 0.5)	p< 0.001 p<0.001
Thakker 2012	Intravenous diazepam	Time to seizure cessation (mean)	Intranasal midazolam : 3.01 min (SD 2.79) Intravenous diazepam : 2.67 min (SD 2.31) *After arrival at hospital* Intranasal midazolam:6.67 min (SD: 3.12) Intravenous diazepam: 17.18 min (SD: 5.09)	Not specified

IQR: interquartile range

Recurrences

Information on recurrences were rarely reported, but were less frequent in midazolam arm than comparator in 3 publications –Bhattacharya, Thakker and Holsti, 2007) and equivalent in one publication (Thakker and Shanbang).

Supportive studies

Eight non comparative studies assessing intranasal midazolam in patients with acute seizures were provided with all age range (less than 2 years to adults), at doses generally between 0.2 and 0.3 mg/kg. One study (Kyrkou *et. al*) assessed the intended dose of 2.5 mg. Overall 6/8 supportive studies suggest an efficacy of IN midazolam in prolonged acute seizure with the above caveats of singles arms, single centres, low sample size, uncertainties on the relevance of the dosages and on the delivery systems.

In 1 study (Scheepers *et al*.), midazolam was administered twice the recommended dose for Tuzodi and in 1 study (Conroy *et al.*), results were in discrepancy with other publications, with a quarter of the patients who had treatment failure, and another quarter who had partial recovery.

Analysis performed across trials (pooled analyses and meta-analysis)

COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

A Common Reference-Based Indirect Comparison Meta-Analysis of Buccal versus Intranasal midazolam for Early Status Epilepticus (Brigo et al. 2015)

Brigo et al., conducted a systematic review with meta-analysis of intranasal midazolam compared with intravenous and rectal diazepam in the treatment of patients with early status epilepticus (SE) using common reference-based indirect comparison meta-analyses. RCTs comparing intranasal or buccal midazolam versus either intravenous or rectal diazepam for early SE were systematically searched. Random-effects Mantel– Haenszel meta-analyses were performed to obtain odds ratios (ORs) for the efficacy and safety of intranasal or buccal midazolam versus either intravenous or rectal diazepam. Adjusted indirect comparisons were then made between intranasal and buccal midazolam using the obtained results. Fifteen studies, with a total of 1662 seizures in 1331 patients (some studies included patients with more than one episode of SE) were included; 1303 patients were younger than 16 years.

Four studies comparing intranasal midazolam versus intravenous diazepam, with 232 seizures were included (Figure 8). There was no statistically significant difference in clinical seizure cessation after drug administration between the intranasal midazolam and intravenous diazepam groups (OR 0.92, 95 % CI 0.34–2.50). Four studies comparing intranasal midazolam versus rectal diazepam with 449 seizures were included (Figure 9). Compared with rectal diazepam, intranasal midazolam had no statistically significant difference in seizure cessation after drug administration (OR 1.71, 95 % CI 0.65–4.52).

Figure 8. Conventional meta-analysis of studies comparing intranasal midazolam versus intravenous diazepam (clinical seizure cessation after drug administration)

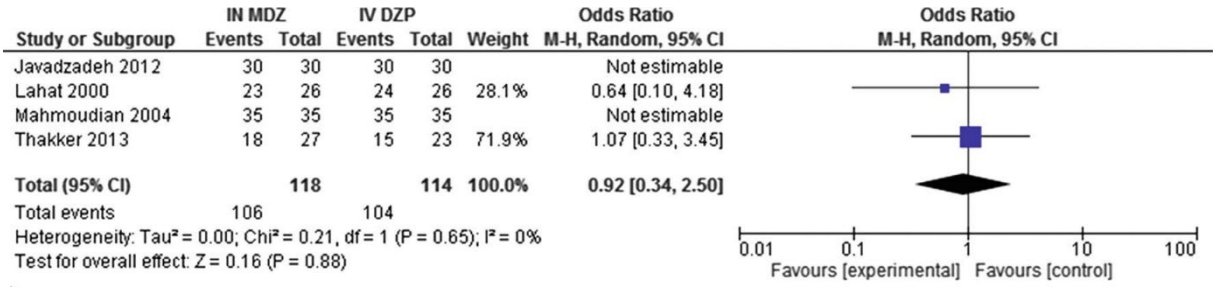
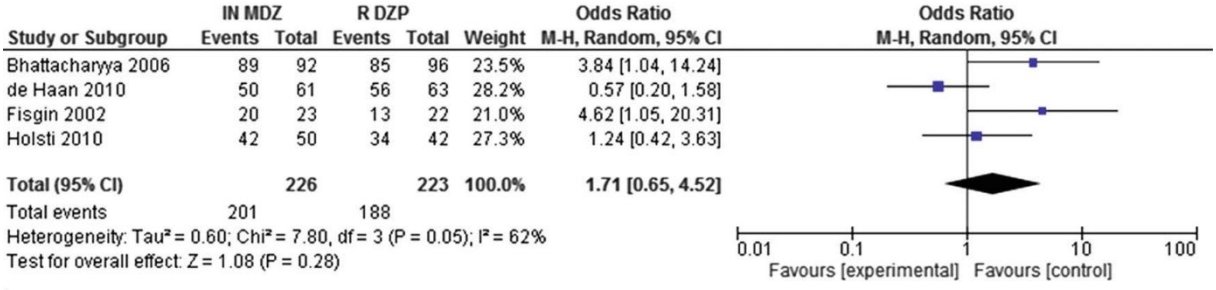


Figure 9 Conventional meta-analysis of studies comparing intranasal midazolam versus rectal diazepam (clinical seizure cessation after drug administration)



Indirect comparisons suggest that intranasal and buccal midazolam share similar efficacy in the treatment of early SE in children. Intranasal midazolam should be used with caution and under clinical monitoring of vital functions. RCTs directly comparing intranasal midazolam with buccal midazolam are required to confirm these findings.

Significant limitations include the indirect nature of the comparison, heterogeneity across studies, lack of prospective protocol registration, limited sensitivity analyses, and imprecision in safety outcomes.

3.3.5. Discussion on clinical efficacy

The applicant is seeking a marketing authorisation for Tuzodi for the treatment of prolonged, acute, convulsive seizures in adults, adolescents, children and toddlers (from 2 years of age).

With regards to clinical efficacy, in the setting of a hybrid application, the module 5 is based on literature only. From a clinical standpoint (not from a regulatory standpoint for which the product reference is Hypnovel), the applicant takes as reference Buccolam which is a buccal midazolam already authorised in prolonged, acute, convulsive seizures in infants from 3 months to adults, thus including the intended population. However, no direct comparison between Tuzodi and Buccolam is available. Therefore, (i) in absence of efficacy studies investigating the effect of Tuzodi and (ii) direct comparison between Tuzodi and Buccolam, the key question is the PK demonstration allowing to rely on Buccolam (see Pharmacological section).

To support the demonstration of the efficacy of intranasal midazolam, the applicant provided then published studies only: (i) 9 studies were comparative assessing intranasal (IN) midazolam versus rectal or intravenous diazepam, and (ii) 8 studies were non-comparative assessing intranasal

midazolam. None of them used the intended device for administration (i.e. nasal spray device). The methodology used to select these publications is not detailed (**OC**), in particular whether some articles were omitted and why, and the lack of direct comparison of oromucosal versus intranasal midazolam is not justified (**OC**).

All class of age were represented in the provided publications, males and females were equally represented in most of the publications, diverse types of seizures (generalised tonic-clonic, simple and complex partial seizure, myoclonic seizures, focal seizures) and etiology (febrile, epilepsy, CNS infection, hypocalcemia, cerebral palsy, cryptogenic, neurocysticercosis) were represented.

Most of the reviewed studies present limitations in key methodological domains including sample size justification, randomisation transparency, statistical analysis robustness, and handling of multiplicity and missing data. While 2 of them (Holsti et al. 2010 and the meta-analysis by Brigo et al. 2015) provide evidence classified as Moderate quality, the majority of the other publications present Low or Very Low levels of evidence according to the GRADE system. The absence of detailed reporting in several areas does not imply that correct methods were not applied during the studies; however, the lack of documentation restricts the ability to fully assess their methodological rigour.

In that perspective, limitations were identified by Brigo et al. in their meta-analysis studying intranasal midazolam compared with intravenous and rectal diazepam in the treatment of patients with early status epilepticus, including reliance on indirect comparisons, wide confidence intervals, limited safety data, and lack of direct PK comparisons. All these further highlight the need for caution when interpreting these findings.

Therefore, all the provided studies can be only considered supportive. Nevertheless, some concerns are raised to address relevant issues, including the methodology used to select the publications, the relevance of the dose of midazolam or comparator, the relevance of the data provided in the elder population, a discussion on recurrences after first seizure cessation, or the heterogeneity of the endpoints and seizures' type. (**OC**) Statements in the SmPC will be reviewed once discussions have been provided.

Regarding the comparatives studies, while no definitive conclusion from the publications can be drawn, and with the reservations of the issues raised above, all the results suggest at least a similar or better efficacy of intranasal midazolam than diazepam (rectal or intravenous) in term of seizure cessation (< 5 or 10 min), or in term of time from arrival at the hospital and cessation of seizure. It is highlighted that although the action of intravenous diazepam from administration to seizure cessation was faster than intranasal midazolam, the time to insert the IV line likely results in a longer total seizure duration. Another point to be considered, is the reported preference of the users for intranasal route over rectal route.

For the non-comparative studies, 6/8 supportive studies suggest an efficacy of IN midazolam in prolonged acute seizure with the above caveats of singles arms, single centres, low sample size, uncertainties on the relevance of the dosages and on the delivery systems.

In one study (Scheepers et al.), midazolam was administered twice the recommended dose for Tuzodi and in another one (Conroy et al.), results were in discrepancy with other publications with a quarter of the patients who had treatment failure. (**OC**)

Furthermore, it is to note that only summaries of the publications are provided in this dossier regarding efficacy, and no discussion is provided by the applicant on the results.

Nonetheless, as commented, buccal midazolam is already authorised in prolonged, acute, convulsive seizures in infants from 3 months to adults, thus including the intended population. Therefore, despite the limitations of the provided publications, the efficacy of midazolam in the treatment of acute seizure

will not be challenged. However, while Buccolam is authorised from 3 months of age, a cut off of 2 years is proposed in the targeted indication despite data are available in the publications in younger patients. (**OC**)

A discussion is also needed on the potential difficulties for lay person to use the delivery system. (**OC**)

Finally, and importantly, while the efficacy of midazolam in the claimed indication can be in principle followed, the use of the intranasal formulation, including the posology in all the claimed populations, need to be reassured by a relevant PK demonstration on exposure and simulations data. However, at the present time, numbers of important uncertainties remain (see pharmacological MO and OC).

3.3.6. Clinical safety

Tuzodi (also referred as to MDZ-2.5) safety is supported by safety data available from the reference product (SmPC Ipnovel 15 mg/3 ml solution for injection; Cheplapharm Arzneimittel GmbH) together with:

- Safety data from the clinical PK study (MDZ-NS-22), an open-label, randomised, 5 periods cross-over study in adults healthy male and female subjects. The primary objective of this study was to assess the pharmacokinetic profiles of intranasally (IN) administered midazolam and its metabolite α-hydroxymidazolam *vs* the intravenous (IV) reference formulation, in male and female healthy subjects. The secondary objectives were to evaluate the general safety, local tolerance of the test drug administered IN, compared to IV reference drug administration, in male and female healthy subjects and to evaluate the sedation level reached with the test drug compared to the reference drug. An exploratory objective was to evaluate the first pass effect after intranasal administration
- Published safety data from studies in adults and children treated with intranasal parenteral, buccal and oral midazolam

Patient exposure, demographic and other characteristics of study population

In MDZ-NS-22 study a single dose of each treatment was administered in randomised order. Each subject received all the 5 treatments as single dose, except two subjects who withdrew the consent before the last administration. Therefore, 28 volunteers were exposed to 1 single dose of MDZ-1 2mg, MDZ-2.5 5mg and Ipnovel, while only 27 were exposed to 1 single dose of MDZ-1 1mg and MDZ-1 4 mg.

Table 10. Demographic characteristics

Characteristic	Statistic	OVERALL
Gender	Female	12 (42.86%)
	Male	16 (57.14%)
Race	White	28 (100.0%)
Age (years)	N (patients)	28 (100.0%)
	Mean (SD)	32.21 (9.78)
	Median	29.00
	Min / Max	18.00 / 49.00

Table 11. Baseline characteristics

Characteristic	Statistic	OVERALL
Body Mass Index (kg/m2)	N (patients)	28 (100.0%)
	Mean (SD)	22.98 (2.91)
	Median	22.25
	Min / Max	18.40 / 27.80
Height (cm)	N (patients)	28 (100.0%)
	Mean (SD)	171.71 (9.08)
	Median	172.50
	Min / Max	154.00 / 191.00
Weight (kg)	N (patients)	28 (100.0%)
	Mean (SD)	68.11 (12.31)
	Median	67.00
	Min / Max	46.00 / 100.00

Table 12. Medical history

Characteristic	Statistic	OVERALL
Medical condition	No	4 (14.29%)
	Yes	24(85.71%)
Involved system	Total	54(100.0%)
	Blood and lymphatic system disorders	1(1.85%)
	Cardiac disorders	1 (1.85%)
	Congenital, familial and genetic disorders	2(3.70%)
	Eye disorders	13(24.07%)
	Gastrointestinal disorders	2(3.70%)
	Hepatobiliary disorders	2(3.70%)
	Immune system disorders	5(9.26%)
	Infections and infestations	2(3.70%)
	Injury, poisoning and procedural complications	10(18.52%)
	Musculoskeletal and connective tissue disorders	6(11.11%)
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1(1.85%)
	Pregnancy, puerperium and perinatal conditions	1(1.85%)
	Renal and urinary disorders	1(1.85%)
	Reproductive system and breast disorders	3(5.56%)
	Respiratory, thoracic and mediastinal disorders	3(5.56%)
	Skin and subcutaneous tissue disorders	1(1.85%)

Table 13. Surgical history

Characteristic	Statistic	OVERALL
Surgery in the past	No	14 (50.00%)
	Yes	14 (50.00%)
Type of surgery	Total	24 (100.0%)
Adenoidectomy		2 (8.33%)
Caesarean Section		3 (12.50%)
Circumcision		1 (4.17%)
Female Sterilisation		1 (4.17%)
Fistulotomy		1 (4.17%)
Flatfoot Reconstruction		1 (4.17%)
Intervertebral Disc Operation		1 (4.17%)
Ligament Operation		1 (4.17%)
Myopia Correction		1 (4.17%)
Nasal Septal Operation		4 (16.67%)
Orthopaedic Procedure		1 (4.17%)
Promotion Of Wound Healing		1 (4.17%)
Skin Neoplasm Excision		2 (8.33%)
Tonsillectomy		1 (4.17%)
Varicocele Repair		3 (12.50%)

3.3.6.1. Adverse events

Overall, 69 adverse events were recorded in 27 subjects during the study. All the 69 adverse events were Treatment emergent adverse events (TEAEs). Three TEAE were evaluated as not related to the study treatment, 4 were assessed as unlikely related and 62 were judged as probably related. Sixty-one TEAE, of the 62 probably related TEAE, were solicited by the Investigator while only one probably related TEAE was spontaneously reported by the subject.

The majority (91.3%) of the TEAEs were of mild severity and only few (8.7%) were moderate.

No Serious TEAE, drug-related Serious TEAE, TEAE with fatal outcome, drug-related TEAE with fatal outcome occurred. No TEAE nor drug-related TEAE leading to premature study discontinuation occurred during the study.

Seven TEAEs occurred when subjects were treated with MDZ-1 1 mg, 11 TEAEs with MDZ-1 2 mg, 16 TEAEs with MDZ-1 4 mg, 26 TEAEs with MDZ-2.5 5 mg and 9 TEAEs with Ipnovel 2.5 mg.

Table 14. TEAEs by SOC and PT

SOC	TEAE (PT)	TEAE no.	Treatment Group	Maximum severity	Relationship to study treatment	Outcome	Study interruption due to AE
General Disorders and Administration Site Conditions	*Hyperpyrexia*	1	MDZ-1 2mg	Moderate	Unlikely	Resolved	No
Musculoskeletal and Connective Tissue Disorders	*Back Pain*	1	Ipnovel	Moderate	Not Related	Resolved	No
Nervous System Disorders	*Anterograde Amnesia*	6	MDZ-1 1mg	Mild	Probable	Resolved	No
		9	MDZ-1 2mg	Mild	Probable	Resolved	No
		16	MDZ-1 4mg	Mild	Probable	Resolved	No
		22	MDZ-2.5 5mg	Mild	Probable	Resolved	No
		8	Ipnovel	Mild	Probable	Resolved	No
	Headache	1	MDZ-1 1mg	Moderate	Unlikely	Resolved	No
		1	MDZ-1 2mg	Moderate	Unlikely	Resolved	No
		2	MDZ-2.5 5mg	Moderate	1 Unlikly 1 Not related	Resolved	No
Psychiatric Disorders	*Insomnia*	1	MDZ-2.5 5mg	Mild	Probable	Resolved	No
Reproductive System and Breast Disorders	*Dysmenorrhea*	1	MDZ-2.5 5mg	Moderate	Not Related	Resolved	No

3.3.6.2. Serious adverse event/deaths/other significant events

Anterograde amnesia

Anterograde amnesia was actively detected by the Investigator, according to a specific procedure: each subject was told a simple sentence 15 minutes after midazolam administration. Then at 30, 60 and 120 minutes the subject was asked to remember the sentence, through a targeted question. If the subject did not remember the sentence, it was repeated to him/her. The test continued if amnesia was still present at 120 minutes after dosing.

An increasing percentage of subjects with anterograde amnesia was observed with higher doses of midazolam: Amnesia was detected in about 22% (n=6 subjects), 32% (n=9 subjects), 59% (n=16 subjects) and 79% (n=22 subjects) of subjects treated respectively with MDZ-1 1mg, MDZ-1 2mg, MDZ-1 4mg, MDZ-2.5 5mg. In the Ipnovel 2.5mg group the 29% (n=8 subjects) of the subjects had the amnesia.

The event anterograde amnesia was registered at each timepoint to evaluate the incidence and duration of the amnesia; at the same time, it was recorded as a TEAE. Overall, considering all the experimental drug administrations, 61 events of anterograde amnesia.

In total, amnesia was detected at least once in 26 subjects (some of whom experienced it on more than one occasion, at different doses).

The duration of the amnesia was analysed by treatment group including the subjects who reported this event: the overall mean value was 74.79 minutes, with a minimum of 30.00 minutes to a maximum of 210.00 minutes. The group with the minimum average duration was MDZ-1 1 mg with 45.00 minutes; the duration increased to 50.00 minutes with MDZ-1 2 mg, 69.50 minutes with MDZ-1 4 mg, and up to 96.82 minutes when MDZ-2.5 5 mg was administered. Ipnovel induced an anterograde amnesia duration of 75.00 minutes.

Nasal tolerability

Table 15. Nasal congestion or stuffiness statistically significant change

No. of subjects per symptom severity and per treatment group and %	Absent	Mild	Moderate	Severe
Nasal congestion or stuffiness at pre-dose				
MDZ-1 1 mg	21 (77.78%)	6 (22.22%)	-	-
MDZ-1 2 mg	24 (85.71%)	4 (14.29%)	-	-
MDZ-1 4 mg	24 (88.89%)	3 (11.11%)	-	-
MDZ-2.5 5 mg	23 (82.14%)	5 (17.86%)	-	-
Ipnovel	23 (82.14%)	5 (17.86%)	-	-
Nasal congestion or stuffiness at time point 5 minutes (p-value=0.0071)				
MDZ-1 1 mg	20 (74.07%)	7 (25.93%)	-	-
MDZ-1 2 mg	12 (42.86%)	12 (42.86%)	4 (14.29%)	-
MDZ-1 4 mg	15 (55.56%)	12 (44.44%)	-	-
MDZ-2.5 5 mg	16 (57.14%)	11 (39.29%)	1 (3.57%)	-
Ipnovel	24 (85.71%)	4 (14.29%)	-	-

Table 16. Nasal irritation or itching statistically significant change

No. of subjects per symptom severity and per treatment group and %	Absent	Mild	Moderate	Severe
Nasal irritation or itching before dosing				
MDZ-1 1 mg	27 (100.0%)	-	-	-
MDZ-1 2 mg	27 (96.43%)	1 (3.57%)	-	-
MDZ-1 4 mg	27 (100.0%)	-	-	-
MDZ-2.5 5 mg	28 (100.0%)	-	-	-
Ipnovel	28 (100.0%)	-	-	-
Nasal irritation or itching at time point 5 minutes (p-value<0.0001)				
MDZ-1 1 mg	12 (44.44%)	12 (44.44%)	3 (11.11%)	-
MDZ-1 2 mg	11 (39.29%)	13 (46.43%)	2 (7.14%)	2 (7.14%)
MDZ-1 4 mg	14 (51.85%)	10 (37.04%)	2 (7.14%)	1 (3.70%)
MDZ-2.5 5 mg	13 (46.43%)	11 (39.29%)	3 (10.71%)	1 (3.57%)
Ipnovel	28 (100.0%)	-	-	-
Nasal irritation or itching at time point 30 minutes (p-value 0.0315)				
MDZ-1 1 mg	23 (85.19%)	3 (11.11%)	1 (3.70%)	-
MDZ-1 2 mg	24 (85.71%)	3 (10.71%)	1 (3.57%)	-
MDZ-1 4 mg	20 (74.07%)	5 (18.52%)	1 (3.70%)	1 (3.70%)
MDZ-2.5 5 mg	19 (67.86%)	8 (28.57%)	-	1 (3.57%)
Ipnovel	28 (100.0%)	-	-	-

Table 17. Runny nose statistically significant change

No. of subjects per symptom severity and per treatment group and %	Absent	Mild	Moderate	Severe
Runny nose before dosing				
MDZ-1 1 mg	24 (88.89%)	3 (11.11%)	-	-
MDZ-1 2 mg	27 (96.43%)	1 (3.57%)	-	-
MDZ-1 4 mg	27 (100.0%)	-	-	-
MDZ-2.5 5 mg	28 (100.0%)	-	-	-
Ipnovel	28 (100.0%)	-	-	-
Runny nose at time point 5 minutes (p-value<0.0001)				
MDZ-1 1 mg	17 (62.96%)	10 (37.04%)	-	-
MDZ-1 2 mg	15 (53.57%)	9 (32.14%)	4 (14.29%)	-
MDZ-1 4 mg	10 (37.04%)	15 (55.56%)	1 (3.70%)	1 (3.70%)
MDZ-2.5 5 mg	14 (50.00%)	13 (46.43%)	1 (3.57%)	-
Ipnovel	28 (100.0%)	-	-	-
Runny nose at time point 30 minutes (p-value 0.0019)				
MDZ-1 1 mg	26 (96.30%)	1 (3.70%)	-	-
MDZ-1 2 mg	20 (71.43%)	8 (28.57%)	-	-
MDZ-1 4 mg	21 (77.78%)	6 (22.22%)	-	-
MDZ-2.5 5 mg	21 (75.00%)	7 (25.00%)	-	-
Ipnovel	28 (100.0%)	-	-	-

Table 18. Nasal pain or discomfort statistically significant change

No. of subjects per symptom severity and per treatment group and %	Absent	Mild	Moderate	Severe
Nasal pain or discomfort before dosing				
MDZ-1 1 mg	27 (100.0%)	-	-	-
MDZ-1 2 mg	27 (96.43%)	1 (3.57%)	-	-
MDZ-1 4 mg	27 (100.0%)	-	-	-
MDZ-2.5 5 mg	28 (100.0%)	-	-	-
Ipnovel	28 (100.0%)	-	-	-
Nasal pain or discomfort at time point 5 minutes (p-value 0.0014)				
MDZ-1 1 mg	17 (62.96%)	9 (33.33%)	-	1 (3.70%)
MDZ-1 2 mg	16 (57.14%)	10 (35.71%)	2 (7.14%)	-
MDZ-1 4 mg	16 (59.26%)	9 (33.33%)	1 (3.70%)	1 (3.70%)
MDZ-2.5 5 mg	16 (57.14%)	8 (28.57%)	3 (10.71%)	1 (3.57%)
Ipnovel	28 (100.0%)	-	-	-
Nasal pain or discomfort at time point 30 minutes (p-value 0.0221)				
MDZ-1 1 mg	25 (92.59%)	1 (3.70%)	1 (3.70%)	-
MDZ-1 2 mg	25 (89.29%)	2 (7.14%)	1 (3.57%)	-
MDZ-1 4 mg	22 (81.48%)	4 (14.81%)	1 (3.70%)	-
MDZ-2.5 5 mg	20 (71.43%)	7 (25.00%)	-	1 (3.57%)
Ipnovel	28 (100.0%)	-	-	-
Nasal pain or discomfort at time point 1 hour (p-value 0.0083)				
MDZ-1 1 mg	27 (100.0%)	-	-	-
MDZ-1 2 mg	28 (100.0%)	-	-	-
MDZ-1 4 mg	24 (88.89%)	3 (11.11%)	-	-
MDZ-2.5 5 mg	23 (82.14%)	4 (14.29%)	1 (3.57%)	-
Ipnovel	28 (100.0%)	-	-	-

No serious adverse event, deaths or other significant events occurred in the clinical PK study (MDZ-NS-22).

3.3.6.3. Laboratory findings

Changes in clinical chemistry, haematology and urinalysis were monitored at screening, to assess subjects' eligibility and at final visit. No change was assessed as relevant or requiring study interruption.

In the five treatment groups the diastolic blood pressure (DBP) decreased as early as 15 minutes after dosing and for up to 2 hours later; after 4 hours from dosing the DBP increased slightly compared to baseline in all groups. Overall, the mean diastolic blood pressure at screening (69.71 mmHg) was similar to that registered at the end of study visit (68.96 mmHg).

A similar behaviour was observed for the systolic blood pressure (SBP): decreases as early as 15 minutes after dosing and up to 2 hours later, after 4 hours the SBP increased slightly compared to

baseline in all groups, except the MDZ-2.5 5 mg group, where the mean value continued to be slightly below the initial one. Overall, the mean systolic blood pressure at screening (116.43 mmHg) was similar to that registered at the end of study (114.39 mmHg).

The mean oxygen saturation at screening visit was 99.21%; before each dosing, the average value was about 99% and varied between 98.74% of MDZ-1 4 mg and 98.93% of MDZ2.5 5 mg. After each dosing session, all subjects had oxygen saturation ≥ 90%.

Overall, the mean pulse rate remained constant during the study: at screening, pulse was 63.00 beats/min and at the end of study 63.82 beats/min. During the study, the trend across Overall, the mean respiratory rate remained constant during the study: at screening, respiratory rate was 15.14 breaths/min and 15.29 breaths/min at the end of study. The average respiratory rate remained constant across treatment groups. There were no differences in the body temperature of subjects during the study; at screening, the average temperature was 36.33 °C, before each dosing average values remained similar to that of the screening and at the end of the study the average temperature was 36.42 °C. Some abnormalities were registered at screening (surgical scarring due to C-section, myopia and presbyopia, surgical scarring caused by nevus removal, sinus arrhythmia, ejective systolic heart murmur, palpable lymph nodes and shoulders hypomobility) but no change was evidenced at following examinations. At screening 57.14% of subjects (16) had normal ECG evaluation and 42.86% (12) had some not clinically significant abnormalities in the ECG trace. A similar behaviour was observed at the end of the study: 50.00% (14) of subjects had normal ECG evaluation and the remaining 50.00% (14) had abnormal not clinically significant ECG evaluation.

3.3.6.4. In vitro biomarker test for patient selection for safety

Not applicable.

3.3.6.5. Safety in special populations

Not applicable.

3.3.6.6. Immunological events

Not applicable.

3.3.6.7. Safety related to drug-drug interactions and other interactions

Not applicable.

3.3.6.8. Discontinuation due to adverse events

Not applicable.

3.3.7. Post marketing experience

Table 19. Overall exposure to midazolam from published studies

	Route	Number of patients
ADULTS	Intranasal	282
	Parenteral	860
	Oral	65
Total adults		1207
CHILDREN	Intranasal	4632
	Buccal	439
	Oral	2518
	Parenteral	558
Total children		8147

Supportive safety data from published studies with midazolam administered intranasally

Table 20. List of published clinical safety studies

Author/ N subjects (route of administration)/Dose	Safety results (%of subjects)
Safety data from published studies treated with midazolam administered intranasally	
Scheepers et al., 2000 N=22 (IT) Dose: 5 mg <50 Kg, 10 mg >50 kg	No adverse events reported
Jeannet et al., 1999 N=26 (IT) Dose: 0.2 mg/Kg	Dizziness (4%) Skin irritation (4%)
Kutlu et al., 2000 N=9 (IT) Dose: 0.3 mg/Kg	Respiratory depression (11%)
Conroy et al., 2000 N=20 (IT) Dose: 0.2 mg/Kg	No adverse events reported
Fisgin et al., 2002 N=22 (IT) Dose: 0.2 mg/Kg	Tachypnea (4%) Tachycardia (4%)
Harbord et al., 2004	Occasionally nasal irritation

N=22 (IT) Dose: 0.2-0.3 mg/Kg	
Mahmoudian and Mohammadi 2004 N=35 (IT) Dose: 0.2 mg/Kg	No adverse events reported
Bhattacharyya et al., 2005 N=23 (IT) Dose: 0.2 mg/Kg	No adverse events reported
Holsti et al., 2010 N=50 (IT) Dose: 0.2 mg/Kg	Respiratory depression (4%) and (1%) requiring intubation
De Hann et al., 2010 N=21 (IT) Dose: 10 mg	Drowsiness (68%) Local irritation (sneezing, coughing, dry mouth, tear flow) (29%) Sedation (45%) Restlessness (9%)
Mellion et al., 2013 N= 4324 (IT) Dose: 0.2 mg/Kg	Airway obstruction (21.7%) Cough (6.5%) Prolonged desaturation (>30 seconds) 12%, (14.1%) required airway support with bag-valve-mask ventilation. Agitation (8.7%)
Thakker and Shanbang, 2013 N=27 (IT) Dose: 0.2 mg/Kg	No adverse events reported
Bancke et al., 2015 N=25 (IT)	Nasal discomfort (84%) Throat irritation (84%)

Dose: 2.5-7.5 mg	Increased lacrimation (76%) Dysgeusia (72%)
Detyniecki et al., 2019 N=134 Dose: 10 mg	*Clinic test dose phase (TDP) N=91* Somnolence (10%) Headache (7%) Dysarthria (2%) Nasal Discomfort (5%) Throat Irritation (2%) Rhinorrhea (3%) Eyes lacrimation Increased (1%) *Comparative phase (CP) N=43* Somnolence (9%) Headache (2%) Dysarthria (2%) Nasal Discomfort (16%) Throat Irritation (7%) Rhinorrhea (5%) Eyes lacrimation Increased (2%)

Supportive safety data from published extensive clinical experience with parenteral buccal and oral exposure of children and adults to midazolam

Bayat and Arscott 2003 N=421(IV) Dose: 0.15–0.35 mg kg	No adverse events reported
Mui et al., 2005 N=65 (O) Dose: 7.5 mg	Hypotension (6.2%) Desaturation (4.5%)
Wilson et al., 2011 N=401 (IV) Dose: 7.6 mg	Respiratory depression (1%) Over-sedation (0.2%)

Scott et al., 1999 N=18 (B) Dose: 10 mg	No adverse events reported
Wilson et al., 2004 N=39 (B) Dose: 0.2 mg/kg	No adverse events reported
Mcintyre et al., 2005 N=92 (B) Dose: 2.5 -10 mg	Respiratory depression (5%)
Baysun et al., 2005 N=23 (B) Dose: 0.25 mg/kg	Non-paroxysmal coughing for 1-2mins, resolved spontaneously (4%)
Mpimbaza et al., 2008 N=165 (B) Dose: 0.5 mg/kg	Aphasia 12 hours after buccal midazolam considered unlikely related (1%) Intense pruritus (1%) Respiratory depression (1%)
Talukdar B et al., 2009 N=60 (B) Dose: 0.2 mg/kg	No adverse events reported
Silbergleit et al., 2012 N=448 (IM) Dose: 5-10 mg	Hypotension (2.7%) IM injection-site complications (0.9%)
Momen et al., 2014 N=50 (IM) Dose: 0.3 mg/kg	No adverse events reported
Papineni et al., 2017 N=486(RCT) (O) N=2032 (NO RCT) (O) Dose: 0.5-1 mg/kg	RCT: Nausea and vomiting (30, 6%). NO RCT: paradoxical reaction (3.8%)

3.3.8. Adverse Drug Reactions (ADRs) in the SmPC

Table 21. Adverse drug reactions in the SmPC

System Organ Class	Frequency	Adverse Drug Reaction
Immune System Disorders	Not known	- Hypersensitivity, - Angioedema, - Anaphylactic shock
Psychiatric disorders	Not known	- Disorientation, - Emotional and mood disturbances, - Changes in libido, - Excitation*, - Physical drug dependence and withdrawal syndrome - Abuse
	Very rare:	- Aggression* - Agitation* - Hostility* - Anger* - Confusional state - Euphoric mood - Hallucination
Nervous system disorders	Common:	- Decreased alertness - Depressed levels of consciousness - Sedation (prolonged and postoperative) - Somnolence
	Very rare	- Headache - Dizziness - Ataxia - Anterograde amnesia** - Involuntary movements (including tonic/clonic movements and muscle tremor) * - Hyperactivity* - Paradoxical reactions The duration of which is directly related to the administered dose - Drug withdrawal convulsions
Cardiac disorders	Very rare	- Bradycardia - Cardiac arrest
Vascular Disorders	Very rare	- Hypotension - Vasodilation
Respiratory system disorders	Common	- Sneezing - Cough - Itching nose - Nasal congestion - Nasal dryness - Rhinorrhoea - Yawning - Respiratory depression

	Very rare	- Apnoea - Dyspnoea - Laryngospasm - Respiratory arrest - Hiccups

Rapporteur's comment :

Overall, the list of ADRs in the proposed section 4.8 of Tuzodi SmPC appears to be derivate from sections 4.8 of Buccolam and Ipnovel as well as from AEs reported in the main PK study. However, the applicant has not provided any justification for the proposed list of ADRs in the SmPC. The methodology used should be explained (**OC**).

As a general remark, Preferred Terms (PTs) from the MedDRA classification should be used to describe ADRs in section 4.8. Comments have been made in the Product Information (PI) in this regard (**see PI**).

Furthermore, some minor changes have been made by the applicant regarding ADRs compared to those in Buccolam and this should be justified (**see PI**).

Additionally, the applicant is requested to justify the reason why some ADR listed in sections 4.8 of Buccolam or Ipnovel are not listed in section 4.8 of Tuzodi. This is the case for Kounis syndrome, thrombophlebitis, thrombosis (listed in section 4.8 of Ipnovel SmPC) and for Seizure (listed in section 4.8 of Buccolam SmPC) (**OC**). To be noted, the ADR Convulsions, reported in premature infants and neonates is listed in section 4.8 of Ipnovel SmPC. This ADR is not considered adequate in Tuzodi PI considering the claimed indication from 2 years of age.

Conversely, some ADRs are listed in the Tuzodi SmPC but not in the Buccolam or Ipnovel SmPCs, and are not considered to be specifically related to the intranasal route of administration. This is the case for Paradoxical reactions, Cough and ADRs under the SOC Eye disorders. A justification should be provided by the applicant (**OC**).

Specifically, the addition of ADR abuse, Physical drug dependence and withdrawal syndrome and Drug withdrawal convulsions is questionable. Indeed, section 4.4 of Ipnovel SmPC states that "Dependence: When midazolam is used in long-term sedation in ICU, it should be borne in mind that physical dependence on midazolam may develop. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a medical history of alcohol and/or drug abuse (cf section 4.8)". Considering that Tuzodi is indicated in the treatment of prolonged, acute, convulsive seizures, no long-term use is anticipated. Hence the applicant is requested to justify the addition of the ADRs abuse and Physical drug dependence and withdrawal syndrome in the context of the clinical context of Tuzodi and to modify according the product information (**OC**).

Finally, regarding ADRs related to intranasal administration, as stated in section 3.5.3.3 of this AR, Itching nose should be replace with the MedDRA PT Nasal pruritus (**see PI**). Based on safety data from the PK study, Rhinalgia and nasal discomfort should be added under the SOC Respiratory system disorders (**OC**). The addition of Nasal dryness, which was not reported in the PK study, should be justify or deleted (**OC**).

In other respects, comments have been made in sections 4.3 and 4.4 of the SmPC. The package leaflet should be updated accordingly (**see PI**).

3.3.9. Discussion on clinical safety

The applicant applied for a marketing authorisation for Tuzodi, a midazolam nasal spray solution, 2.5mg/spray, as an hybrid of the reference product Ipnovel 15 mg/3 mL solution for injection, 2.5 mg. To support this application, the applicant provided the following safety data:

i. A clinical pharmacokinetic (PK) study (MDZ-NS-22): an open-label, randomised, 5 periods cross-over trial in adult healthy subjects. The primary objective was to assess the PK profile of intranasally (IN) midazolam and its metabolite *vs* the intravenous (IV) reference formulation. The secondary objectives were to evaluate the general safety, local tolerance and sedation level compared to Ipnovel. An exploratory objective was to evaluate the first pass effect after intranasal administration.

ii. Published safety data from studies in adults and children treated with intranasal parenteral, buccal and oral midazolam.

Midazolam is a benzodiazepine currently approved in the EU for insomnia, anaesthetic premedication and/or sedation that is available for intravenous, intramuscular, rectal or oral use. An oromucosal solution, Buccolam, was authorised in 2011 (EMEA/H/C/002267 – hybrid application) for the treatment of prolonged, acute, convulsive seizures in infants from 3 months to adults. Since the applicant is proposing an hybrid application as legal basis and considering that midazolam is a substance for which the safety profile is well-known, the PK clinical study and review of published safety data is acceptable.

PK study MDZ-NS-22

Exposure, demographics and baseline characteristics

In the clinical PK study (MDZ-NS-22), 28 healthy subjects were planned and enrolled in the study. Each patient received successively each single dose of midazolam IN MDZ-1 1 mg, MDZ-1 2 mg, MDZ-1 4 mg, MDZ-2.5 5 mg [the claimed posology] and Ipnovel IV 2.5 mg, in randomised order.

Regarding characteristics of the study population, the sex ratio was of 1.3 in the PK study, all subjects were Caucasian and the median age was 29 [18 –48 years]. Among baseline characteristics, median and mean BMI, weight and height were similar, respectively around 22 kg/m², 67 kg and 172 cm.

Twenty-four (86%) participants had a medical history. The most frequent belonged to the SOCs Eye disorders (n=13, 24%) and Injury, poisoning and procedural complications (n=10, 19%). The applicant did not detail the PT associated with these SOCs nether discussed the possible impact of such medical history on the safety of midazolam (**OC**). Fifteen patients (54%) had ongoing medical conditions at screening, mainly from the SOC Eye disorders (PT myopia, presbyopia, astigmatism and conjunctivitis allergic) and Immune system disorders (allergy to chemicals, seasonal allergy, allergy to plants). Half of the participants reported past surgery, mainly nasal septal operation (n=4, 17%), varicocele repair and caesarean section (n=3, 13% each). A discussion about TEAEs observed in patients with past surgery of nasal septal operation should be provided by the applicant (**OC**).

Overall, demographics and baseline characteristics does not raise particular concerns from a safety point of view.

Adverse events

Among the 28 patients exposed to midazolam during the clinical PK study, 69 treatment emergent adverse events (TEAEs) were reported in 27 subjects. The majority was considered to be related to midazolam (n=62, 90%) whereas 7 (10%) TEAEs were considered as not related or unlikely related to the midazolam. The majority (91%) of the TEAEs were of mild severity while the remaining 9% were of moderate severity.

A dose-related toxicity was observed: 7 (26%) TEAEs occurred when subjects were treated with MDZ-1 1 mg, 11 (39%) TEAEs with MDZ-1 2 mg, 16 (59%) TEAEs with MDZ-1 4 mg, 26 (93%) TEAEs with MDZ-2.5 5 mg and 9 (32%) TEAEs with Ipnovel 2.5 mg.

Most of the TEAEs were in the SOC Nervous System Disorders SOC (n=65, 94%) with the PT anterograde amnesia reported in 61 (88%) participants and the PT headache in 4 (6%) participants. Anterograde amnesia was actively monitored as part of the study (see below). Additionally, one TEAE of each hyperpyrexia (unlikely related to midazolam), back pain (not related), insomnia (probably related) and dysmenorrhea (not related) were also reported. Section 4.8 of the proposed SmPC did not list Insomnia as an adverse reaction. Given that the applicant has reported a case of insomnia considered probably related to MDZ-2.5 5 mg, a justification for the absence of this TEAE in the product information is required (**OC**). No TEAE led to premature interruption of the study.

Adverse events of special interest (AESI)

The applicant actively detected anterograde amnesia during the clinical PK study (MDZ-NS-22) by using a specific procedure: each subject was told a simple sentence 15 minutes after midazolam administration and the subject was asked to remember it at 30, 60 and 120 minutes. Overall, anterograde amnesia was detected at least once in 26 subjects (93%); some of whom experienced it on more than one occasion, at different doses. 79% of participants had anterograde amnesia after receiving the IN MDZ-2.5 5 mg dose compared to 29% after Ipnovel administration (2.5 mg) meaning that participants receiving the IN MDZ-2.5 5 mg had more than 2 times the frequency of this AE compared to the IV 2.5 mg reference. A dose-related toxicity was observed in terms of number of participants and duration of the anterograde amnesia with the highest values for the claimed IN dosage. All anterograde amnesia cases were mild and considered as probably related to the study drug. This is a known effect for midazolam and the proposed SmPC well reflects this AESI but the frequency of this ADR should be justified (**OC**).

Local tolerability was assessed through the analysis of subjective nasal symptoms evaluation and nasal examination by Ear Nose Throat (ENT) specialist. Subjective nasal symptoms evaluation and nasal examination were summarised using frequencies and percentages of subjects in each category by treatment. midazolam hydrochloride exhibits high water solubility at low pH (<4.0) and increased lipid solubility at physiological pH. This behaviour is driven by the molecule's ionisation and the pH-dependent opening and closing of its benzodiazepine ring, mechanisms that facilitate rapid absorption and blood-brain barrier penetration. Although Tuzodi is formulated at a pH of 3.3–3.8, that is lower than the typical human nasal mucosal pH of 5.5–6.5, experience with a similarly formulated product (Nasolam) and favourable local tolerability findings from the MDZ-NS-22 study indicate that significant local irritation is unlikely.
The applicant specifically observed nasal congestion of stuffiness; nasal irritation or itching; runny nose; nasal pain or discomfort at different time points:

- For Nasal congestion of stuffiness, the percentage of nasal congestion of stuffiness (all mild) remained similar for subjects receiving MDZ-1 1 mg (IN) and Ipnovel (IV) at time point 5 min but strongly increased for MDZ-1 2 mg (4, 14% to 16, 57% including 14% of moderate); MDZ-1 4 mg (3, 11% to 12, 44%); MDZ-2.5 5 mg (5, 18% to 12, 44% including 4% of moderate).
- Nasal irritation or itching was mainly reported at 5 minutes, then decreased at 30 minutes (without returning to pre midazolam values), in terms of number of participants and severity. At 5 min, 10 (37%) participants experienced mild TEAEs, 2 (7%) moderate TEAEs and 1 (4%) severe TEAE. At 30 min, 5 (19%) participants experienced mild TEAEs, 1 (4%) moderate TEAE and 1 (4%) severe TEAE. After receiving MDZ-1 2 mg and MDZ-1 1 mg, a similar trend was observed. For the claimed MDZ-2.5 5 mg, results were similar at 5 min but 8 participants (30%) still had mild nasal irritation or itching at 30 min compared to 5 (19%) for MDZ-1 4 mg and 3 (11%) for

MDZ-1 2 mg and 1 mg, meaning that this effect appears to be longer-lasting in patients treated with the claimed dose.

- Runny nose was mainly reported at 5 min post administration from 37% after MDZ-1 1 mg to 63% after MDZ-1 4 mg (including 1 severe TEAE). At 30 min, runny nose (all mild) were reported in less than 30% of participants for all dosages.
- For nasal pain or discomfort, between 10 (37%) and 12 (43%) of participant had this TEAE at 5 min in each dose of midazolam. For MDZ-1 1, 2 and 4 mg, nasal pain decreased at 30 minutes (from 7% to 19%) and only 3 participants with MDZ-1 4 mg (11%) had mild TEAE at 1 hour. In participants with MDZ-2.5 5 mg, this TEAE persisted at 30 min in 8 (29%) participants and decreased to 5 (18%) at 1 hour.

The applicant listed Nasal congestion, Itching nose (to be replaced by the MedDRA term Nasal pruritus, **OC**) and Rhinorrhoea in section 4.8 of the SmPC and accordingly in the PL. This is endorsed. Rhinalgia and nasal discomfort should be added (**OC**) based on these results. Overall, TEAEs related to nasal tolerability spontaneously resolved within one hour of administration.

The applicant also indicated that "almost none of the subjects had loss or impairment of smell at any time point". A detail of case is requested, with details of clinical examination and outcome of the cases is requested with a discussion on the need to complete section 4.8 of the SmPC and accordingly in the PL (**OC**). Additionally, the applicant is requested to justify the common frequency of the proposed AE in section 4.8 (**OC**).

No data was provided regarding one of the secondary objective of the PK study, namely "To evaluate the sedation level reached with the test drug compared to the reference drug" (**OC**).

Serious adverse event/deaths/other significant events

No serious adverse event, deaths or other significant events occurred in the clinical PK study.

Safety related to the second administration of midazolam

Tuzodi intranasal spray contains two doses of midazolam. According to the SmPC, most patients will likely require a single dose/spray (2.5mg) to achieve seizure cessation. A second dose can be administered if the seizure has not stopped within 10 minutes after medical advice. Two sprays/doses (5 mg) is recommended for patients with renal/hepatic impairment and obesity. In comparison, Buccolam (buccal midazolam, centralised procedure) is a single dose administration as well as Nasolam (intranasal midazolam), approved decentrally following a CHMP referral procedure (EMEA/H/A-29(4)/1511) triggered due to the safety risks associated with the second dose if seizure cessation did not occur within 10 minutes after the initial dose.

Based on the fact that 2 doses of midazolam could be administered, the applicant is requested to discuss

- the possible risks associated with the second dose: the applicant should assess how this increase (1.8–1.9-fold increase in mean Cmax) may impact the medication's safety, especially for respiratory depression and anterograde amnesia. This should also be assessed in comparison with other IN midazolam formulation. The need for additional warnings and recommendations in case of overdose in the PI should be discussed.

- the potential risk for medication errors as the device contains two doses of midazolam: although the Tuzodi device has red indicators to show whether a dose has been administered, prolonged acute seizures is a medical emergency setting and Tuzodi will be administered in this high stress outpatient setting by a layperson. Indeed, the rev. 3 of the EMA epilepsy guideline (CHMP/EWP/566/98 Rev.3) states that "For a medicinal product intended to be used by non-medically trained caregivers, it is necessary to justify that the new product is suitable for

administration by caregivers in an out of hospital setting. If the intended medicinal product is a drug-device combination, safe and effective use of the integral medicinal product by the intended user population needs to be demonstrated in line with the requirements set out in the Guideline on quality documentation for medicinal products when used with a medical device (EMA/CHMP/QWP/BWP/259165/2019)".

Laboratory findings, vital signs, physical findings

In the 5 treatment groups, the mean diastolic blood pressure (DBP) and systolic blood pressure (SBP) were comparable at screening *versus* at the end of the study, respectively 69.71 and 116.43 mmHg vs 68.96 and 114.39 mmHg. The mean oxygen saturation at screening visit was 99.21%; before each dosing, the average value was about 99% and varied between 98.74% of MDZ-1 4 mg and 98.93% of MDZ2.5 5 mg. After each dosing session, all subjects had oxygen saturation ≥ 90%. Overall, the mean pulse rate, respiratory rate and body temperature remained constant during the study. Regarding ECG, 12 participants (43%) at screening had some not clinically significant abnormalities in the ECG trace and this slightly increased to 14 (50%) at the end of the study. Some abnormalities were registered at screening but no change was evidenced at following examinations.

Safety in special population

The applicant has not provided any information about safety in special population, in particular the paediatric population concerned by the indication. Considering that the safety profile of midazolam is already known in this population, notably with the use of Buccolam in infants from 3 months to adults, no additional information is required (see PK assessment). Nevertheless, the overall usability of the device in children should be evaluated and justified in accordance with regulatory guidelines **(OC).**

Post-marketing experience / supportive literature safety review

The applicant provided 23 published studies in support of its application: 14 studies in which midazolam was administered intranasally and 12 studies in which midazolam was administered buccally or orally. The applicant is requested to provide the criteria used to make the research and select the articles (**OC**). Overall, studies gathered an exposition of midazolam in 1,207 adults (including 282 exposed intranasally, 860 exposed parenterally and 65 exposed orally) and 8,147 children (including 4,632 exposed intranasally, 439 exposed buccally, 558 exposed parenterally and 2,518 exposed orally).

- Fourteen publications reported the use of intranasal midazolam (mainly at the dose of 0.2 mg/kg) to including 11 studies in children, 2 studies in adults, and 1 study in both adults and children. There were no safety data from 5 publications. Among the other publications describing safety data of intranasal midazolam administered in patients, all but one were conducted in patients with epilepsy. Overall, all publications reported known adverse reaction with midazolam except in 2 studies in which the adverse reactions of increased lacrimation and eye irritation were reported. As these adverse reactions are not listed in the proposed SmPC nor in Buccolam / Ipnovel, the applicant should provide further investigation about these effects and propose a modification of the PI if necessary (**OC**).
- Twelve supportive publications reported the use of buccal or oral midazolam in adults (n=3) or in children (n=9). In adults, all adverse effects reported were well known (hypotension, respiratory depression and over-sedation). None of these publications were in the claimed or approaching indication. No relevant information emerged. In the paediatric population, when adverse effects were reported, all were known with the use or midazolam or could not be attributed to midazolam. No relevant information emerged.

Product information

Overall, the list of ADRs in the proposed section 4.8 of Tuzodi SmPC appears to be derived from sections 4.8 of Buccolam and Ipnovel as well as from AEs reported in the main PK study. However, the applicant has not provided any justification for the proposed list of ADRs in the SmPC. The methodology used should be explained (**OC**). As a general remark, Preferred Terms (PTs) from the MedDRA classification should be used to describe ADRs in section 4.8. Comments have been made in the Product Information (PI) in this regard (**see PI**).

Furthermore, some minor changes have been made by the applicant regarding ADRs compared to those in Buccolam and this should be justified (**see PI**).

Additionally, the applicant is requested to justify the reason why some ADR listed in sections 4.8 of Buccolam or Ipnovel are not listed in section 4.8 of Tuzodi. This is the case for Kounis syndrome, thrombophlebitis, thrombosis (listed in section 4.8 of Ipnovel SmPC) and for Seizure (listed in section 4.8 of Buccolam SmPC) (**OC**). To be noted, the ADR Convulsions, reported in premature infants and neonates is listed in section 4.8 of Ipnovel SmPC. This ADR is not considered adequate in Tuzodi PI considering the claimed indication from 2 years of age.

Conversely, some ADRs are listed in the Tuzodi SmPC but not in the Buccolam or Ipnovel SmPCs, and are not considered to be specifically related to the intranasal route of administration. This is the case for Paradoxical reactions, Cough and ADRs under the SOC Eye disorders. A justification should be provided by the applicant (**OC**).

Specifically, the addition of ADR abuse, Physical drug dependence and withdrawal syndrome and Drug withdrawal convulsions is questionable. Indeed, section 4.4 of Ipnovel SmPC states that "Dependence: When midazolam is used in long-term sedation in ICU, it should be borne in mind that physical dependence on midazolam may develop. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a medical history of alcohol and/or drug abuse (cf section 4.8)". Considering that Tuzodi is indicated in the treatment of prolonged, acute, convulsive seizures, no long-term use is anticipated. Hence the applicant is requested to justify the addition of the ADRs abuse and Physical drug dependence and withdrawal syndrome in the context of the clinical context of Tuzodi and to modify according the product information (**OC**).

Finally, regarding ADRs related to intranasal administration, as stated in section 3.5.3.3 of this AR, Itching nose should be replace with the MedDRA PT Nasal pruritus (**see PI**). Based on safety data from the PK study, Rhinalgia and nasal discomfort should be added under the SOC Respiratory system disorders (**OC**). The addition of Nasal dryness, which was not reported in the PK study, should be justify or deleted (**OC**).

In other respects, comments have been made in sections 4.3 and 4.4 of the SmPC. The package leaflet should be updated accordingly (**see PI**).

In conclusion, the data provided by the applicant to support the clinical safety of intranasal midazolam in the claimed indication consisted of a PK study and supporting scientific publications. Overall, the clinical safety profile of midazolam from the authorised uses is well established, mainly AEs related to the benzodiazepine mechanism of action: anterograde amnesia (for which the frequency might be largely increased in case of a second administration of midazolam IN), respiratory depression, agitation and somnolence. Additionally, adverse events related to the intranasal route of administration have been reported and resolved spontaneously within one hour of administration. At this stage, a final safety conclusion regarding the proposed posology in paediatric and special populations cannot be drawn, as further PK analysis and exposure data are expected. Moreover, the applicant is requested to provide further data and justifications concerning the second administration of midazolam in terms of potential risk of medication errors and in terms of safety. Providing responses

to the LoQ and clarifications regarding the product information, the safety profile of midazolam could be considered acceptable.

3.3.10. Conclusions on clinical aspects

Regarding pharmacokinetics, there are several points to be clarified on the PK study provided.

Both the population PK/PD and the PBPK model showed several critical deficiencies that render them presently unfit for purpose i.e. to support the claimed posology on all populations.

Although the current formulation can be bridged to the Buccolam® and Ipnovel® formulation—thereby supporting midazolam's efficacy in treating prolonged, acute, convulsive seizures in healthy adult subjects—concerns remain regarding the applicability of the PBPK model for accurately estimating drug exposure in paediatric and special populations. Although Tuzodi is indicated for the treatment of prolonged, acute, convulsive seizures in adults, adolescents, children, and toddlers (from 2 years of age), no clinical studies have been conducted in these paediatric populations; the proposed dosing regimen for these groups is based solely on PBPK simulation results. Similarly, posology in special populations—including elderly, obese, liver-impaired, and renal-impaired individuals—has not been directly investigated and is solely based on PBPK simulations. While the presented PBPK approach provides valuable insights into optimizing posology for paediatric and special populations, the provided PBPK-based simulations are insufficient to support paediatric dosing recommendations, as they do not represent any paediatric or special population PK data for the proposed product. At a minimum, sparse pharmacokinetic data are expected for the newly developed intranasal (IN) dosage form. (see LoQ, MO). Posology extrapolation through popPK modelling is the preferred approach and should be considered when clinical pharmacokinetic data becomes available.

The applicant will have to demonstrate higher predictive performance of PK/PD model. This includes providing satisfactory responses to all questions listed below. In addition, to justify the similarity in exposure ranges, the applicant should place particular emphasis on both absorption and Cmax variability, and/or provide direct comparisons with Buccolam. (see **MO**)

The following measures are considered necessary to address the clinical issues:

- Provide additional PK data in paediatric and special populations, or

- Exclude paediatric and special populations from the indication.

Overall, no definitive statement on midazolam efficacy can be drawn from the provided publications considering all the methodological uncertainties described above and additional discussions requested. However, the efficacy of midazolam in acute seizure, will not be challenged considering that Buccolam (oromucosal midazolam) is authorised in prolonged, acute, convulsive seizures in infants from 3 months to adults, thus including the intended population. Nevertheless, some concerns are raised to address some issues, including the methodology used to select the publications, the relevance of the dose of midazolam or comparator, the relevance of the data provided in the elder population, a discussion on recurrences after first seizure cessation, or the heterogeneity of the endpoints and seizures' type. In addition, a justification is requested on the proposed cut off of 2 years in the intended indication, considering that Buccolam is authorised from 3 months, and data are available in the publications in younger patients.

The clinical safety profile of midazolam is well established, mainly related to the benzodiazepine mechanism of action. Additionally, adverse events related to the intranasal route of administration have been reported. At this stage, a final safety conclusion regarding the proposed posology in paediatric and special populations cannot be drawn, as further PK analysis and exposure data are expected. Moreover, the applicant is requested to provide further data and justifications concerning the

second administration of midazolam in terms of potential risk of medication errors and in terms of safety. Providing responses to the LoQ and clarifications regarding the product information, the safety profile of midazolam could be considered acceptable

A summary of the literature with regard to clinical data of midazolam and a justification the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product (Buccolam for efficacy and safety aspects) were provided. However, if they are accepted by the CHMP is pending to additional justifications.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 22 (SVIII.1). Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Respiratory depression
Missing information	Device not working in critical situation Exposure during pregnancy and breast-feeding

3.4.2. Discussion on safety specification

As a preliminary remark, the RMP of the reference product Ipnovel 15 mg/3 ml infusion for injections was not provided by the applicant (**OC**).

No important identified risk was identified by the applicant which is acceptable.

The addition of respiratory depression as an important potential risk is not considered acceptable. Indeed, this adverse effect is listed in section 4.8 of midazolam containing products (Ipnovel and Buccolam) and is not listed as a safety concern for Buccolam. Routine pharmacovigilance activities are considered sufficient and routine risk minimisation measures (sections 4.2, 4.3, 4.4 and 4.8 of the SmPC and sections 2 and 4 of the PL) are providing necessary information on respiratory depression.

The applicant proposed the missing information 'Device not working in critical situation'. The device for Tuzodi is a Class I non-sterile, non-reusable according to the Regulations (EU) 2017/745 and (EU) 2017/746. Based on the Q&A EMA/37991/2019 Rev. 5, the applicant included a statement of compliance with the relevant GSPRs of the MDR Annex I for the medical device in the Module 3.2.R. So, while it cannot be ruled out that the device may not function in a critical situation, there is no sufficient scientific rationale to considered it as missing information in the RMP. In addition, the applicant should focus specifically on device-related issues and product quality issues in the PSUR sub-section "Medication errors" by performing an appropriate MedDRA search. Moreover, lack of efficacy related to the device should also be carefully assessed in future PSURs (**OC**).

Regarding the missing information 'Exposure during pregnancy and breast-feeding', given that there is no justification suggesting that the nasal route poses a higher risk compared to other already marketed routes of administration (intravenous, Oromucosal, etc.), it is proposed to align with this observation and not include "use during pregnancy and breastfeeding" as a safety concern in the RMP.

Overall, the applicant is requested to delete 'Respiratory depression', 'Exposure during pregnancy and breast-feeding' and 'Device not working in critical situation' from the list of safety concerns (**OC**). As a general remark, the applicant is requested to update relevant parts of the RMP in line with the raised comments related to the indication, dosage, ADRs and safety specifications (**OC**).

3.4.3. Conclusions on the safety specification

Having considered the data in the safety specification,

- The Rapporteur considers that the following issues should be addressed:

The Rapporteur considers that the following should not be a safety concerns: 'Respiratory depression', 'Exposure during pregnancy and breast-feeding' and 'Device not working in critical situation'.

PRAC Rapporteur's comment on the list of safety concerns:

Regarding the safety concerns proposed by the CHMP Rapporteur:

The CHMP Rapporteur does not propose new safety concerns. The CHMP Rapporteur proposes to remove all safety concerns from the RMP. This is endorsed by PRAC Rapporteur, and some further arguments for removal of the safety concerns are also provided by the PRAC Rapporteur below.

Regarding the safety specification as proposed by the applicant:

Important potential risks:

Respiratory depression

'Respiratory depression' should be removed from the summary of safety concerns. All relevant parts of the RMP should be updated accordingly.

Rationale: Respiratory depression is a well-known risk for benzodiazepines, and is included in the draft SmPC of Tuzodi section 4.8 as a common ADR (to be further assessed by CHMP rapporteur). In addition, there is a warning in section 4.4 to use midazolam with caution in patients with chronic respiratory depression. In general, the risk on respiratory depression is sufficiently characterised for midazolam-containing products when used according to the label.

Reference is made to the recommendations of the PRAC AR on the PSUR of midazolam (oromucosal solution, treatment of prolonged, acute, convulsive seizures) (PSUSA/00010118/201909) to remove respiratory depression from the list of safety concerns.

To be noted, regarding the proposed IFU in the PIL, there is some room for improvement, to further minimise the risk of respiratory depression. The following points could be addressed:

- The need to seek medical advice/call the ambulance – this is included in the current SmPC, but not in the current IFU in the PIL. Reference is also made to the PI including 'When to call an ambulance' of Buccolam (EMEA/H/C/002267).

- Timing of the administration of the second dose, when needed/appropriate (i.e., after 10 minutes) - this is included in the current SmPC, but not in the current IFU in the PIL. The addition of further illustrations to make the IFU more patient friendly may also be considered, for example, by adding an illustration of a clock displaying 10 minutes.

Missing information:

Device not working in critical situation

'Device not working in critical situation' should be removed from the summary of safety concerns. All relevant parts of the RMP should be updated accordingly.

Rationale: According to the proposed RMP, the device may be malfunctioning in critical situations, though the likelihood of malfunction is considered minimal by the applicant. Further, the RMP states that patients/ parents/ caregivers may be misinformed about the correct administration of the medication, but, according to the applicant, the product is easy to use, and prior to starting treatment, the HCP should instruct patients/ parents/ caregivers on how to use Tuzodi appropriately. Based on the information as currently provided, a potential impact on the B/R by this risk is not expected. The PRAC rapporteur would like to emphasise that if there is a risk that the device does not work in critical situations, this should be solved prior to marketing authorisation; the applicant should make sure that the device is of sufficient quality in pre-authorisation phase (see quality part of dossier). Furthermore, the applicant should make sure that the PIL instructions on how use the device should be sufficient clear to the reader (i.e., patients/ parents/ caregivers) prior to marketing authorisation, to enable appropriate usage of device (see also other parts of dossier).

Exposure during pregnancy

'Exposure during pregnancy' should be removed from the summary of safety concerns. All relevant parts of the RMP should be updated accordingly.

Rationale: exposure during pregnancy does not qualify as safety concern for inclusion in the RMP. The use of Tuzodi concerns an incidental use in situations that may be life-threatening. At this moment, there is no argument that intranasal administration has different teratogenic risk than intravenous and buccal administrations.

Reference is made to the currently approved list of safety concerns of the RMP for midazolam SUN 1 mg/ml; 2 mg/ml injection/infusion solution in a pre-filled syringe (version 0.3 dated 10.04.2019) (https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Pharmacovigilance_Legislation/RMPs/CMDh_330_2015_Rev36_2023_10_correction_2024_02.xlsx) in which exposure during pregnancy is not included as safety concern in the RMP. In addition, reference is made to the recommendations of the PRAC AR on the PSUR of midazolam (oromucosal solution, treatment of prolonged, acute, convulsive seizures) (PSUSA/00010118/201909) to remove 'use during pregnancy' from the list of safety concerns.

Exposure during breast-feeding

'Exposure during breast-feeding' should be removed from the Summary of safety concerns. All relevant parts of the RMP should be updated accordingly.

Rationale: exposure during breast-feeding does not qualify as safety concern for inclusion in the RMP for the following reasons: (1) the safety profile of midazolam is well-known and the small amounts of midazolam excreted into breastmilk would not be expected to cause adverse effects in most breastfed infants (LactMed®*), (2) there is already information available regarding the use of Tuzodi during breastfeeding in the draft SmPC of Tuzodi, which states that "*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 dose of midazolam"*, (3) 'use during breastfeeding' is not included as safety concern in RMPs of other midazolam products (Buccolam (EMEA/H/C/002267) oromucosal solution and Nasolam (NL/H/5089/001/DC), nasal spray). Similar statement regarding use during breast-feeding is included in the SmPCs of these products, and (4) the use of Tuzodi concerns an incidental use with minimum

expected effect on the infant. Short-term treatment with midazolam is found to be compatible with breastfeeding (Hägg et al.** 2000).

*Drugs and Lactation Database (LactMed®)

**Hägg S, Spigset O. Anticonvulsant use during lactation. Drug Saf. 2000 Jun;22(6):425-40. doi: 10.2165/00002018-200022060-00002. PMID: 10877037.

3.4.4. Pharmacovigilance plan

Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are not proposed by the applicant.

Additional pharmacovigilance activities

None proposed.

PRAC Rapporteur's comment:

The applicant proposes no additional pharmacovigilance activities, which is considered acceptable by the PRAC rapporteur.

Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Plans for post-authorisation efficacy studies

Summary of Post authorisation efficacy development plan

Table 23 (Part IV.1). Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study **Status**	**Summary of objectives**	**Efficacy uncertainties addressed**	**Milestones**	**Due Date**
Efficacy studies which are conditions of the marketing authorisation				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				

PRAC Rapporteur's comment:

The need for a PAES is assessed by the CHMP rapporteurs. In case a PAES is considered needed (i.e., primary objective focusing on efficacy rather than safety), the post-authorisation study should be described under PART IV of the RMP.

3.4.5. Risk minimisation measures

Routine Risk Minimisation Measures

Table 24 (Part V.1). Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Respiratory Depression	Routine risk communication: - SmPC sections 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects; - PL sections 2 What you need to know before you use Tuzodi, and 4 Possible side effects. Routine risk minimisation activities recommending specific clinical measures to address the risk: - recommendations for patients at increased risk of respiratory depression from benzodiazepines are included in SmPC sections 4.2 Posology and method of administration, and 4.4 Special warnings and precautions for use and PL section 2 What you need to know before you use Tuzodi. Other routine risk minimisation measures beyond the Product Information: - Pack size: single use. - Legal status: medical prescription.
Device not working in critical situation	Routine risk communication: - SmPC sections 4.2 Posology and method of administration; - PL section 3 How to use Tuzodi. Routine risk minimisation activities recommending specific clinical measures to address the risk: - recommendations for patient and patient's immediate associates (e.g. parents, caregivers) on how to use Tuzodi appropriately are included in SmPC sections 4.2 Posology and method of administration and PL section 3 How to use Tuzodi. Other routine risk minimisation measures beyond the Product Information: - Legal status: medical prescription.
Exposure during pregnancy and breast-feeding	Routine risk communication: - SmPC sections 4.6 Fertility, pregnancy and lactation; - PL sections 2 What you need to know before you use Tuzodi. Routine risk minimisation activities recommending specific clinical measures to address the risk: - recommendations for pregnancy and breast-feeding are included in SmPC section 4.6 Fertility, pregnancy and lactation and PL section 2 What you need to know before you use Tuzodi.

	Other routine risk minimisation measures beyond the Product Information: - Pack size: single use. - Legal status: medical prescription.

PRAC Rapporteur's comment:

The applicant provides an overview of the routine risk minimisation measures to minimise the safety concerns of Tuzodi. This section requires further update following comments made on the safety specification (see comments above).

Additional risk minimisation measures

The applicant states that routine risk minimisation activities as described in Part V.1 of the RMP are sufficient to manage the safety concerns of the medicinal product.

PRAC Rapporteur's comment:

The applicant considered routine risk minimisation measures sufficient to manage the safety concerns of the medicinal product. This is endorsed by PRAC Rapporteur.

Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

3.4.6. Conclusion on the RMP

The RMP could be acceptable provided an updated RMP and satisfactory responses to the <list of questions below is submitted.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

<It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.>

<Having considered the data submitted in the application, it is not appropriate to conclude on pharmacovigilance system at this time.><See list of questions>.

<Having considered the data submitted in the application, a pre-authorisation pharmacovigilance inspection is required>.

3.5.2. Periodic Safety Update Reports submission requirements

Based on the pharmaceutical form and requested indication of the product applied for, the PRAC Rapporteur request the EMA to amend the already existing entry for midazolam oromucosal solution, treatment of prolonged, acute, convulsive seizures, to also include the nasal route of administration in this entry.

Based on the current recommendations to remove all safety concerns from the RMP, there is no need to change the current PSUR cycle of latter existing entry.

4. Benefit/risk assessment

This hybrid application concerns a midazolam nasal spray 25mg/ml indicated for the treatment of prolonged, acute, convulsive seizures in adults and children > 12 kg and aged 2 years and older. The reference product Hypnovel/Dormicum 5 mg/5 ml, 5 mg/1 ml, 15 mg/3 ml and 50 mg/10 ml solution for injection is indicated for conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia; anaesthesia; sedation in intensive care units. Nonclinical studies have been provided for this application and considered sufficient. From a clinical perspective, this application does contain new data on the pharmacokinetics and pharmacodynamics as well as safety of the active substance; However, clinical efficacy was justified based on literature data only.

The bioequivalence study forms the pivotal basis with a comparison to Hypnovel 15 mg/3 ml IV solution which is indicated for sedation and premedication related to procedures or anaesthesia. The main study is a phase I, monocentre, open label, randomised, 5-single-dose (5 treatment sessions per volunteer) cross-over clinical PK study (MDZ-NS-22) to assess pharmacokinetics, pharmacodynamics, safety and local tolerance of single doses of midazolam nasal spray (MDZ) in respect to the reference product Ipnovel. Based on this study and literature data the applicant developed popPK and PBPK models for extrapolation of posology, efficacy and safety in indication population.

The study design is considered adequate to evaluate the PK of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate but still some clarifications on the PK study conduct in healthy adults (Study-MDZ-NS-22) are to be provided.

The popPK/PD modelling was developed to derive PK/PD properties of midazolam by describing the observed response in terms of sedation in healthy volunteers. Pending few clarifications (see LoQ), the model is considered to provide adequate estimates, showing that the investigational intranasal product is comparable to Ipnovel supporting an acceptable safety profile in healthy adults. However, since clinical PK data for the paediatric population is unavailable, the popPK model is not applicable for posology extrapolation to paediatric patients (MO).

Presented PBPK modelling is not enough qualified to support dose recommendations in these populations due to critical limitations in the model structure and lack of clinical data (MO). At current stage, the proposed posology for special populations and paediatric patients remains unconvincing.

Efficacy is inferred from Buccolam which is an oromucosal midazolam solution in doses of 2.5 mg, 5 mg, 7.5 mg, and 10 mg indicated for the treatment of prolonged, acute, convulsive seizures in children from 3 months to under 18 years old.

Overall, no definitive statement on midazolam efficacy can be drawn from the provided publications considering all the methodological uncertainties described above and additional discussions requested. However, the efficacy of midazolam in acute seizure, will not be challenged considering that Buccolam (oromucosal midazolam) is already authorised in the treatment of prolonged, acute, convulsive seizures in infants from 3 months to adults, thus larger than the intended indication. Nevertheless, some concerns are raised to address some issues, including the methodology used to select the publications, the relevance of the dose of midazolam or comparator, the relevance of the data provided in the elder population, a discussion on recurrences after first seizure cessation, or the heterogeneity of the endpoints and seizures' type.

Overall, the clinical safety profile of midazolam is well established, mainly related to the benzodiazepine mechanism of action. The results of the study MDZ-NS-22 were consistent with available safety information and PK-bridge to Ipnovel support safety extrapolation in adult population but as discussed above extrapolation to paediatric patients is not supported. Additionally, adverse events related to the intranasal route of administration have been reported, mostly mild and moderate transient symptoms of congestion, irritation, runny nose, pain and discomfort. Few participants reported severe symptoms. No alteration in the sense of smell was perceived by the subjects. Intranasal administration appears to be well tolerated in adult population. There were no significant changes observed in haematology, blood chemistry parameters, vital signs and physical examinations. Providing responses to the LoQ in particular the risk associated with a possible second administration of midazolam, and clarifications regarding the product information, the safety profile of midazolam could be considered acceptable.

A benefit/risk ratio comparable to the reference product can therefore not be concluded.

Having considered the data submitted in the application and available on the chosen reference medicinal product, no additional risk minimisation activities are required beyond those included in the product information.

The application contains inadequate quality, non-clinical and clinical data, the PK has not been properly established. The aspects that are inadequately demonstrated are outlined in the List of Questions.

4.1. Conclusions

The overall benefit /risk balance of Tuzodi is currently negative, given the major objections raised in the list of questions.

5. References

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