EMA/662938/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Buccolam

midazolam

Procedure No.: EMEA/H/C/002267

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 the Curve
CEP	Certificate of Suitability
CHMP	Committee for Medicinal Products for Human Use
Cmax	Maximum plasma Concentration of the drug
CNS	Central Nervous System
EC	European Commission
EEA	European Economic Area
EEC	European Economic Community
EMA	European Medicines Agency
GABA	Gamma-aminobutyric acid
GC	Gas-Chromatography
GCP	Good Clinical Practice
HDPE	High Density Poly Ethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	International Non-proprietary Name
MAH	Marketing Authorization Holder
PBPK	Physiologically Based Pharmacokinetic
PDCO	Paediatric Committee
Ph.Eur	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
pKa	Logarithmic measure of the acid dissociation constant
PP	Polypropylene
PUMA	Paediatric Use Marketing Auhtorisation
SE	Status epilepticus
SmPC	Summary of Product Characteristics

1. Background information on the procedure

1.1. Submission of the dossier

The Applicant ViroPharma SPRL submitted on 31 August 2010 an application for a Paediatric Use Marketing Authorisation in accordance with Article 30 of Regulation (EC) No 1901/2006, to the European Medicines Agency (EMA) for Buccolam, through the centralised procedure under Article 31 of Regulation (EC) No 1901/2006. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 December 2009.

The Applicant applied for the following indication treatment of acute seizures in children (from 3 months to <18 years) known to have epileptic seizures.

The legal basis for this application refers to:

Article 10(3) of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, a pharmacokinetic study and appropriate non-clinical and clinical data.

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
  - Product name, strength, pharmaceutical form: Hypnovel 10mg/2ml solution for injection
  - Marketing authorisation holder: Roche Products Limited
  - Date of authorisation: 08-12-1982
  - Marketing authorisation granted by:
    -Member State (EEA) : UK
  - Marketing authorisation number: PL0031/0126

- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
  - Product name, strength, pharmaceutical form: Hypnovel 10mg/2ml solution for injection
  - Marketing authorisation holder: Roche Products Limited
  - Date of authorisation: 08-12-1982
  - Marketing authorisation granted by:
    - Member State (EEA) : UK
  - Marketing authorisation number: PL 0031/0126

Information on Paediatric requirements

Pursuant to Article 30 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMEA-C-000395-PIP01-08 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was completed.

The PDCO issued an opinion on compliance (P/155/2009).

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice

The Applicant received Scientific Advice from the CHMP on 25 September 2008. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer of the active substance

Cambrex Profarmaco Milano S.r.l.
Via Cucchiari 17
I-20155 Milan
Italy

Manufacturer of the finished product

SCM Pharma Limited
Unit 6, Regents Drive
Low Prudhoe Industrial Estate,
Northumberland
United Kingdom

Manufacturer responsible for batch release

Auralis Ltd.
Daresbury Innovation Centre
Keckwick Lane, Daresbury, Halton
Cheshire WA4 4FS
United Kingdom

1.3. Steps taken for the assessment of the product

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

Rapporteur: **Barbara van Zwieten-Boot** Co-Rapporteur: **Ian Hudson**

- The application was received by the EMA on 31 August 2010.
- The procedure started on 22 September 2010.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 December 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 December 2010.
- During the meeting on 20 January 2011, the CHMP agreed on the consolidated List of Questions to be sent to the Applicant. The final consolidated List of Questions was sent to the Applicant on 21 January 2011.
- The Applicant submitted the responses to the CHMP consolidated List of Questions on 11 February 2011.
- The Applicant submitted the additional responses to the CHMP consolidated List of Questions on 04 March 2011.
- The Rapporteurs circulated the Joint Assessment Report on the Applicant's responses to the List of Questions to all CHMP members on 25 March 2011.
- During the CHMP meeting on 14 April 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the Applicant.
- The Applicant submitted the responses to the CHMP List of Outstanding Issues on 24 May 2011.
- The Rapporteurs circulated the Joint Assessment Report on the Applicant's responses to the List of Outstanding Issues on 09 June 2011.
- The Applicant submitted the responses to the Rapporters' Joint Assessment Report on 15 June 2011.
- The Rapporteurs circulated the updated Joint Assessment Report on 17 June 2011.
- During the meeting on 20-23 June 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Buccolam on 23 June 2011.

2. Scientific discussion

2.1. Introduction

A seizure is defined as a transient occurrence of signs and/or symptoms due to abnormal excessive and synchronous neuronal activity in the brain. Status epilepticus (SE) is defined as more than 30 minutes of either continuous seizure activity two or more sequential seizures without full recovery of consciousness between seizures.

Convulsive status epilepticus is the most common childhood neurological emergency in developed countries and can lead to neurocognitive sequelae and death. The incidence of status epilepticus is bimodally distributed, occurring most frequently during the first year of life and after the age of 60 years. Amongst children (under 15 years of age), infants younger than 12 months have the highest incidence and frequency of the disease.

An acute seizure occurs as the first stage of SE. The Applicant has proposed that Midazolam treats the acute seizure with the objective of preventing the development of SE.

In clinical practice and most clinical guidelines, treatment is indicated in case of SE, acute seizures with loss of consciousness, seizures with (risk of) generalisation and prolonged seizures. Multiple drugs are available for treatment. The first line treatment is benzodiazepines such as lorazepam or diazepam. Other drugs such as phenytoin (or fosphenytoin), phenobarbital and thiopentone are used in resistant

cases. In the hospital setting these drugs are often administered intravenously. Rectal administration (diazepam) is the current alternative authorized route. Important benefits of rectal diazepam are a quick onset of action in case and applicability in situations where intravenous access cannot be obtained i.e. outside the emergency room setting. Practical disadvantages of rectal diazepam include the need to remove clothing and the route of administration itself which is deemed to be socially embarrassing or unacceptable by some individuals with epilepsy, their parents or caregivers. Additionally, administration may be difficult during tonic-clonic seizures and for wheelchair users.

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

Midazolam has been used as a systemically administered drug in the European Union (Hypnovel) and USA (Versed, now marketed generically) since December 1982 and December 1985, respectively when first authorisations were granted to Roche. There is currently extensive clinical experience with midazolam. It is authorised for use in children (including neonates < 32 weeks gestational age in intensive care units) and adults as a sedative and in anaesthesia, and may be given by the intravenous, intramuscular or rectal route of administration. In addition, an oral formulation has been approved in the USA (October 1998 - Versed Oral Syrup 2mg/ml, now marketed generically) and Germany (January 2007 - Midazolam-ratiopharm®) for preoperative sedation in children.

This is an application submitted via the Centralised Procedure, in accordance with Regulation No. EC/726/2004, for Buccolam Oromucosal Solution, containing 5 mg/ml of the active substance, midazolam. The application is for a paediatric use marketing authorisation only (PUMA) under Article 30 of Regulation (EC) no. 1901/2006, and is submitted under article 10(3) of Directive 2001/83/EC, as amended, as an hybrid application, with proposed changes to

- the therapeutic indication,
- pharmaceutical form,
- route of administration

with regard to the reference medicinal product, Hypnovel 10 mg/2 ml solution for injection, marketed by Roche Products Ltd.

The reference medicinal product is not protected by a supplementary protection certificate under Regulation (EEC) no. 1768/92, or by a patent which qualifies for the granting of the supplementary protection certificate.

Scientific advice was obtained from the EMA for the development programme on 25 September 2008, in relation to the robustness of the clinical data publicly available and the pharmacokinetic study performed by the Applicant (Ref:EMEA/H/SA/1132/1/2008/PED/SME/III).

A paediatric investigation plan (PIP) has been approved; decision no. EMEA-000395-PIP01-08, and the application has been subject to PIP compliance verification (PDCO compliance opinion no. P/155/2009).

The indication applied for initially was the following:

- Treatment of acute seizures in children (from 3 months to <18 years) known to have epileptic seizures.

The finally approved indication is as follows:

- Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years)

  BUCCOLAM must only be used by parents/carers where the patient has been diagnosed to have epilepsy

  For infants between 3-6 months of age treatment should be in a hospital setting where monitoring is possible and resuscitation equipment is available.

The proposed dosing regimen is a single administration of 2.5 mg, 5 mg, 7.5 mg or 10 mg of midazolam depending on the age of the child.

The product is to be presented in pre-filled oral syringes, containing 0.5 ml, 1 ml, 1.5 ml or 2 ml of solution.

2.2. Quality aspects

2.2.1. Introduction

The drug product Buccolam is an oromucosal solution (available in 4 strengths : 2.5 mg , 5 mg, 7.5 mg, 10 mg) that contains midazolam as the active substance.

The excipients used in the formulation are: sodium chloride (isotonic agent), sodium hydroxide (pH adjuster), hydrochoric acid (pH adjuster) and water for injection.

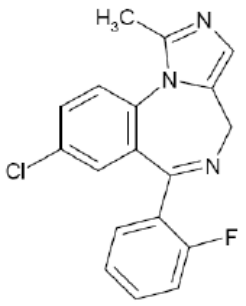
The different strengths of the drug product have the same quantitative composition but different filling volumes.

The solution is filled into amber polypropylene (PP) pre-filled oral syringes (with a nominal capacity of 1 or 3 ml) with HDPE cap and PP plunger rod with silicon seal. The syringes contain 0.5 ml, 1 ml, 1.5 ml or 2 ml of solution.

2.2.2. Active Substance

The active substance midazolam (INN) or 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine is a benzodiazepine derivative. Its chemical structure is depicted as below.

The information has been provided in a Certificate of Suitability from the Ph.Eur. (R0-CEP 2006-025-Rev 00) with a declaration of access on behalf of the active substance manufacturer. In addition to the tests described in the Ph.Eur. monograph, the CEP includes specifications regarding: residual solvents, stability and absence of TSE risk.



General physico-chemical properties including appearance, solubility, optical rotation (no chiral centre), melting point and pKa have been included in the file. No information on particle size and polymorphism were provided but since the intended drug product is manufactured as a solution this was found acceptable.

Manufacture

This section is covered by the CEP.

Specification

The active substance specification provided by the finished product manufacturer is in line with the Ph.Eur. monograph on midazolam with additional tests for microbial contamination. The specification includes the following tests: description (visual) and appearance (Ph.Eur. 2.2.1/2.2.2), solubility, identification (melting point, IR, TLC, colour reaction, chloride reaction, Ph.Eur.), sulphated ash (Ph.Eur.2.4.14), loss on drying (Ph.Eur. 2.3.32), assay (HPLC Ph.Eur.), related substances (TLC Ph.Eur. 2.2.27 and HPLC Ph.Eur.2.2.29), residual solvents (in-house GC), microbiological contamination (in-house method).

Analytical methods have been described and non-compendial methods validated in accordance with ICH requirements.

Batch analysis data on three consecutive production batches of midazolam have been provided. All the results were found in line with the specification. Limits for residual solvents and related substances do not raise any safety concern and comply with the ICH requirements.

This section on container closure is covered by the CEP. The packaging of the active substance consists of double polyethylene bags enclosed in high density polyethylene (HDPE) containers.

Stability

This section is covered by the CEP and a retest period of 5 years is applied to the active substance when stored in the approved packaging.

Comparability exercise for Active Substance

Not applicable

2.2.3. Finished Medicinal Product

The finished product is an oromucosal solution that is a clear, colourless, ready-to-use solution containing midazolam hydrochloride as the active substance.

The excipients used in the formulation are: sodium chloride (isotonic agent), sodium hydroxide (pH adjuster), hydrochloric acid (pH adjuster) and water for injection.

The excipients and packaging materials are widely used in pharmaceutical preparations. The drug product contains no preservatives, thickening agents, colorants, flavourings or buffering agents and the proposed excipients are considered acceptable for use in the paediatric population.

The drug product is available in four different strengths and presentations indicated for different target age groups respectively: 2.5 mg (age group 3 months to 1 year), 5 mg (1 year to less than 5 years), 7.5 mg (5 years to less than 10 years old), 10 mg (10 years to less than 18 years). The different

strengths are differentiated by the different colours for the labels (yellow, blue, purple and orange). The different strengths of drug product have the same quantitative composition but different filling volumes.

The product is a single-use product and the doses are respectively 2.5 mg, 5 mg, 7.5 mg and 10 mg.

The full amount of the solution should be inserted slowly into the space between the gum and the cheek. It is expected that the volume to be inserted (ranging from 0.5 to 2 ml) is acceptable in view of the target age groups.

The solution is filled into an amber polypropylene (PP) syringe (with a nominal capacity of 1 or 3 ml) with High-Density Polyethylene (HDPE) cap and PP plunger rod with silicon seal.

Pharmaceutical Development

The formulation is essentially similar to the reference injectable product Hypnovel 10mg/2ml ampoules. This injectable formulation was used for buccal administration in the 4 pivotal comparator-controlled clinical efficacy and safety studies conducted in children presented for this PUMA application.

Aspects of formulation development considered relevant to an oromucosal solution have been considered individually namely the taste, and the pH.

The taste was not considered a critical parameter in view of the emergency situation in which the product will be administered.

The excipients are the same as used in Hypnovel: sodium chloride, hydrochloric acid, sodium hydroxide and water for injections. The choice of the excipients and their functions were explained. The target pH of the formulation is based on the pH of the reference product. An acidic pH of 3.3 may enhance tooth decay. However, since the drug product is used only in emergency situations, the issue of tooth decay is not considered a major concern. In general an acidic solution is better tolerated than an alkaline solution. Given the fact that the formulation is not a buffered solution and is administered in a relatively small volume, it is expected that it will rapidly adapt to the physiological pH in the oral cavity. No irritation/local intolerance was reported during the PK study by the Applicant. The pH of 3.3 is considered acceptable

Elaboration on the pH-dependent nature of midazolam absorption has been presented (ionised molecule minimally absorbed). Ring-closure occurs at higher pH, increasing lipophilicity and transmucosal permeation. Since the proposed formulation has minimal buffering capacity, its pH is rapidly increased to physiological pH of 7.4 on administration, such that virtually all of the active substance will exist in the closed ring structure.

The proposed manufacturing process, using conventional equipment, was developed to incorporate the effective dissolution of active ingredient into an aqueous solution, with appropriate sampling arrangements to provide for full control of quality attributes of the bulk and filled oral syringes: including the key parameters of pH, bioburden and fill weights.

The drug product is packed in amber plastic pre-filled syringes. Currently available stability data confirm the compatibility between the drug product and packaging material.

Although it is not a sterile medicinal product, the aseptic filtration ensures that the product is released with low bioburden. No preservative was added to the formulation however contamination during in-use is not an issue since it is a single-use product. The currently available release and stability data demonstrate compliance with the Ph.Eur.5.1.4 requirements.

The pharmaceutical development provided was considered adequate in view of the simplicity of the formulation and its similar composition to the already approved injectable product.

Adventitious agents

No excipients of human or animal origin will be used in the manufacture of the product / excipients. Therefore no TSE risk is anticipated.

Manufacture of the product

A description and flow chart of the manufacturing process including in-process controls are included in the dossier. The manufacturing consists of mixing of dispensed midazolam base in sodium chloride solution with the appropriate targeted volume, and the addition of hydrochloric acid to form midazolam hydrochloride and reach the target pH. The manufacturing process has been described in sufficient detail. The final bulk solution is filtered through an aseptic filter into pre-autoclaved holding bottles. Afterwards, the solution is filled into syringes.

The control of critical steps and intermediates were presented. Controls applied during the critical step of bulk solution preparation have been adequately defined. The bulk solution, prior to filtration is considered as the critical intermediate, and is tested for bioburden, pH, appearance, identification, assay and related substances. Syringe filling is monitored by weight checking; target fill weights, and upper and lower acceptable limits have been defined for each presentation.

The manufacturing process was validated on three batches of drug product per strength (made from three production batches of bulk solution). The Applicant provided a summary of the process validation. Based on the available information it shows that the process is adequately under control and is suitable for consistent manufacture of the drug product. It was concluded that the manufacturing process was suitably controlled and of consistently producing of the required quality.

All excipients used comply with the requirements of the Ph.Eur. No analytical validation is required and no further justification of the specification. Sodium hydroxide and hydrochloric acid comply with their respective Ph Eur monograph, release was based on review of suppliers' certificates of analysis together with a confirmatory identification test performed by the finished product manufacturer.

Product specification

The release and end of shelf-life drug product specifications include the following parameters to be controlled: description (visual), pH (Ph.Eur.), identification (IR Ph.Eur. and HPLC in-house), uniformity of dosage unit (mass variation, Ph. Eur. 2.9.40), midazolam content (HPLC in-house), related substances (HPLC British Ph.), microbial contamination (Ph.Eur. 5.1.4).

Analytical methods have been adequately described and the non-compendial methods validated in line with the corresponding ICH guidelines and the British Ph. Method was shown suitable for its use.

The specification was considered appropriate however the Applicant will follow the recommendation to include minor updated tests with no impact on the safety and efficacy of the product.

Batch analysis data are provided on three production scale batches per strength (same batches as used in the stability studies), showing compliance with the drug product specification. The limit for individual related substances is consistent with the ICH identification threshold for a product with a maximum daily dose of 10 mg (as per CPMP/ICH/2738/99). Microbiological limits are consistent with the acceptance criteria for aqueous preparations for oral use, as prescribed in Ph Eur 5.1.4.

No additional impurities were found in the drug product in comparison with the active substance.

The drug product is packed in amber pre-filled syringes to protect from light. The individual closed syringes are placed into outer plastic tubes that are sealed with a cap before insertion into suitable external cartons. Each carton contains 4 syringes. The primary container closure consists of an amber polypropylene (PP) syringe barrel with a nominal volume of 1 ml or 3 ml, an HDPE syringe tip cap, a coloured PP plunger rod and an opaque silicon plunger rod seal. The syringes are purchased as non-sterile and are tested for bioburden control as part of the release testing / acceptance specification.

Although the Applicant did not declare specific compliance with EU food legislation or the relevant Ph.Eur. monographs, compliance with Medical Devices Directive 93/42/EEC as amended by Medical Devices Directive 2007/47/EC is considered sufficient to confirm the suitability of the oral syringes for the drug product.

An investigation into the impurity profile of the product in the filled container (using analysis by LC-MS) did not indicate the presence of container related extractables/leachables including elastomers, accelerants and plasticizers. The compatibility between the drug product and the primary packaging material was confirmed by the currently available stability data.

Stability of the product

Stability studies have been initiated on 12 validation batches (3 x batches of each strength) filled from production scale batches of bulk solution, kept in the commercial packaging. Samples have been studied under ICH storage conditions (long-term: 12 months at 25 oC/60% RH; intermediate: 12 months at 30 oC/65% RH; accelerated: 6 months at 40 oC/75% RH). Samples have been tested, according to methodology described for the finished product, for appearance, pH, assay, related substances, uniformity of dosage units and microbiological quality.

The stability data show an increase of impurities but results for assay are slightly variable and show no clear decreasing trend. The other parameters remain constant. Overall, all the parameters remain within the specified limits under all storage conditions.

Photostability data have been generated on Buccolam 2.5 mg and 10 mg samples stored in the amber plastic syringes stored in plastic tubes because to mimic the conditions of use. The samples were exposed to the full 100% exposure conditions referenced in the ICH guideline Q1B: Photostability Testing of New Drug Substances and Products. Samples were tested for appearance, pH, identification, assay and related substances. All results complied with the release and shelf life specifications. These data confirm that Buccolam is photostable.

In addition, since no freeze-thaw studies have been performed. "Do not refrigerate or freeze" has been added to the Buccolam labelling.

Based on the stability study results, the shelf-life mentioned in the SmPC can be granted.

Comparability Exercise for Finished Medicinal Drug Product

Not applicable

GMO

Not applicable

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Quality Development

Information on development, manufacture and control of midazolam and the drug product have been presented in a satisfactory manner. The results of the tests carried out indicate satisfactory consistency and uniformity of the product quality characteristics, and these turn in lead to the conclusion that the product should have uniform and satisfactory performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the product is considered to be satisfactory when used in the conditions defined in the SPC.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- Development and implementation of a satisfactory in-process test for seal integrity.
- Revision of the in-process specification limits for fill-weight, based on the results from available and ongoing batch validation data.
- Development and implementation, as part of routine release testing, of the identification test for the primary packaging materials of the oral syringe.
- Review the suitability of the proposed in-process specification and limits as an integral part of a commitment to formally validate the first three commercial production batches post approval. Furthermore, the Applicant commits to determine if a +/- 5% specification can be achieved by various technical changes and make this change and validate if technically possible by Q2/2012.

2.3. Non-clinical aspects

2.3.1. Introduction

In line with the CHMP scientific advice, no new studies have been conducted in support of this application. The non-clinical data are supported by references to relevant published scientific literature.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Midazolam is an imidazo benzodiazepine derivative.

Benzodiazepines modulate gamma-aminobutyric acid (GABA)-evoked chloride currents through a binding site on the GABA A receptor-operated chloride channel. Midazolam binds to benzodiazepine receptors in various regions of the brain such as the spinal cord, brain stem, cerebellum, limbic system, and the cerebral cortex.

It acts as a CNS depressant on CNS reflexes via the brain stem reticular formation.

Animal studies show that midazolam has anxiolytic and sedative properties but the hypnotic effects that it shows in humans are not evident in animals even at high doses. Midazolam has a more rapid onset of action and shorter duration of effect than diazepam in most animal test systems.

Midazolam has a marked anticonvulsant effect with a non-linear relationship between concentration and effect without an apparent ceiling at higher concentrations.

Antagonism of the anticonvulsant effect of midazolam by flumazenil suggested that there might be two separate sites of action, of which only one is antagonised by flumazenil. A study quoted concluded that the effect of benzodiazepines on seizures induced by cortical stimulation in vivo cannot be fully accounted for by an interaction at the GABA A receptor. At high concentrations, midazolam can inhibit calcium entry into cells by a non-GABA-dependent mechanism and thereby relaxes bronchial and vascular smooth muscle, but the relevance of this finding to the concentrations achieved in humans is doubtful.

Midazolam has anticonvulsive activity in models employing young animals, however sedative effects of midazolam were lacking in neonatal animals.

Secondary pharmacodynamic studies

Midazolam at therapeutic doses had almost no effect on the cardiovascular system of conscious dogs after PO or IV administration. No direct effects of the drug on autonomic functions were found.

Midazolam is a potent inhibitor of the nucleoside transporter (ventricle: pKi = 5.22±0.41, Ki = 6 μM). In isolated hearts, midazolam (5, 10 or 20 μM) significantly augmented coronary flow in a concentration-dependent manner in the presence of adenosine (30 nM), an effect reversed by ZM 241385, a selective A2A-receptor antagonist. In contrast, midazolam did not increase the effect of adenosine (30 nM) on atrioventricular conduction. Similarly, midazolam potentiated A2A- but not A1-receptor-mediated effects of endogenous adenosine released during hypoxia, thus this drug did not show any negative dromotropy.

Midazolam has an anti-inflammatory action by inhibiting inducible nitric oxide synthase and cyclo-oxygenase-2 expression, possibly through suppression of NF-κB and p38 mitogen-activated protein kinase activation.

Safety pharmacology programme

Safety pharmacology data indicate that midazolam exerts mild haemodynamic effects in conscious dogs at systemic exposure estimated to be several fold 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 by the CHMP.

Pharmacodynamic drug interactions

Midazolam has been found to have synergistic effects with dexmedetomidine on the reactions to various stimuli measuring anaesthetic action and ventilatory side-effects in rats. The cardiovascular side-effects of dexmedetomidine were reduced in the presence of midazolam.

2.3.3. Pharmacokinetics

Absorption

Following intravenous administration, the pharmacokinetics in rats was most adequately described by a bi-exponential equation. Following oral administration, midazolam was rapidly absorbed with an estimated systemic availability of 45 ± 9%. No non-clinical studies evaluating buccal administration were performed.

Distribution

Midazolam is extensively bound to plasma proteins (94-98%).

Metabolism

Midazolam is extensively metabolised by the cytochrome P450-dependent mixed-function oxidase system (CYP) in the liver.

In mouse and human liver microsomes, the enzymes responsible for midazolam hydroxylation were CYP 3A4 with a minor contribution from CYP 3A1.

The principal metabolite is 1-OH-midazolam, which is rapidly conjugated with glucuronic acid, although a small proportion is further hydroxylated to 1,4-dihydroxymidazolam. The other metabolite is 4-OH-midazolam. 1-OH-midazolam is biologically active but has a shorter half-life than midazolam (< 1 h). It may contribute to the pharmacological activity of the drug after oral administration. However, using classical pharmacological methods (rotarod test, chimney test, and anticonvulsant tests in mice) it was found that 1-OH-midazolam was clearly less potent than midazolam (1/10 to 1/40) when measured 30 minutes after IP administration in mice. 4-OH-midazolam, which is formed only in very small amounts in man, had on the whole the same potency as 1-OH-midazolam. 1,4-OH-midazolam was virtually inactive. Therefore, the three metabolites account only to a negligible extent, (if at all) for the pharmacological effects of midazolam in the mouse 30 minutes after IP administration.

Midazolam hydroxylation, a reaction considered to be cytochrome P-4503A (CYP3A)-mediated in humans, was examined in mouse and human liver microsomes. Ketoconazole potently inhibited midazolam metabolite formation in human liver microsomes (IC50 range, 0.038–0.049 mM).

Ketoconazole also inhibited the formation of 4-OH-midazolam in mouse liver microsomes (IC50 range, 0.0076-0.025 μM; see also: Pharmacokinetic Drug Interactions). However, ketoconazole (10 μM) did not produce 50% inhibition of α-OH-midazolam formation in mouse liver microsomes. The pharmacokinetic interactions studies cited by the Applicant indicate that compounds inhibiting or inducing cytochrome P450 enzymes involved in midazolam metabolism affect midazolam and metabolite concentrations both in vitro and in vivo. Cytochrome P450 3A isoenzymes appear to be major contributors in midazolam metabolism and are subject to potential pharmacokinetic interactions, but other isoenzymes may be involved as well.

Excretion

Less than 1% midazolam is excreted unchanged in the urine and the drug is cleared virtually entirely by liver metabolism.

2.3.4. Toxicology

Single dose toxicity

Doses up to 1600 mg/kg (oral administration) have been reported as LD50 in the mouse by the originator. This value declined to about 1000 mg/kg when the same dose was administered on five

successive days. Reported data in the literature quoted by the Applicant are 215 (oral rat) and 50 or higher for parenteral routes in rats or mice.

Repeat dose toxicity

Repeat dose toxicity of midazolam was studied in several species. Hepatotoxicity, indicated by increased or decreased liver weights, centrilobular hepatocytic hypertrophy, fatty change, hepatic masses or nodules, mottled liver and other changes, was observed in mice (at 8.5-80 mg/kg/d PO), rats (1-80 mg/kg/d PO), rabbits (0.1-2.5 mg/kg/d IV) and dogs (7-45 mg/kg/d PO) given midazolam daily for 4 weeks to 24 months. Other adverse effects of repeated dosing in animals were increased or decreased white blood cell counts, increased or decreased body weight gain, urinary inflammation, increased adrenal cortical weight or adrenal cortical hypertrophy, increased thyroid and kidney weights, decreased testes and pituitary gland weights, decreased serum glucose, increased serum urea nitrogen and albuminuria, increased or decreased alkaline phosphatase, decreased haemoglobin or red blood cells or haematocrit, proteinuria and increased gamma glutamyltranspeptidase activity.

Genotoxicity

Midazolam was negative in vitro and in vivo genotoxicity studies.

Carcinogenicity

No evidence of carcinogenic potential was seen in rats or mice receiving oral midazolam maleate dosages up to 9 mg/kg daily (about 25 times the recommended human oral dosage) for 24 months. However, an increased incidence of liver tumours was observed following oral administration of 80 mg/kg daily for 24 months in female mice, and an increased incidence of benign thyroid follicular cell tumours was observed following this dosage in male rats. As clinical use will usually be short-term (single use), the non-clinical carcinogenicity findings are of no concern to the therapeutic use of midazolam. Furthermore, knowing midazolam is an enzyme-inducer, the occurrence of liver and follicular thyroid tumours in mice is not unexpected and might be related to a rodent-specific mechanism of carcinogenesis.

Reproduction Toxicity

No evidence of impaired fertility was observed in rats following administration of midazolam maleate dosages up to 10 times the recommended adult human IV dosage of 350 µg/kg.

Based on experimental animal studies, midazolam use during pregnancy is not expected to increase the risk of congenital anomalies. Use near delivery may result in neonatal respiratory depression. Considering the lack of controlled studies on the use of midazolam in early pregnancy, a cautionary approach is still to be recommended.

Toxicokinetic data

No toxicokinetics data have been presented, which is considered acceptable.

Local Tolerance

No non-clinical studies have been conducted to evaluate the local tolerance of the oromucosal route of delivery of the drug substance or the proposed formulation. This is in accordance with EMA scientific

advice and the adopted PIP on the basis that clinical data are available to support the local tolerance of the oral mucosa following oromucosal administration of midazolam in children.

Other toxicity studies

Studies in juvenile rats suggest that short-term oral administration (up to two weeks) up to 10 mg/kg is well-tolerated. No toxicokinetic data are available from these studies.

There are indications that the main target organ in juvenile rats was the liver, although only slight effects were recorded, presumably because of the relatively low doses used. This provides some reassurance that juvenile animals are not more susceptible to the known toxicity of midazolam and that there was no new toxicity in juvenile animals.

Literature data suggest anti-inflammatory properties of midazolam. This may be considered a signal that midazolam has immunomodulatory effects. Nevertheless, in the absence of a clinical concern and in view of the usually short-term administration in humans, there is currently no need for further data on the immunotoxic potential of midazolam.

2.3.5. Ecotoxicity/environmental risk assessment

The Applicant submitted a Phase I Environmental Risk Assessment.

The log of the partition coefficient (Log KOW) of Midazolam was determined to be 3.30, 3.39 and 3.34 at pH 7, 8 and 9 respectively. Based on a refined Fpen, the estimated PECsurfacewater is far below the action limit of 0.01 µg/L.

Midazolam PECsurfacewater value is below the action limit of 0.01µg/L and is not a PBT substance as log KOW does not exceed 4.5. Therefore no Phase II ERA is required.

Table 1: Summary of main study results

Substance (INN/Invented Name):midazolam hydrochloride / BUCCOLAM			
CAS-number (if available): 59467-96-8			
PBT screening		***Result***	***Conclusion***
Bioaccumulation potential- log K_{ow}	OECD 123 (slow stirring method)	pH 7 Log Kow=3.30 pH 8 Log Kow=3.34 pH 9 Log Kow=3.34	No Potential for PBT (Log Kow values <4.5)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.000006	µg/L	< 0.01 threshold action limit
Other concerns (e.g. chemical class)	-	-	N

2.3.6. Discussion on non-clinical aspects

The pharmacology, toxicity, kinetics and clinical adverse effects of midazolam following systemic administration are well known and documented in numerous scientific publications. The standard toxicological and pharmacological particulars are well documented. The Applicant provided a

satisfactory analysis of the nonclinical data of midazolam HCl to support this application. Reference has been made to relevant published scientific literature, with special emphasis on detailed pharmacological monographs, to provide an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicological evaluation of the active ingredient, with particular emphasis on its proposed oromucosal use in the paediatric population (children aged from 3 months to <18 years).

The available data do not suggest that there are any differences in pharmacokinetics between juvenile and adult animals that would be relevant to clinical use.

Studies in juvenile rats suggest that short-term oral administration (up to two weeks) up to 10 mg/kg is well-tolerated and provide reassurance that infants are not expected to be more susceptible to the known toxicity of midazolam. No toxicokinetic data are available from these studies.

Based on experimental animal studies, midazolam use during pregnancy is not expected to increase the risk of congenital anomalies. Use near delivery may result in neonatal respiratory depression. Considering the lack of controlled studies on the use of midazolam in early pregnancy, a cautionary approach is still to be recommended. The product information reflects that the risk for new-born infants should be taken into account in the event of administration of midazolam in the third trimester of pregnancy.

No non-clinical studies have been conducted to evaluate the local tolerance of the oromucosal route of delivery of the drug substance or the proposed formulation. This is in accordance with EMA scientific advice and the adopted PIP on the basis that clinical data are available to address this aspect of the product.

2.3.7. Conclusion on the non-clinical aspects

General aspects on the pharmacology, pharmacokinetics and toxicology of midazolam are addressed by the Applicant on the basis of literature data. The extensive literature review of the pharmacology, pharmacokinetics and toxicology of midazolam is considered appropriate and acceptable to support the non-clinical aspect of Buccolam.

Several aspects specifically relevant for this application, including the pharmacokinetics and safety in young children are only to a limited extent addressed in the non-clinical part. These aspects are, however, further discussed in the clinical part.

2.4. Clinical aspects

2.4.1. Introduction

Published data from clinical efficacy and safety studies with midazolam hydrochloride administered by the proposed route of administration (oromucosal) for the treatment of acute seizures in the target population (children) are available.

In addition, the standard clinical pharmacological particulars are well documented. However, the available published pharmacokinetic data of midazolam administered by the oromucosal route are not adequate. Therefore, in accordance with the EMA scientific advice and the adopted PIP, a PK study was conducted in children to characterise the pharmacokinetic profile of the proposed formulation administered oromucosally.

To support the application the clinical pharmacology package included:

- a PK study sponsored by Applicant on the proposed buccal formulation in children [MID001]

- in silico simulation data generated from PBPK modelling
- 3 published studies on standard pharmacology and comparative bioavailability of buccal midazolam

To support the application the clinical efficacy/safety package included:

- published efficacy/safety data from studies in children with prolonged seizures treated with buccal midazolam+ midazolam by other administration routes
- supportive efficacy/safety data from published studies in adults treated with buccal midazolam for the same indication
- supportive safety data from extensive clinical experience from systemic/oral exposure of children and adults to midazolam for currently approved indications in EU and USA for Hypnovel and Versed, respectively

GCP

The sponsored clinical trial MID001 was performed in accordance with GCP as claimed by the Applicant.

Regarding the non-Applicant-sponsored bibliographic data, the Applicant could not confirm that the studies were conducted in accordance with GCP as this was not mentioned in the publications. However, those studies were conducted in countries where GCP and ethical principles are applied and the Applicant assumes that these studies complied with that. There are no indications of violations of GCP principles in the submitted study reports.

The publications on all of the controlled studies, and the majority of the uncontrolled studies, mention ethics approval and/or parental informed consent. All studies were conducted within the last 15 years and therefore are likely to have been conducted in accordance with current research practices.

With respect to the pivotal studies all of the publications, except one (Baysun S et al., 2005), state that ethics approval and parental consent was obtained.

For the above-mentioned reasons the CHMP considered the lack of confirmation of the GCP status acceptable.

2.4.2. Pharmacokinetics

This is a hybrid application for a new pharmaceutical form (but not a new formulation), new route of administration (oromucosal route) and new indication. The (BUCCOLAM) formulation is essentially similar to the authorised originator product midazolam hydrochloride injection (Hypnovel® 10mg/2ml), which has been authorised in the EU for more than 25 years.

Midazolam is a water soluble imidazo benzodiazepine derivative. It is metabolised into an active metabolite 1-hydroxymidazolam and 2 minor inactive metabolites: 4-hydroxy metabolite and 1,4 -hydroxy metabolite. Only midazolam and 1-OH midazolam have been considered in this application.

The Applicant submitted the following 5 PK studies to support the application:

1. Population PK study in paediatric patients undergoing routine elective surgery [MID001]
2. In silico (computer simulation) investigation of systemic exposure and pharmacokinetic linearity of buccal midazolam in children [Simcyp Report 2009]
3. Published study in healthy adults using 10 mg midazolam in 2ml peppermint flavoured fluid formulation [Scott RC et al., 1998]

4. Published study in paediatric patients (acute seizures and malaria) using Hypnovel 10mg/2ml formulation [Muchohi SN et al 2008]
5. Published study in healthy adults using Hypnovel 10mg/2ml formulation [Schwagmeier R et al., 1998]

The Applicant stated that a bridging PK study to demonstrate relative bioavailability or bioequivalence to the formulation used in the pivotal studies (i.e. a pharmacokinetic comparison to the Hypnovel formulation delivered oromucosally) was not required since the proposed buccal formulation is identical to the Hypnovel 10mg/2ml formulation. This was agreed as BUCCOLAM has been proven to be essentially similar to Hypnovel 10mg/2ml.

Only the first 2 studies were performed by the Applicant to support this application. Study MID001 is an open-label, sparse sampling of single-dose study of 0.2 mg/kg buccal midazolam in patients from 3 months to <18 years in children undergoing routine elective surgery who are otherwise healthy and was designed to collect the PK data necessary for the population pharmacokinetic analysis. The study design was in accordance to the comments made by EMA during scientific advice and in accordance to the PIP application review process. Study Simcyp is a silico modelling (computer simulation) investigation which predicted the age - dose linearity of buccal midazolam using published data on midazolam.

These 2 studies are summarised below:

Table 2

Study	Objectives	Design	Midazolam Treatments (Dose, Dosage Form, Route)	Subjects (No., M/F, Type) Age: Mean (range) Weight: Mean (range)	PK parameters
MID001	a. Determine PK profile of a single dose BUCCOLAM formulation in children. b. Safety	Open label, single dose, sparse sampling PK modelling	0.2mg/kg, single dose, buccal, BUCCOLAM formulation	50 (37/13) (for PK)) **Paediatric** patients undergoing elective surgery Age: 5.81 (0.3-17) yrs Weight: 25.7 (6.0-83.0) kg	Primary: a. Absorption Function b. Clearance (CL/F)* , c. Volume of distribution (V/F) Secondary T_{max}, C_{max}, AUC, Half-life (t1/2)
Simcyp Report 2009	Predict systemic exposure and PK linearity of buccal midazolam in neonates, infants and children	*In silico* modelling and simulation (Simcyp Paediatric) using Simcyp Population-Based ADME simulator (V8.1)	0.05, 0.1, 0.2, 0.25, 0.5 and 1mg/kg, single dose, buccal midazolam simulations	Simulations in **children** (M&F) aged 1 day; 1 week; 1, 3 and 6 month; 1, 2, 5, 10 and 18 yrs	

* Cl/F is the only primary parameter determined in the active metabolite

No pharmacokinetic studies were performed in the target population. In accordance with scientific advice, study MID001 was conducted in the surgical setting in which the buccal midazolam was administered as a premedication agent in children undergoing routine elective surgery (and otherwise healthy). This setting provided a robust dataset from a homogeneous population.

Since the formulation of Buccolam is the same as that of Hypnovel 10mg/2ml, the pharmacokinetic data from the other 3 studies in children and adults which used the Hypnovel 10mg/2ml formulation are directly supportive of the pharmacokinetic profile expected for Midazolam Hydrochloride Oromucosal Solution (BUCCOLAM).

1. Study MID001

The study was conducted in 50 paediatric patients (3 months - <18 years; 37 males and 13 females) who were undergoing routine surgery and required premedication with midazolam. Blood samples were taken from time zero up to 8 hours post dose or just prior to the removal of the cannula (whichever was the latest). A maximum of 4 blood samples were taken in children under 2 years old and 6 samples in children over 2 years old.

Patients were administered a single dose of 0.2mg/kg bw of BUCCOLAM (up to a maximum 10mg [2ml]) by the buccal route (inserted into the space between the gum and the cheek).

Sampling and analytical methods

A total of 263 blood samples from 50 patients collected from 9 minutes to 5 hours 33 minutes were evaluated for the pharmacokinetic profiles of the parent drug and its metabolite 1-hydroxy (1-OH) midazolam metabolite. Protein precipitation and liquid chromatography with tandem mass

spectrometric detection was used for the determination of the plasma concentrations of midazolam and 1-hydroxy midazolam.

The duration of the samplings appeared to be sufficient as the elimination half-life was captured. Based on the validation report, the analytical method is sufficiently validated and the criteria used for acceptance are in accordance to the guidelines. The handling, processing and analysis of the plasma samples were performed according to established standard procedures and that the analytical analysis took place within the tested 3-month stability period. Sufficient supporting evidence has been provided attesting to the reliability of the bioanalytical analysis.

Results

Table 3: Simulated pharmacokinetic parameters for the recommended posology in children aged 3 months to less than 18 years, based on a population pharmacokinetic study are provided in tabulated format below:

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

Table 4: Summary of 1-OH midazolam PK parameters as determined by POP-PK -Study MID001

Age group	C_{max} (ng/ml)	AUC (ng.ml/h)	T_{max} (hour)	Clearance (L/min/5 yr old)	Volume distribution (L/5 yr old)	AUC ratio (metabolite / parent)
3 months - <2 years	22.91 ± 14.8	56.84 ± 33.5	0.75 ± 0.15	np	np	0.58 ± 0.29
2 years - 11 years	18.99 ± 13.5	52.79 ± 13.5	0.86 ± 0.15	np	np	0.41 ± 0.18
12 - <18 years	19.55 ± 10.4	65.10 ± 32.0	0.96 ± 0.19	np	np	0.32 ± 0.08
Population Mean	20.67 ± 13.4	56.87 ± 30.1	0.84 ± 0.18	1.56 ± 8.72	39.2 ± 11.05	0.46 ± 0.24

Values ± SD

np = not provided

2. In Silico Simulation

As a part of the paediatric investigation plan approved by the PDCO, the Applicant justified the use of a dose of 0.2 mg/kg in their new pharmacokinetic study in children as being representative of the higher doses used in this indication (0.25 – 0.5 mg/kg) based on the expectation of pharmacokinetic linearity. This expectation was derived from an in silico modelling and simulation approach (Simcyp paediatric), using prior in vitro and in vivo information on the metabolism and kinetics (PK) of midazolam, to predict exposure and PK linearity of buccal midazolam in children of different ages. Predictions of plasma drug concentration-time profiles were performed using a population of virtual paediatric individuals. Each population was generated using values and formulae describing demographic, anatomical and physiological variables.

Simulations to reflect buccal administration of midazolam at doses of 0.05, 0.1, 0.2, 0.25, 0.5 and 1mg/kg to children aged 1 day, 1 week, 1, 3 and 6 months, 1, 2, 5, 10 and 18 years were conducted.

Two model types were explored, one compartment model and a full PBPK (physiologically based pharmacokinetic) model that aims to represent drug distribution more realistically.

The predictions from the two models are shown in the figures below:

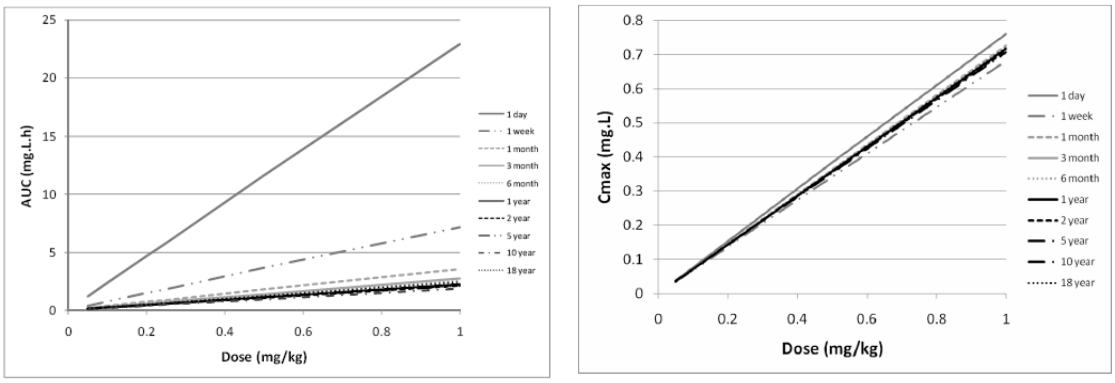


Figure PK- 1. Simulated AUC (left panel) and Cmax (right panel) of midazolam as a function of dose and age after administration of a single dose by zero order infusion over 20 min (to replicate buccal administration) (dose range 0.05 to 1 mg/kg) and based on the one compartment model (median values from 10 trials of 10 subjects each).

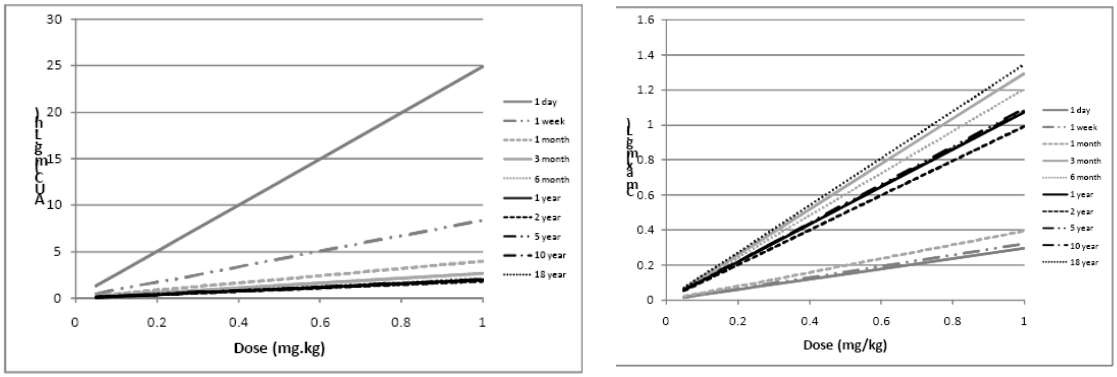


Figure PK- 2. Simulated AUC (left panel) and Cmax (right panel) of midazolam as a function of dose and age after administration of a single dose by zero order infusion over 20 min (to replicate buccal administration) (dose range 0.05 to 1 mg/kg) and based on the PBPK model (median values from 10 trials of 10 subjects each).

The approach taken by the Applicant to justify a priori the appropriateness of the dose selected for the population PK study of midazolam in children, based on current knowledge of the ontogeny of the enzymes responsible for midazolam metabolism and the physiological development of children was initially approved as part of the PIP.

The 'Simcyp Paediatric Simulator' has been evaluated against in vivo studies in predicting of the clearance of a number of drugs in neonates, infants and children.

Both models used in the simulation predicted the same behaviour: proportionality between AUC (as well as Cmax) and Dose. This approach is considered valid and it is agreed that, given the assumptions and limitations of the IVIVE process, no evidence of PK non linearity is expected over the dose range simulated (0.05 - 1mg/kg) in any of the age bands from 1 day to 18 years of age. Thus, it is agreed that based on these simulations, it is appropriate to extrapolate from the dose of 0.2 mg/kg used in MID001 to the proposed posology (~0.25 – ~0.5 mg/kg) for seizure control in paediatric patients.

The data used in the simulations, however, do not entirely reflect the conditions in this application (i.e. buccal formulation data are from adults and data from the paediatric population are from iv injections while this application concerns buccal formulation in paediatric population. Drug and metabolite concentration-time data collected in study MID001 was not used to inform the paediatric simulation model, to add value to the understanding of midazolam and metabolite pharmacokinetics in the paediatric population and aid to appropriate dosing in all paediatric patients categories. The Applicant claimed that this exercise may not necessarily give additional understanding of buccal midazolam and 1-OHMDZ pharmacokinetics and consequently no further confirmation of the paediatric dose or changes to the SPC would be obtained.

The CHMP concluded that the current paediatric simulation model could not be accepted as a reliable basis for bridging the pharmacokinetics and efficacy data for midazolam (or its active metabolite, 1-OH midazolam). However, the results on age-dose linearity are to be considered.

3. Study in healthy adults using 10 mg midazolam in 2ml peppermint flavoured fluid formulation [Scott RC et al., 1998]

The CHMP noted that the dose used in this study is slightly lower than the dose (0.15mg/kg) used in Study MID001. Nevertheless, this study in adults also demonstrated a similar rapid and very high bioavailability.

4. Study in paediatric patients using Hypnovel formulation [Muchohi SN et al 2008]

The rapid (15 minutes) and very high bioavailability (87%) of the buccally administered midazolam in this study is in line with the PK estimates obtained from the population modelling study MID001.

There was approximately a two-fold variation in plasma midazolam clearance. This high variability is in accordance with the literature.

The dose used in the above study is slightly higher than in Study MID001 (0.3 mg/kg vs 0.2 mg/kg). Four out of the 31 children experienced respiratory depression in the former study while no respiratory depression was reported in the latter study. The higher dose could explain the high respiratory depression observed in the study.

5. Study in healthy adults using Hypnovel formulation [Schwagmeier R et al., 1998]

The dose used in the study is 3-fold lower than the dose used in Study MID001. Nevertheless, this study in adults demonstrated again a rapid (Tmax =30 minutes) and very high (75.5%) bioavailability of the buccally administered midazolam and support the estimates obtained from the population modelling study MID001.

Absorption

Study MID001 showed that absorption of buccally administered midazolam is high (C = 73.2 ng/ml, AUC = 130.5 ng/ml/hour) with a Tmax of 24 minutes. When midazolam is given by the buccal route it passes directly to the superior vena cava, avoiding first-pass hepatic metabolism. Bioavailability is therefore much higher than when given orally which involves intestinal absorption and first-pass metabolism in the liver and intestine before it enters the systemic circulation. The absolute bioavailability of oromucosal midazolam is about 75% in adults. This is in contrast to the 30-50% expected after oral dosing.

Analysis of Cmax across the age categories showed no significant differences. There appears to be a positive correlation of AUC with age (r2 = 0.55) and bodyweight (r2 = 0.48). Analysis of AUC showed significantly differences across the age categories (p=0.0003).

No studies were done on the effect of food. Based on the literature, food has no effect on the absorption and disposition of midazolam in adults. Therefore, food is not expected to have a significant effect on PK parameters in the emergency setting where BUCCOLAM is to be used.

Distribution

Study MID001 showed that Midazolam by buccal administration appears to have a very extensive distribution (steady state volume distribution of 5.3 L/kg) reflecting its high lipid solubility.

No studies on protein binding were performed. However, data in the literature showed high and concentration independent plasma protein binding of midazolam. In adults and paediatric patients older than 1 year, approximately 96-98% of midazolam is bound to plasma proteins, principally albumin. This information is stated in section 5.2 of the SPC.

Elimination

In study MID001, the mean clearance for midazolam was 30ml/kg/min and the initial and terminal elimination half-lives (mean ± SD) were 26.7 ± 13.8 and 203.7 ± 86.8 minutes, respectively.

Weight and age appeared to exert effects. Midazolam clearance increases non-linearly while volume distribution increases proportionally. 1-OH midazolam clearance and volume distribution are affected non-linearly with age.

The CHMP expressed its concern in relation to the lower age limit as infants below 6 months are expected to have a greater exposure in comparison with older children on a fixed dosing based on age due to slower metabolism (CYP3A activity is only 50 % of older children and adults), longer elimination half-life and decreased clearance and the risk to respiratory insufficiency and hypoventilation.

The Applicant claimed that based on the simulated data from the MID001 study the exposures in the 3 - 6 month age group (149 ng.min/ml and 94ng/ml, AUC and Cmax, respectively) are comparable to the children younger than 1 year (146 ng/min/ml and 94 ng/ml, AUC and Cmax, respectively) and the age group 1-5 years (212 ng.min/ml and 139ng/ml, AUC and Cmax, respectively) with overlapping values. As to the higher AUC ratio between 1-hydroxy midazolam and midazolam, in the age group 3 months – 2 <years, it has been argued that this may be due to younger children swallowing a higher proportion of the dose as they were conscious.

Concerning safety, it was argued that there is significant experience in the use midazolam (and its metabolite) in neonates and young infants by oral and iv administration and the available data indicate

that the absolute risk for respiratory depression is extremely small including those from 3 months, whether given in a hospital or community setting.

The simulations provided to support the posology in children between the ages of 3 and 6 months are based on the population PK analysis of data from MID001. The study population included only three children between the ages of 3 and 6 months, one of whom had the highest concentrations of active metabolite observed in the study. Also, there was a trend for a higher metabolite to drug ratio in younger children.

The CHMP concluded that there are insufficient data to support the safe use in the community in children less than 6 months. Therefore, it is advised to limit the use of buccolam in the 3-6 month age group to the hospital setting where monitoring is possible and resuscitation equipment is available, as it can not be excluded that these infants may be more vulnerable to respiratory insufficiency and hypoventilation as compared to children elder than 6 months of age. The Applicant agreed to add children of less than 6 months of age to the list of important missing information and closely monitoring in the RMP, signal detection and discussion in PSURs.

The CHMP also expressed some uncertainties on the posology for adolescents >12 years of age (>40 kg), including children with excessive body-weight, which could need adjustment to ensure an efficacious dose.

The data submitted by the Applicant based on the simulations of study MID001, confirm that systemic exposures can be expected to be in similar range between age- and weight groups using the proposed posology. It should be noted though, that the dosage by bodyweight varies considerably and in some cases lies well outside the range reported in the literature (0.25 – 0.5 mg/kg). The reason for this appears to be associated with the variability of exposure between individuals of similar age and weight treated with identical doses. The graphs submitted by Applicant suggest 10-fold differences in Cmax and AUC. It is considered unlikely that this magnitude of variance would be explained solely by variable swallowing, especially at the older age groups. Other factors contributing to this variance remain unclear.

Nonetheless, the median level of exposure by age or weight appears comparable for all age- and weight groups which is in accordance with the efficacy and safety results in the pivotal studies. This supports the proposed posology. The risk of under dosing of adolescents has in any case been should be added to the RMP as a potential and will be addressed in PSURs as a special item in case a higher formulation strength needs to be provided.

Metabolism and excretion

Midazolam is metabolised into an active metabolite 1-hydroxymidazolam and 2 minor inactive metabolites: 4-hydroxy metabolite and 1,4 -hydroxy metabolite.

Based on the AUC ratio of 1-hydroxy midazolam and midazolam 46% of midazolam is converted into 1-OH midazolam with an estimated half-life of 0.84 hour. In the literature it is reported that 50 -70 % of midazolam is converted into this metabolite with a half-life of 1-3 hours. The discordance of the estimated values with reported data is not surprising as it is known that the PK of midazolam and its active metabolite show high variability.

No excretion study was performed. According to the literature, however, the urinary metabolites are excreted mainly as conjugates, with only a small proportion (less than 0.03%) excreted unchanged in the urine.

Dose proportionality and time dependencies

The pharmacokinetics of the drug is similar in adults regardless of it being given as a single IV dose or as an infusion. Following oral administration of 10, 20 and 40mg in adult volunteers, peak plasma levels occur within 30 minutes with a linear relationship between plasma levels and dosage.

The pharmacokinetics of orally administered midazolam has also demonstrated linearity in the paediatric population in a study conducted by the originator in support of the Versed Oral Syrup NDA. Midazolam exhibited dose proportionality in the oral dose range 0.25 to 1.0mg/kg (to a maximum of 40mg) across the age range of 6 months to 16 years. Midazolam also exhibits dose-proportionality between doses of 0.25 to 1.0mg/kg within the age group of 2 years to <16years. However, the small sample size did not permit meaningful assessment of dose-proportionality within the age groups of 6 months to < 2 years and 12 years to <16 years.

The in silico modelling study of buccal midazolam in children (Study Simcyp) also predicted dose linearity by the buccal route. No evidence of PK non-linearity was detected over the buccal midazolam dose range studied (0.05 – 1mg/kg) in any of the age bands from 1 day to 18 years of age. Thus the study predicted dose linearity of buccal midazolam PK in the range 0.05-1mg/kg across the paediatric age range 0 – 18 years. Therefore, this justified linear extrapolation of the PK data generated in the buccal midazolam PK study using a dose of 0.2mg/kg to the doses proposed for licensing (fixed doses banded by age [range ~0.25 – ~0.5mg/kg]).

Special populations

Overall, no studies were performed on pharmacokinetics in special populations. This was agreed by CHMP since the medicinal product is essentially similar to the originator product Hypnovel.

- **Impaired renal function**

In renal failure, 1-hydroxymidazolam, the active metabolite of midazolam can be expected to accumulate prolonging the pharmacological effects.

No studies of midazolam in children with chronic renal failure (CRF) are provided or known. From the limited studies in adults, it is advised to titrate to the desired effect of midazolam in patients with chronic renal disease. Section 4.4 of the proposed BUCCOLAM SmPC advises caution in this group of patients.

However, in the setting of treatment of an acute epileptic seizure, a single dose of buccal midazolam is unlikely to accumulate to the extent that the prolongation of pharmacological action is of great clinical significance.

- **Impaired hepatic function**

No studies of midazolam in children with chronic liver disease are provided or known. Studies in adults showed that chronic hepatic disease alters the pharmacokinetics of midazolam. Section 4.4 of the proposed BUCCOLAM SmPC advises caution in this group of patients.

The CHMP considered that it is unlikely that any prolongation of pharmacological action is of great clinical significance in this indication.

- **Gender**

Based on the PK population analysis (MID001) gender was not a significant factor.

The CHMP agreed with this conclusion, which is in line with existing data on midazolam.

- **Race**

Ethnic differences in CYP3A polymorphisms are known to exist, though there is insufficient evidence to date to suggest that the major polymorphic variants in CYP3A4 have any association with CYP3A4 activity. Therefore, no difference in dosing based on race is recommended.

- **Age and weight**

Plots of midazolam and 1-hydroxy midazolam AUC and Cmax using the empirical Bayes parameter estimates from the final covariate models for the study population of Study MID001 at the proposed posology doses were presented. These plots (midazolam and its metabolite) indicate no correlation of either parameter, AUC/AUCm or Cmax/Cmaxm, with age or weight i.e. exposures across the age and weight range for the study MID001 population are similar at the proposed posology doses.

- **Elderly**

Not applicable

Pharmacokinetic interaction studies

No new specific studies with the current formulation were performed.

Drug-(non)drug interaction studies reported in the literature have been conducted in healthy adult volunteers. These are summarised in the Hypnovel EU SmPC. The drug-drug interactions based on the Hypnovel EU SmPC are accepted as the medicinal product is essentially similar to Hypnovel.

Agents inhibiting the main metabolising cytochrome p-450 3A4 sub enzyme may increase midazolam plasma concentrations.

2.4.3. Pharmacodynamics

No pharmacodynamic studies were performed. One published pharmacodynamic study in adults [Scott RC et al., 1998] was submitted. In this study, the buccal route administration of 10 mg midazolam has been shown to produce a rapid (≤5 – 10 minutes) neurophysiological effect in healthy adults (EEG).

The pharmacodynamics of midazolam delivered by the authorised routes of administration is well-known. Midazolam pharmacologic effects include anticonvulsant, anxiolysis, sedation, hypnosis, and skeletal relaxation. Anterograde amnesia of short duration can occur following its administration.

The therapeutic as well as adverse effects of midazolam are due to its effects on the GABAA receptors; midazolam does not activate GABAA receptors directly but, as with other benzodiazepines, it enhances the effect of the neurotransmitter GABA on the GABAA receptors (increased frequency of Cl− channel opening) resulting in neural inhibition.

The anticonvulsant activity of midazolam is mediated by inhibition of the spread of seizure activity. Midazolam anxiolytic, sedative and hypnotic effects are mediated by enhancement of gamma-aminobutyric acid (GABA) neurotransmission at the limbic, thalamic and hypothalamic levels of the central nervous system (CNS). Skeletal relaxation is produced by inhibition of spinal polysynaptic and monosynaptic afferent pathways, blockade of excitatory synaptic transmission and depression of motor nerve and muscle function.

Published reports show that 1-hydroxymidazolam (major metabolite) is equipotent to midazolam and contributes significantly to the efficacy of midazolam after an oral dose compared to an IV dose (AUC0-∞ ratio of 1-hydroxymidazolam to midazolam after an oral dose is about two fold higher than after an IV dose). Data obtained using saccadic eye movements and EEG changes as surrogate effects following separate administration of intravenous midazolam 0.1mg/kg and 1-OH-midazolam 0.15mg/kg suggest that 1-OH-midazolam is at least as potent as the parent compound.

The metabolism and clearance of midazolam may be affected by a wide range of drugs that inhibit or induce cytochrome P450 3A as this will interfere with the metabolic removal of midazolam. The same drug interactions apply as for the other licensed routes of administration and these have been included in the proposed SmPC.

2.4.4. Discussion on clinical pharmacology

In general, the PK estimates of buccal midazolam, using population modelling, is in accordance to the published data for buccal, oral, im and iv midazolam. The provided information on pharmacokinetic analysis show that the handling, processing and analysis of the plasma samples were performed according to established standard procedures and that the analytical analysis took place within the tested 3-month stability period. Hence, sufficient supporting evidence has been provided attesting to the reliability of the analysis.

There are almost no actual data to support the safe use of midazolam in the proposed dose in children less than 6 months of age. The paediatric simulation model cannot be accepted as a reliable basis for bridging the pharmacokinetics and efficacy data for midazolam and its active metabolite, 1-OH midazolam. Given the trend for a higher metabolite to drug ratio in younger children, a delayed respiratory depression as a result of high metabolite concentrations in the 3-6 months age group cannot be excluded.

Therefore, considering the seriousness of the condition, it is advised to limit the use of midazolam in the 3-6 month age group to the emergency room setting as where respiratory function can be monitored and equipment for respiratory assistance, if needed, is available.

In the data provided by the Applicant, the median level of exposure by age or weight appears comparable for all age- and weight groups, which is in accordance with the efficacy and safety results in the pivotal studies. This supports the proposed posology. Nevertheless, the risk of under dosing of adolescents should be added as a potential risk in the RMP and need to be addressed in PSURs as a special item.

In the study by Scott et al (1998) EEG monitoring was performed on 10 healthy adults who received 10 mg buccal midazolam to be held in their mouth for 5 minutes. The pharmacodynamic phase of that study was double blind and used EEG to monitor PD effects. Most subjects reached blood levels of 5 µg/l within 10 minutes. A mean maximum concentration of 32.73 µg/l +/- 6.4 µg/l (2SD) was achieved in 48 minutes +/- 28 minutes (2SD). The EEG data showed changes in the 8- to 30-Hz frequencies in ≤5-10 minutes in test but not in control subjects; the interaction between drug and time on the relative power of these frequency bands was statistically significant. The effect on the EEG was more rapid than expected from the venous absorption data indicating the speed of cerebral effect of the drug delivered buccally.

The same drug interactions apply as for the other licensed routes of administration and these have been included in the proposed SmPC.

2.4.5. Conclusions on clinical pharmacology

No full reports on dose-effect studies or PK/PD studies in the target age group have been submitted. However, observed EEG effects are in accordance with the buccal PK profile and clinical effects of buccal midazolam.

2.5. Clinical efficacy

2.5.1. Dose-response studies and main clinical studies

No dose finding studies were submitted by the Applicant.

The clinical package to support the efficacy of BUCCOLAM comprises bibliographic data only. The efficacy dataset defined from the literature search comprises:

- A total of 9 efficacy/safety studies in the target population (children with acute seizures) treated with buccal midazolam:
  - 5 comparator controlled studies (1 vs intravenous diazepam, 4 vs rectal diazepam
  - 4 non-controlled studies on the buccal route of administration of the ('Hypnovel') midazolam aqueous solution, currently marketed for intravenous use in children.
- Supportive studies in the target population but where midazolam had been administered by the parenteral or nasal route and a study in adults on the buccal route.

For ethical reasons, placebo-controlled comparative trials of midazolam in children with seizures are not available. Therefore, the controlled studies included are comparative with either IV Diazepam or rectal diazepam.

In table 5 an overview of the studies with single dose buccal midazolam versus rectal or intravenous diazepam in treatment of children with acute seizures is presented. All studies included diazepam treatment as comparator.

All pivotal trials used a single buccal dose of about 0,25–0,5 mg /kg body weight midazolam in 10mg/2ml. solution (Roche IV injection). In two studies this was dosed as a fixed dose according to age stratum: 2.5mg: 3-11mths, 5mg: 1-4 yrs, 7.5mg: 5-9 yrs, 10mg: >10 yrs. Rectal diazepam was used as active comparator in four pivotal studies. In two of these four studies it was dosed according to age identical to midazolam dosing, which is claimed by Applicant to be broadly in line with the authorised dose of 0.5 mg / kg. In one study rectal diazepam was dosed either at 0.5mg/kg (<5 yrs.) or 0.3 mg/kg (>5 yrs). Applicant argues that dosing by body weight is not feasible in the community and emergency settings and therefore a fixed dose product, banded by age (and as suggested by EMA Scientific Advice) is proposed as investigated in the pivotal studies. However, in the studies by Baysun et al. and by Talukdar et al. dosages of buccal midazolam and intravenous diazepam were calculated by weight.

The primary objective of the pivotal studies was to compare the efficacy and safety of buccal midazolam to rectal diazepam in the treatment of prolonged seizures in children. Objectives such as assessment of superiority or non-inferiority of buccal midazolam as compared to rectal or intravenous diazepam were not specified, but the power calculations suggest the objective of superiority testing.

Primary endpoint was cessation of visible seizure activity within 10 minutes in the study by Scott at al. and the study by Baysun et al. In the Scott study the endpoint was defined as: "cessation of visible epileptic phenomena and the return of purposeful response to external stimuli". Primary endpoint was cessation of visible signs of seizure activity within 10 minutes without recurrence in the subsequent hour in the Mpimbaza study and the McIntyre study. The Mpimbaza study included an evaluation of the risk for seizure recurrence over 24 hours as a secondary endpoint. Primary endpoint in the Talukdar study was cessation of visible seizure activity within 5 minutes. This was the only pivotal study that did not include cessation of visible seizure activity within 10 minutes as either the primary or a secondary endpoint.

In table 6 the age distribution within the studies is presented.

Acute convulsive seizures of all types were included. Partial seizures were included in all trials except the McIntyre trial. In the McIntyre trial seizures had lasted for 30 minutes (Buccolam, 10-49 min.) to 41 (diazepam, 10-61 min.) before start of treatment. Mpimbaza et al reported that in their trial 269 (81.5%) convulsions were generalized and 61 (18.5%) were focal. In the Scott study 24 of 40 seizures were generalised in the Buccolam group and 22 out of 39 seizures in the diazepam group. On the Baysun trial it was reported that 'the most common type of convulsive episode was generalized tonic-clonic seizures'. In the Talukdar report partial seizures were included but proportion of patients by seizure type were not reported.

Table 5: Overview of the main studies

Author	Design, setting	Patients/ Age range/ Treatment arms N of subjects *(n of seizures)* / Dose	Endpoint: proportion of subjects with seizure cessation defined as:
Mpimbaza et al. 2008 (Uganda)	Rd, Sib, AC PA Single dose Emergency Room	Convulsing or who experienced a seizure that lasted >5 minutes, no documented evidence of having received IV diazepam or IV phenobarbital within 24 hours before presentation, documented seizure persisting at the time of administration of study drug Age range: 0.25 – 12 Buccolam : 165 *(165)*, Dab Rectal diazepam: 165 *(165)*, Dab Dose: 2.5mg: 3-11mths, 5mg: 1-4 yrs, 7.5mg: 5-9 yrs, 10mg: 10-12 yrs.	< 10 min lasting 1 hour Mann-Whitney (means), χ2
McIntyre et al. 2005 (United Kingdom)	PR, O, AC PA Single dose Emergency Room	Acute seizure without established IV access. - Pre-hospital rescue treatment not excluded. - Partial or non-convulsive seizures excluded. Age range : 0.6 –15 yrs Buccolam: 92 *(109)* Rectal diazepam: 85 *(110)*, Dose: 2.5mg: 3-11mths, 5mg: 1-4 yrs, 7.5mg: 5-9 yrs, 10mg: 10-12 yrs.	< 10 min lasting 1 hour Logistic regression (multivariate)
Scott et al. 1999 (United Kingdom)	Rd, O, AC PA Single dose Residential; area	Seizure duration >5 minutes Previous treatment with rectal diazepam for acute seizures Age range: 5 – 19 yrs (90% > 10 years) Buccolam 14 *(40)*, Dose: 10 mg. Rectal diazepam: 14 *(39)*, Dose 10 mg.	< 10 min Mann-Whitney (means), χ2
Baysun et al. 2005 (Turkey)	PR, O, AC PA Single dose Emergency Room	Convulsive symptoms regardless of type of convulsion and aetiology, assumed prolonged Age range 0.16 – 12 yrs Buccolam: 23 *(23)* Dose: 0.25mg/kg Rectal diazepam: 20 *(20)* Dose: 0.5mg/kg (≤5 yrs) / 0.3mg/kg (≥6 yrs)	< 10 min Students t-test (means)
Talukdar et al. 2008 (India)	Rd, O, AC PA Single dose Emergency Room	Convulsive symptoms regardless of type of convulsion and aetiology. Only the first episode in case of recurrent convulsions Age < 12 yrs Buccolam: 60 *(60)* Dose: 0.2mg/kg Intravenous diazepam Dose:: 60*(60)* 0.3mg/kg	< 5 min Students t-test (means), χ2, Fishers exact test

Sib=Single (patient) blind; Rd=Randomised, AC PA=Active Control, Parallel Group; O=open; PR= pseudo-randomised (McIntyre: treatment allocation by calendar weeks; Baysun: odd or even days of the month; BM=buccal midazolam; RD=rectal diazepam; ID=intravenous diazepam; Dab=dose by age: 2.5mg: 3-11mths, 5mg: 1-4 yrs, 7.5mg: 5-9 yrs, 10mg: 10-12 yrs.

Table6 : Age distribution of treated seizures in the pivotal trials:

	<12 maths	1-4 yrs	5-9 yrs	10-18 yrs	Total
Mpimbaza et al. 2008	Not specified	Not specified	Not specified	Not specified	330 (100%)
McIntyre et al. 2005	13 (6%)	136 (62%)	50 (23%)	20 (9%)	219 (100%)
Scott et al. 1999	0 (0%)	0 (0%)	2 (2.5%)	77 **(97.5%)**	79 (100%)
Baysun et al. 2005	13 (30%)	14 (33%)	15 (35%)	1 (2%)	43 (100%)
Talukdar et al. 2008	64 (53.3%)	24 (20.2%)	32 (26.7%, 5-12 yrs)		120 (100%)

Results

In table 7 the results from the individual studies and meta-analyses are presented. See also figures 3 and 4 below. The percentage cessation of seizure activity within 10 minutes ranged between 56 and 78 % for buccal midazolam and 41 - 85% for rectal diazepam. Differences by treatment were statistically significant in favour of midazolam in the meta-analyses.

Table 7: Results of pivotal studies, meta-analyses

Study	No. of Seizures Evaluated	Proportion of responders	P Value	Risk ratio, 95% CI Risk difference, 95% CI	Meta-Analysis[2]	
Mpimbaza et al. 2008 (Uganda)	BM: 165 RD: 165	<u><10 min., 1 hour:</u> BM: 115 (69.7%) RD: 94 (57.0%) <u><10mins:</u> BM: 125 (75.8%) RD: 114 (69.1%)	p=0.016 p=0.175	Risk ratio: 1.10 $CI_{95\%}$ 0.96 ; 1.25 Risk difference: 6.67% $CI_{95\%}$ -2.9% ; 16.1%	1.24 (95%CI: 1.11 - 1.39), P=0.002	. . .
McIntyre et al. 2005 (United Kingdom)	BM:109 RD: 110	<u><10 min., 1 hour:</u> BM: 61 (56%) RD: 30 (27%) <u><10mins:</u> BM: 71 (65%) RD: 45 (41%)	p<0.001[1] p<0.001	Risk ratio: 1.59 $CI_{95\%}$ 1.22 ; 2.07 Risk difference: 24.2% $CI_{95\%}$ 11.0% ; 36.3%		
Scott et al. 1999 (UK)	BM: 40 RD: 39	<u><10mins:</u> BM: 30 (75%) RD: 23 (59%)	P=0.16	Risk ratio: 1.27 $CI_{95\%}$ 0.93 ; 1.75 Risk difference: 16.0%% $CI_{95\%}$ -4.6% ; 35.0%		
Baysun et al.2005 (Turkey)	BM: 23 RD: 20	<u><10mins:</u> BM: 18 (78%) RD: 17 (85%)	p>.0.05	Risk ratio: 10.92 $CI_{95\%}$ 0.69; 1.22 Risk difference: -6.7% $CI_{95\%}$ -29.1% ; 17.5%		
Talukdar et al. 2008 (India)	BM: 60 ID: 60	<u><5 mines</u> BM: 51 (85%) ID: 56 (93.3%)	p=0.142	Not reported		

BM: buccal midazolam; RD: rectal diazepam; ID: intravenous diazepam

1 when logistic regression adjusted for centre, age, epilepsy diagnosis, presence of fever, use of anti-epileptic drugs, prior treatment, and duration of seizure before treatment (odds ratio 4.1; 95% CI 2.2-7.6)

2 Mantel-Haenszel Weighted Risk Ratio (buccal midazolam/rectal diazepam) – cessation of visible seizure activity within 10 minutes

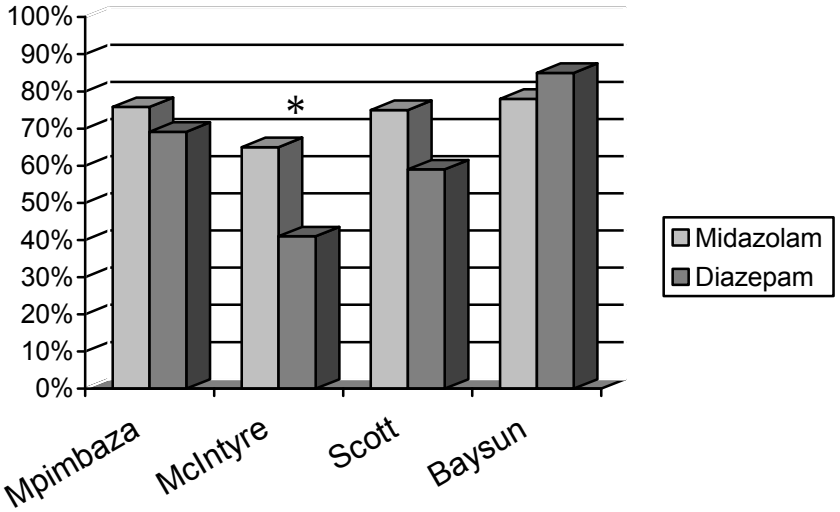


Figure 3: Percentage of treatments resulting in seizure cessation within 10 minutes (*=p<0.05)

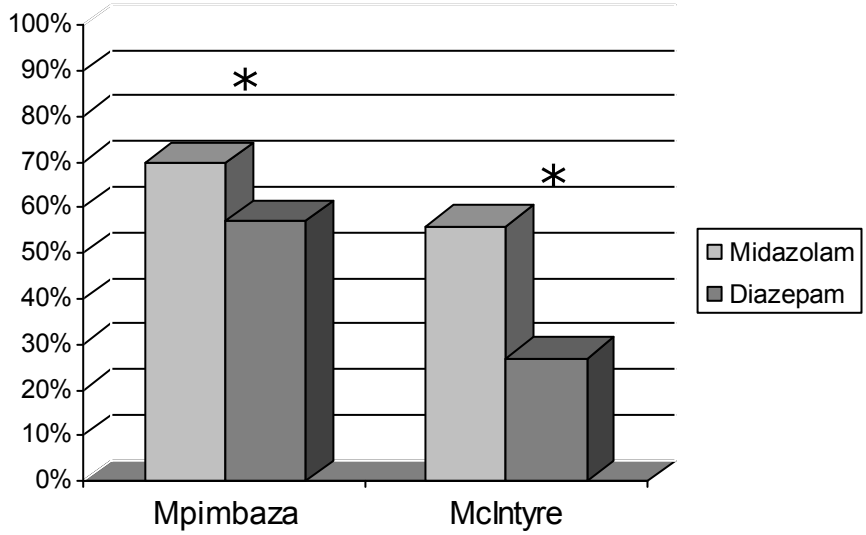


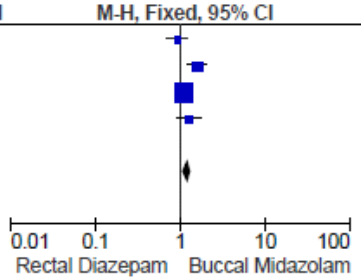
Figure 4: Percentage of treatments resulting in seizure cessation within 10 minutes without recurrence in subsequent hour (*=p<0.05)

In addition a meta-analysis over the studies conducted by Mpimbaza, McIntyre, Scott and Baysun was performed. The risk ratio was statistically significant in favour of midazolam (Weighted Risk Ratio 1.21, p=0.0005, fixed effect model). There was a substantial heterogeneity in the pooled data from the Mpimbaza, McIntyre and Scott studies (I2≥ 70%) but this disappeared when patients with malaria were excluded from the analysis ((I2=0%).

Table 8

	Buccal midazolam		Rectal Diazepam			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Baysun 2005	18	23	17	20	9.1%	0.92 [0.69, 1.22]	
McIntyre 2005	71	109	45	110	22.4%	1.59 [1.22, 2.07]	
Mpimbaza 2008	125	165	114	165	56.9%	1.10 [0.96, 1.25]	
Scott 1999	30	40	23	39	11.6%	1.27 [0.93, 1.75]	
Total (95% CI)		337		334	100.0%	1.21 [1.09, 1.35]	
Total events	244		199				

Heterogeneity: Chi² = 9.98, df = 3 (P = 0.02); I² = 70%
Test for overall effect: Z = 3.48 (P = 0.0005)



A pooled analysis of treatment response (cessation of seizure activity within 10 minutes without recurrence within one hour) in the Mpimbaza and McIntyre study also indicated superiority of buccal midazolam (WRR 1.42, p<0.00001).

Onset of effect

In the McIntyre study, median time to cessation of seizure activity was 8 minutes for midazolam and 15 minutes for rectal diazepam (p=0.01). In the Scott study these rates were 6 minutes and 8 minutes respectively (NS). In the Baysun study there were no statistically significant differences in the median response period.

In the Scott study, one patient with 15 treated seizures and one with 24 treated seizures were analysed separately. The first of these two patients was treated 8 times with midazolam and 7 times with diazepam. The other patient was treated 12 times with each product. In both patients average time from drug administration to end of seizure did not differ between drugs.

In the Talukdar study time to onset of drug effect (counted from treatment initiation) was significantly shorter for intravenous diazepam. However, total time to onset of seizure control was significantly shorter for midazolam due to time needed to establish venous access. It was reported that it took 'quite some time to get an intravenous line in place' in some patients, especially infants. Treatment initiation within 1 minute was achieved only in case of midazolam treatment (12 out of 60 treatments. Treatment initiation within 1-2 minutes was achieved in most (46 out of 60) midazolam treatments but only 14 out of 60 intravenous diazepam treatments. Treatment preparation between 2 and 3 minutes was required in 32 diazepam treatments but only 2 midazolam treatments, and 3 to 4 minutes preparation was required for another 11 diazepam treatments (but no midazolam treatments). Among 51 seizures controlled within 5 minutes using buccal midazolam and 56 seizures controlled within 5 minutes using intravenous diazepam, total controlling time of less than 2 minutes was achieved in 11 patients using buccal diazepam versus 2 patients receiving intravenous diazepam. Controlling time of four or five minutes occurred in 8 patients receiving buccal midazolam versus 13 patients receiving intravenous diazepam. Most seizures were controlled in 2-4 minutes. As no observer blinding was performed in any of these studies these result must be interpreted with caution. A claim of earlier onset of the effect is considered not justified.

See table below.

Table 9

Treatment initiation time (Time B–Time A), drug effect (Time C–Time B) and total controlling time (Time C–Time A) related to number of episodes and time fractions.

Time (min)	No. of episodes and treatment initiation time		p	No. of episodes and drug effect		p	No. of episodes and total controlling time		p
	BMDZ ($n = 60$)	IVDZ ($n = 60$)		BMDZ ($n = 51$)	IVDZ ($n = 56$)		BMDZ ($n = 51$)	IVDZ ($n = 56$)	
<1	12	0	<0.001	8	10	0.764	0	0	0.004
1–2	46	14	<0.001	18	38	0.001	11	2	0.456
2–3	2	32	<0.001	16	6	0.008	18	16	0.065
3–4	0	11	<0.001	6	2	0.102	14	25	0.327
4–5	0	3	0.242	3	0	5.8	8	13	0.004

24-hour maintenance of effect

In the Mpimbaza study the rate of recurrence of seizure activity was studied. In treatment responders these rates were 8% for midazolam and 17.5% for rectal diazepam (p=0.026) for recurrence within one hour and 39,1% versus 46,3% for a 24-hour period (NS). Median time to recurrence was 5.11 hour for midazolam and 1.81 hour for rectal diazepam (p=0.001). Response times differed statistically significant in favour of midazolam in malaria patients as well. It is noted that based on the differences in t½ of midazolam and diazepam the opposite would have been expected.

2.5.2. Supportive studies

Supportive studies were four uncontrolled studies using buccal midazolam in children demonstrating both efficacy and safety, and a small uncontrolled study among 10 adult encephalopatic patients using a 5 mg buccal midazolam dose yielding cessation of seizure activity within 2 minutes in 80.7% of all cases.

Five controlled studies conducted with intravenous midazolam (0.2 mg/kg average parenteral dose) among 106 children demonstrated efficacy and safety in comparison with parenteral diazepam, lignocaine or rectal sodium valproate.

In addition, the Applicant submitted five additional controlled studies comparing intranasal midazolam (0.2 mg/kg) with intravenous or rectal diazepam in the treatment of 214 seizures in 140 children,

which reported intranasal midazolam to be as effective and safe as diazepam. Ten further uncontrolled studies of intranasal midazolam supported those results.

2.5.3. Discussion on clinical efficacy

Use of benzodiazepines such as diazepam and clonazepam are well established treatments of epileptic and febrile seizures. Midazolam is also a benzodiazepine, used primarily for purposes of sedation in elective surgery also in children and is known for its rapid onset of action.

Clinical efficacy is based on literature data. Five published comparative studies were submitted evaluating treatment of acute seizures in children with buccal midazolam.

Overall the studies have several methodological flaws i.e. no double blinding, no placebo control and in some studies no adequate randomisation. It is questioned whether, with the exception of the randomisation, these flaws could have been avoided given the urgency of acute seizure treatment.

It should be noted that older children in each age-band (i.e. children aged 11 months or 4 or 9 years old) in the pivotal studies received only about 0.25 mg/kg of the active comparator. Most guidelines recommend dosage of rectal diazepam for acute (non-febrile) seizures at 0.5 mg/kg. For tonic-clonic status epilepticus even higher rectal diazepam dosage (0.5 – 1 mg/kg) has been recommended. Therefore, effect sizes in the studies may be artificially inflated in favour of buccal midazolam. Although superiority of buccal midazolam over rectal diazepam is not justified on these grounds, non-inferiority appears sufficiently plausible and suffices in view of the practical advantages of buccal administration for the benefit risk ratio.

With respect to types and duration of seizures this was rather heterogeneous. In most study reports the duration of seizures at the start of treatment was not specified. However, it is reasonable to expect that in an emergency room and specialised residence setting only seizures that require treatment with a benzodiazepine will be treated, but for the community setting this is ambiguous.

Not all acute seizures develop into status epilepticus and particularly partial seizures without impaired consciousness may rapidly resolve spontaneously. In most pivotal studies only initial response to treatment was described, partly concerning partial seizures without observed (secondary) generalisation or perseverance into SE. In all but one pivotal study no recurrence rates of seizure symptoms have been reported, though rebound effects of short-acting midazolam may actually lower the cortical seizure threshold after initial treatment, possibly increasing risk of development of status epilepticus in the post-treatment period. Therefore lowering the risk of complications of status epilepticus has not been shown in four out of five pivotal trials. Therefore, the claim that midazolam reduces the risk of status epilepticus, is not justified by data as this has formally not been evaluated. Hence, only a claim of treatment of prolonged, acute, convulsive seizures is acceptable.

The common outcome parameter in the four pivotal studies comparing Buccolam to rectal diazepam was cessation of seizure activity within ten minutes. Only one of these four pivotal studies demonstrated significant and clinically relevant superiority of buccal midazolam over rectal diazepam on that parameter. A non-significant trend in favour of midazolam was observed in two other pivotal studies using rectal diazepam as comparator.

Two pivotal studies report significant superiority of midazolam for the primary endpoint of termination of seizure activity and prevention of recurrence of convulsions for one hour period.

The meta-analysis of the results of the pivotal studies suggests a significant benefit of buccal midazolam over rectal diazepam in the treatment of acute seizures in children and adolescents showing termination of seizure activity within 10-minutes. The result appears to be independent of variables

such as initial versus recurrent seizure, use of antiepileptic medication or use of rescue medication prior to trial treatment. Though placebo comparisons have not been performed for ethical reasons, clinical superiority or at least non-inferiority as compared to standard treatment suffices as evidence for efficacy. As stated above superiority of buccal midazolam over rectal diazepam might not be justified. However, the CHMP was of the opinion that non-inferiority appears plausible.

Results of the supportive studies that were referred to by the Applicant were in accordance with the results of the pivotal studies and there were no submitted studies suggesting inferiority of buccal midazolam in comparison with standard treatments.

Although one pivotal study reported a faster onset of effect of buccal midazolam as compared to rectal diazepam, this result is highly prone to observer bias as the study was not blind. Therefore these results should be interpreted with caution. Claims of earlier onset of the effect are not justified.

However in the pivotal study using intravenous diazepam as comparator total controlling time was also shorter for buccal midazolam. Although subject to observer bias as well, this result does highlight the disadvantage of intravenous treatments i.e. time needed to gain venous access that may delay onset of action and termination of seizure activity, indicating the potential benefit of both rectal diazepam and buccal midazolam even in the emergency room setting.

The posology section of the SmPC of rectal diazepam recommends administration of a second dose in refractory cases whereas efficacy of buccal midazolam has been demonstrated for single use only, and the proposed SmPC recommends single use. In the Mpimbaza study the rate of recurrence of seizure activity within one hour was 8% for midazolam and 17.5% for rectal diazepam (p=0.026) and recurrence within 24 hour 39,1% and 46,3% respectively.

Although this indicates less need for retreatment under midazolam in case of treatment failure, the Applicant calculated that a second dose administered at 10, 30 and 60 minutes after the first dose results in an increase of the Cmax with an factor 1.6 to 2 after 10 minutes, 1.2 to 2 after 30 minutes and a less pronounced increase of Cmax after 60 minutes. Therefore re-treatment of midazolam in case of non-response is not recommended and can only take place under medical supervision in emergency medical setting.

The clinical studies were all performed in an emergency room or residence setting. However, the rates of observed respiratory depression were similar for Buccolam and rectal diazepam. As rectal diazepam has been safely used in the community on an extensive scale, midazolam can be expected to show similar safety.

2.5.4. Conclusions on clinical efficacy

Although the pivotal studies are may have several methodological flaws as they were not designed as registration trials, overall these trials support the clinical efficacy of buccal midazolam in the treatment of acute seizures in children and adolescents irrespective of cause, with a magnitude of effect similar to standard treatments, a sufficiently rapid onset of effect and some evidence for efficacy in the prevention of recurrence of seizures up to 24 hours. Re-treatment should only be applied under medical supervision in emergency medical setting.

2.6. Clinical safety

The clinical safety profile of midazolam (and other benzodiazepines) from the authorised uses is well established. The main adverse effects associated with midazolam and precautions applicable to the buccal route of administration in children include cardiorespiratory adverse events (respiratory depression, apnoea, respiratory arrest and/or cardiac arrest), anterograde amnesia, and paradoxical

reactions. Precautions are required for patients with impaired respiratory function or cardiovascular instability. Paediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation.

The Clinical Safety data package to support the PUMA application comprises:

- published (efficacy/) safety data from studies in children with acute seizures treated with buccal midazolam, together with supportive data from studies of midazolam by other administration routes
- supportive (efficacy/) safety data from published studies in adults treated with buccal midazolam for the same indication

Together with:

- safety data from the pharmacokinetic study conducted with the proposed buccal formulation (BUCCOLAM) in 53 children (MID001)
- safety data from published studies in 18 adults with buccal midazolam which have been used to support the pharmacokinetic/pharmacodynamic sections
- clinical experience from systemic/oral exposure of children and adults to midazolam for currently approved indications in EU and USA for Hypnovel and Versed, respectively.

Patient exposure

Table 10: Overall Exposure to Midazolam in the reviewed studies

	Route	number of patients	number of treatments
CHILDREN	Buccal	~496	~539
	Parenteral	106	106
	Intranasal	~330	~552
Total Children		~932	~1197
ADULTS	Buccal	28	70
Overall Total		~960	~1267

Adverse events

Following buccal midazolam, respiratory depression occurred in 1.5% of treated patients in the Mpimbaza study. In that study, respiratory depression was defined as a persistent decrease in oxygen saturation to <92% or a decrease in respiratory effort sufficient to warrant assisted breathing. In the McIntyre study, respiratory depression was defined as a fall in oxygen saturation or decrease in respiratory effort sufficient to require assisted breathing. This occurred in about 5% of midazolam- as well as diazepam-treated patients in that study, amounting to 5 children requiring intubation. Whether these cases of respiratory depression were related to the product or the treated seizure was not reported. Frequency of respiratory depression was not reported by Scott et al., but median oxygen saturation was reported to be 97% in both groups, with a lowest recorded saturation of 93% after midazolam treatment, returning to normal within 2 minutes. In the Baysun study, 1 patient had bradypnea and oxygen saturation of 84% at 5 minutes after rectal diazepam, returning to normal at 10 minutes. Baysun et al. report that they did not observe any cardio respiratory events in either group.

Most published studies only stated that no severe events had been reported, or that there was no significant difference between the 2 treatments. In the five pivotal studies the safety of buccal midazolam was stated to be equal to the comparator. In the reviewed studies using buccal midazolam, four AE's were reported among a total of 443 children, one of which (pruritus) was attributed to the product. See table 11 below.

Table 11

Reference	Safety Results	
	Buccal Midazolam Group	Comparator Group
Controlled studies		
Buccal Midazolam vs IV Diazepam		
Talukdar B et al. 2009	(N =60)	(N=60)
	No significant adverse events reported. Vital signs at 0, 5 and 10 mins did not show any abnormal CNS depression, respiratory depression, apnea or cardiac dysrhythmia.	
Buccal Midazolam vs Rectal Diazepam		
Mpimbaza A et al. 2008	(N = 165) Total AE Incidence: not reported 1 aphasia 12 hours after buccal midazolam (severe malaria and multiple convulsions), considered unlikely related. 1 intense pruritus (had concomitant oral phenobarbitone), considered possibly related. 2 respiratory depression (1 with SE with increased intracranial pressure - full recovery after treatment; 1 with severe malaria - full recovery) 8 deaths – disease/illness related	(N= 165) Total AE Incidence: not reported 2 respiratory depression (1 with cerebral malaria - died after seizure cessation; 1 with meningitis - recovered) 12 deaths – disease/illness related
McIntyre J et al 2005	(N = 92) 2 children required intubation Respiratory depression: 5%	(N = 85) 3 children required intubation Respiratory depression: 6%
	Total AE Incidence: not reported No AEs related to route of administration	
Scott RC et al 1999	(N = 18) Total Incidence: not reported No clinically important adverse events	
Baysun S et al 2005	(N = 23) Total Incidence: not reported 1 report of non-paroxysmal coughing for 1-2 mins, resolved spontaneously;	(N = 20) Total Incidence: not reported 1 report of bradypnea and SaO_2, of 84% at 5 mins - respiratory pattern returned to normal at 10 mins spontaneously.
	No significant difference in adverse effects between the 2 treatments (P=0.09). No adverse cardiorespiratory events were observed in either group.	
Uncontrolled studies		
MID001*	(N=53) 59 AEs reported in a total of 39 patients - only 2 considered related: vomiting (moderate, definitely related), nausea (mild, probably related). No respiratory events attributed to buccal midazlolam	
Muchohi SN et al 2008	(BM: N =8) Deaths: n = 3 (all occurred at least 24 hours after dosing and all attributed to complications associated with severe falciparum malaria, e.g. severe metabolic acidosis and hypoglycaemia). Respiratory Depression: n =2 (reversed with flumazenil)	
Frelih J et al 2007	(N = 42) No severe adverse effects reported	
Wilson MT et al 2004	(N = 39) Cardiorespiratory events not discussed. 1 child reported to be euphoric after administration	
Kutlu NO et al 2003	(N = 19) No respiratory or cardiovascular depression and vital sign parameters were within normal limits	

BM: buccal midazolam; BP: Blood pressure; HR: heart rate; RD: rectal diazepam; RR: respiratory rate; SaO_2: oxygen saturation

* MID001 - PK study in children undergoing surgery in which buccal midazolam administered as premedication

In the Mpimbaza study 6.1% deaths were reported (20 patients: rectal diazepam 12; buccal midazolam 8 (NS)), which were attributed to underlying diseases/illness. Malaria was diagnosed in 67.3% of treated patients as the underlying cause of febrile seizures.

In the PK-study, using doses below the target dose in 53 patients, 55 AE's were reported by 39 patients. Two adverse events in two patients were considered related to treatment: vomiting (moderate, related to midazolam), and nausea (mild, probably also related). No obvious difference in adverse event reporting pattern was reported across the different age groups. No events were reported for any patient in the 7 days following treatment. Two adverse events had led to discontinuation and withdrawal from the PK-study: one case of nausea which resulted in the patient spitting out the medication; and one case of vomiting (discussed above). Three AE's indicated possible respiratory depression: one case of mild bronchospasm, a case of increased upper airways secretion and one case of moderate pulmonal obstruction. These were rated as unrelated to midazolam in these patients undergoing surgical procedures. One case of severe bradycardia occurring almost two hours after study medication was also considered to be unrelated. The most common AE's were pain and vomiting post-operatively.

In this study, the oromucosal tissue at the site(s) to be used for the buccal administration was examined visually by the investigator at baseline (pre-dose) and prior to discharge for any local clinically relevant changes. There were no reports of local irritation. This is stated to be consistent with a PSUR on midazolam oral syrup marketed in the US from 1998 until 2002.

In the studies using intranasal midazolam, in about 300 treated children, there were more AE's: a case of tachypnoea, one tachycardia, two patients with shallow breathing and one with respiratory depression, one case of increased heart rate and one of increased respiratory rate together with decreased heart rate, a case of dizziness and a patient with skin irritation.

In a 2002 Indian study (Singhi et al., 2002) using parenteral midazolam, hypotension occurred in 29% of children treated with midazolam versus 37% in those treated with intravenous diazepam. In that study 19% and 16% suffered respiratory depression after midazolam a diazepam respectively.

Serious adverse events and deaths

In the Mpimbaza study 6.1% deaths were reported (20 patients in total: 12 patients receiving rectal diazepam and 8 patients receiving buccal midazolam (NS)). These deaths were attributed to underlying diseases/illness. Malaria was diagnosed in 67.3% of treated patients as the underlying cause of febrile seizures. Causes of death were eight cases of cerebral malaria and two cases of malaria with severe anaemia, three patients with severe malnutrition, three cases of septicaemia and two with HIV-associated pneumonia and two patients with meningitis.

In the 2002 study by Singhi et al. using intravenous midazolam, 8 patients died in the midazolam group (5 meningo-encephalitis, 1 acute hyponatremia due to diarrhoea, 1 hepatic encephalopathy, 1 unspecified). One further death (cause not specified) following intravenous midazolam was reported in a study in neonates (Boylan et al., 2004). No deaths were reported in 28 adults treated with buccal midazolam in 3 studies, and in about 300 children treated with intranasal midazolam.

Laboratory findings

There were no reports on laboratory findings in the submitted dossier. Laboratory evaluation in the PK-study was considered 'not applicable'.

Safety in special populations

There were no reports on safety in children with renal, hepatic or cardiac impairment in the dossier, though it is suggested that clearance of midazolam may be affected in some cases.

Safety related to drug-drug interactions and other interactions

For interactions, the Applicant refers to studies on the originator product. In these studies inducers of CYP3A4 (rifampicin, carbamazepine, and phenytoin) markedly decreased (>90%) the Cmax and AUC and pharmacologic effects of oral midazolam. Erythromycin, fluconazole, diltiazem, verapamil, and especially ketoconazole and itraconazole, all markedly increased midazolam Cmax and AUC and pharmacologic effect, with up to a possible 10 to 15-fold increase in AUC for 200 mg/day itraconazol and 400 mg/day ketoconazol respectively. Grapefruit juice, cimetidine and ranitidine cause moderate increase in midazolam plasma concentration. However, no serious consequences are expected from the potential interaction with Cytochrome p450 3A4 inhibitors, considering the broad therapeutic window of midazolam and midazolam oromucosal solution is only administered as a single dose according to the proposed indication.

Discontinuation due to AES

Due to the single dose nature of treatment of acute seizures this is not applicable in most trials. Two adverse events had led to discontinuation and withdrawal from the PK-study: one case of nausea which resulted in the patient spitting out the medication; and one case of vomiting.

2.6.1. Discussion on clinical safety

The data referred to by the Applicant as well as the submitted data are limited. However, even if the data submitted are limited, the safety profile of midazolam is well known, and the data submitted allow concluding that buccal midazolam is generally and locally well tolerated in children in the proposed age-stratified dosage.

However, given that there is a risk of delayed respiratory depression as a result of high metabolite concentrations in the 3-6 months age group, infants between 3-6 months of age treatment should be in a hospital setting where monitoring is possible and resuscitation equipment is available. The CHMP also noted that even if the data presented support the age stratified dosage, in adolescents (> 12 years of age (> 40 kg weight) there is a potential risk of under dosing based on the PK results. Therefore, this point has been addressed as a potential risk in the RMP and will be followed up in PSURs as a special item.

Clinical safety data (post-marketing and development data) have been made available to the Applicant by the originator company (Hoffman-La Roche). It is estimated that >32 million paediatric patients have been treated with IV or IM formulations of midazolam from the time of introduction in September 1982 until April 30, 1997, and that 874 million patients (children and adults) were treated with parenteral or oral formulations of midazolam in the 10-year period from May 1998 – August 2008. Findings in the post-marketing data are in accordance with the reference safety information for midazolam as summarised in the proposed SPC. Literature data on respiratory depression reported with midazolam use was submitted confirming this adverse effect to be rare and generally benign. In a total of 69 studies on use of oral midazolam as premedication prior to anesthesia in children (2400 patients) only six cases of respiratory depression or excessive sedation were reported, and no reported deaths or serious sequel secondary to hypoventilation in all published studies on oral midazolam in paediatric patients and two Roche sponsored studies in 508 patients together. In a study by Alldredge et al published in 2001, out-of-hospital treatment of status epilepticus in adults using benzodiazepines were studied in comparison with placebo. In that study a trend towards fewer complications in the active treatment groups was found.

In relation to the packaging, the CHMP had concerns that parents, carers, or patients will carry the secondary packaging (one tube containing the syringe) instead of the entire carton and will not have the Patient Leaflet available at all time. Since, there is insufficient space to have all the information from the outer carton on the tube, the CHMP recommended ViroPharma investigate the attachment of a Patient Leaflet to the secondary packaging or the extension of the label to include further information.

2.6.2. Conclusions on clinical safety

Safety data drawn from published studies using midazolam in all age-groups and the PK study conducted by the Applicant, confirm the safety of the proposed dose recommendations for children from 6 months of age to 18 yeasrs. However, as stated before, there is a risk that children younger than 6 months of age are more vulnerable to respiratory insufficiency and hypoventilation as compared to children older children. Since there are insufficient data to support the safe use in children between 3 to 6 months of age in the community setting, when used by parents or cares, it is advised to limit the use of midazolam in the 3 to 6 month age group to the hospital setting where monitoring is possible and resuscitation equipment is available.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the Applicant fulfils the legislative requirements.

Risk Management Plan

The Applicant submitted a risk management plan.

Table 12: Summary of the risk management plan

Important identified risks

Safety concern	**Agreed pharmacovigilance activities**	**Agreed risk minimisation activities**
Respiratory/cardiac insufficiency	Routine pharmacovigilance	The SPC provides the following statements and warnings: 4.8 Undesirable effects, The table indicates that respiratory depression is an adverse reaction associated with Buccolam administration in clinical studies.
Anterograde amnesia	Routine pharmacovigilance	The SPC provides the following statements and warnings: *4.4 Special warning and precautions for use* *Midazolam may cause anterograde amnesia* *4.8 Undesirable effects* *anterograde amnesia is listed in the table of adverse drug reactions*

Paradoxical reactions	Routine pharmacovigilance	The SPC provides the following statements and warnings: 4.8 Undesirable effects *Paradoxical reaction:s agitation, involuntary movements, hyperactivity, hostility, rage reaction, aggressiveness, paroxysmal excitement and assault, have been reported, particularly among children.*
Nausea/vomiting	Routine pharmacovigilance	The SPC provides the following statements and warnings: 4.8 Undesirable effects, The table indicates that nausea and vomiting are adverse reactions associated with Buccolam administration in clinical studies.
Pruritus	Routine pharmacovigilance	The SPC provides the following statements and warnings: 4.8 Undesirable effects, Table 2 indicates that pruritus is an adverse reaction associated with Buccolam administration in clinical studies.

Important potential risks

Safety concern	**Agreed pharmacovigilance activities**	**Agreed risk minimisation activities**
Abuse/diversion	Routine pharmacovigilance	The SPC provides the following statements and warnings: 4.4 Special warning and precautions for use *Midazolam should be avoided in patients with a medical history of alcohol or drug abuse*
Accidental exposure	Routine pharmacovigilance	No specific risk minimisation activities are deemed necessary.
Asphyxiation/aspiration	Routine pharmacovigilance	4.2 Posology and method of administration indicates that BUCCOLAM is for oromucosal use and that laryngo-tracheal insertion should be avoided to prevent accidental aspiration of the solution.
Buccal irritation	Routine pharmacovigilance	Dry mouth is listed as a rare event in the SPC 4.8 Undesirable effects

Choking on the oral syringe cap	Routine pharmacovigilance	The SPC provides the following statements and warnings: 4.2 Posology and method of administration *Remove the oral syringe cap before use to avoid risk of choking.* Prominent text on the carton label, tube label and oral syringe label stating: *Remove the oral syringe cap before use.* A large additional component affixed around the end of the existing tip cap (10.1 mm in diameter) of the syringe, will result in one integrated tip cap component sufficiently large to ensure it is very obvious to the user that the cap needs to be removed before use.
Misuse/attaching lines to syringe	Routine pharmacovigilance	The SPC provides the following statements and warnings: 4.2 Posology and method of administration *No needle, intravenous tubing or any other device for parenteral administration should be attached to the oral syringe.* The orifice of the oral syringe has been designed so that it will not inadvertently accept needle or tubing fittings.
Overdose	Routine pharmacovigilance	The SPC provides dosing information in 4.2 Posology and method of administration. Specifically it is recommended that carers should only administer a single dose of midazolam and that a second or repeat dose when seizures re-occur after an initial response should not be given without prior medical advice. Additionally, the SPC provides information concerning overdose in Section 4.9. including information on Symptoms and Treatment.
Interaction with CNS acting substances	Routine pharmacovigilance	The SPC provides information in Section 4.5 Interaction with other medicinal products and other forms of interaction: *The co-administration of midazolam with other sedative/hypnotic agents and CNS depressants, including alcohol, is likely to result in enhanced sedation and respiratory depression.*
Under dosing in adolescents	Routine pharmacovigilance	The SPC provides detailed dosing information by age groups in Section 4.2 Posology and method of administration.

Important Missing Information

Safety concern	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Use in patients with chronic renal failure	Routine pharmacovigilance	The SPC provides the following statements and warnings: 4.4 Special warning and precautions for use *Midazolam should be used with caution in patients with chronic renal failure and impaired hepatic function because midazolam may accumulate, or with impaired cardiac function due to decreased clearance.*
Use in patients with impaired hepatic function	Routine pharmacovigilance	The SPC provides the following statements and warnings: 4.4 Special warning and precautions for use *Midazolam should be used with caution in patients with chronic renal failure and impaired hepatic function because midazolam may accumulate, or with impaired cardiac function due to decreased clearance.*
Use in patients with myasthenia gravis	Routine pharmacovigilance	The SPC provides the following statements and warnings: 4.3 Contraindications: *myasthenia gravis.*
Use in patients with a history of drug or alcohol abuse	Routine pharmacovigilance	The SPC provides the following statements and warnings: 4.4 Special warning and precautions for use *Midazolam should be avoided in patients with a medical history of alcohol or drug abuse.*
Use in pregnancy	Routine pharmacovigilance	The SPC provides information and warnings in 4.6 Fertility, pregnancy and lactation indicating that insufficient data are available on midazolam to assess its safety during pregnancy and that Midazolam should be used in pregnancy only if clearly necessary. *Breast-feeding Midazolam passes in low quantities (0.6%) into breast milk. As a result it may not be necessary to stop breast feeding following a single dose of midazolam.* *Fertility Animal studies did not show an impairment of fertility (See section 5.3).*

Use in children less than 6 months of age	Routine pharmacovigilance	The SPC provides information in Section 4.1 Therapeutic indications and detailed dosing information by age groups in 4.2 Posology and method of administration.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the Applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Based on the clinical data submitted, midazolam showed efficacy in termination of acute prolonged seizures (any visible sign of convulsions) at 0.25-0.5 mg/kg bodyweight buccal in children 3 months - 18 years old in emergency room and specialized residential settings. At least midazolam is considered non-inferior and possibly superior efficacy to rectal diazepam (i.e. current non-intravenous seizure treatment).

Buccolam is presented in a new dosage form developed for buccal use in children. The route of administration is better assessable compared to the intravenous route and rectal use. Compared to the intravenous route, the onset of action may be slightly later. However taking into account the time needed to get access to the intravenous route, especially in children, there is less time to seizure control as no time is lost for gaining intravenous access. Compared to the rectal, route there is a larger social acceptability.

Midazolam given bucally has a favourable local tolerability.

Uncertainty in the knowledge about the beneficial effects

Superiority as compared to rectal diazepam has not been established.

Whether midazolam decreases seizure recurrence rates is unclear. Seizure recurrence rates in initial treatment responders were reported in only one study. The results appear in favour of buccal midazolam but conflicts with the much faster clearance of midazolam.

Benefits were only demonstrated in the emergency room and specialised residential setting.

Unfavourable effects

The major risk of midazolam and its active metabolite is the risk of respiratory depression.

There might be a risk of overtreatment due to misclassification i.e. treatment of self-limiting (partial) seizures of short duration. This may induce unnecessary sedation.

Uncertainty in the knowledge about the unfavourable effects

The reporting of adverse events in the dossiers appears limited. In is unclear how adverse events were assessed in the pivotal studies and whether underreporting has been excluded.

Uncertainty persists whether respiratory failure has occurred in fatal cases in the post-marketing database on oral and intravenous midazolam in children undergoing elective surgery.

Uncertainty persists whether a second gift after non-responsiveness or recurrence respiratory failure is safe especially with respect respiratory depression.

There are insufficient data to support the safe use in children between 3- 6 months of age in the community setting. It can not be excluded that these infants are more vulnerable to respiratory insufficiency and hypoventilation as compared to children elder than 6 months of age.

Given the proposed posology, there is a potential risk that adolescents (>12 years of age, weights above 40 kg) might be under dosed.

Benefit-risk balance

On the whole the benefit-risk balance is considered positive.

Discussion on the benefit-risk assessment

Efficacy of midazolam in termination of acute prolonged seizures in children has been established. The termination of prolonged seizures by the simple and socially acceptable intervention of buccal administration of midazolam adds an important means to prevent complications of paediatric status epilepticus to the existing treatment options.

The risk of respiratory failure is comparable to current treatments. The risk of overtreatment is limited by the constraints included in the indication-statements.

As it can not be excluded that these infants are more vulnerable to respiratory insufficiency and hypoventilation the use of midazolam in children 3-6 months of age needs to be limited to the emergency room setting as where respiratory function can be monitored and equipment for respiratory assistance, if needed, is available. In addition, the Applicant should add children of less than 6 months of age to the list of important missing information In the RMP for at least closely monitoring, signal detection and discussion in PSURs.

Given the proposed posology, there is a potential risk that adolescents (>12 years of age, weights above 40 kg) might be under dosed. This should be added as a potential risk in the RAMP and will be addressed in Spurs as a special point of attention.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Buccolam in the:

> *Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years).*

BUCCOLAM must only be used by parents/carers where the patient has been diagnosed to have epilepsy.

For infants between 3-6 months of age treatment should be in a hospital setting where monitoring is possible and resuscitation equipment is available.

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Strength 2.5 mg: Medicinal Product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Strenghts 5mg, 7.5mg and 10 mg: Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 4 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

The PSUR cycle for the product will follow the standard requirements.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.