Annex II

Scientific conclusions

Scientific conclusions

Midazolam is a benzodiazepine that exerts its anti-epileptic effects by the inhibition of the spread of seizure activity. The current product concerns an intranasal (IN) formulation of midazolam, for which approval is sought through an Article 10 (3) hybrid application with Dormicum 5mg/mL solution for injection (Cheplapharm Arzneimittel GmbH) as reference medicinal product. The proposed indications are those of the reference medicinal product (conscious sedation and premedication) plus an additional indication i.e. "the treatment of prolonged, acute, convulsive seizures, both in adults and children from 2 years", which is the subject of this referral.

For a similar indication, midazolam is currently approved as an intrabuccal (IB) formulation both centralised (Buccolam, EMEA/H/C/002267) as well as decentralised (Epistatus, [SE/H/1958/001] approved in UK (NI), Germany, Hungary and Sweden) for use in paediatric and adolescent patients. The use of midazolam, including both the buccal and intranasal routes of administration, for the cessation of prolonged seizures, is considered well established and incorporated in epilepsy treatment guidelines across Europe.

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

Overall summary of the scientific evaluation by the CHMP

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

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

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

subsequent neuronal damage, outweighs the potential safety risk. No distinction has been made in dose recommendations for this age population in the national treatment guidelines. In addition, the same safety risks have also been accepted for other benzodiazepines used within the same setting, such as intramuscular midazolam or rectal diazepam.

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

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

Grounds for the CHMP opinion

Whereas,

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

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