Annex II

Scientific conclusions

Scientific conclusions

Alcover granules in sachet contains the active substance sodium oxybate, which is the sodium salt of Gamma-hydroxybutyric acid (GHB), a derivative of gamma-aminobutyric acid (GABA). Sodium oxybate is a partial agonist on both $GABA_A$ and $GABA_B$ receptors and also binds with high affinity to GHB-specific receptors. Like GABA, it exerts an overall inhibiting effect on the central nervous system (CNS).

The applicant Debrégeas & Associés (D&A) submitted an application for marketing authorisation (MAA) for Alcover 750 mg, 1250 mg and 1750 mg through the Decentralised Procedure (DCP) under the legal basis of Article 8(3) of Directive 2001/83/EC, as a full-mixed application for the treatment of long-term maintenance of alcohol abstinence and alcohol withdrawal syndrome in alcohol-dependent adult patients.

The application was submitted to the reference Member State (RMS): Austria and the concerned Member States (CMS): Denmark, Spain, Finland, France, Germany, Ireland, The Netherlands, Poland, Portugal, Sweden and the United Kingdom. The application in Germany was withdrawn during the DCP.

The reference Member State RMS Austria considered that based on the studies submitted within the application, a lack of efficacy, as raised by some Member states, could not be supported. Furthermore, safety was considered to be acceptable taking into account the proposed risk minimisation measures (RMM).

However the objecting concerned Member States (CMSs) were of the view that although there were trends towards positive results across a few of the studies submitted and some level of statistical significance, there were also some failed studies. Considering that the presented evidence mainly relied on *post-hoc* analyses, and that there is also significant heterogeneity in the study populations, the overall evidence for efficacy was not considered robust enough. Regarding safety, concerns were expressed with regards to the potential risk of misuse/abuse/dependence, and other identified safety issues, which considered too substantial and difficult to mitigate by the proposed RMMs.

As the objections raised on the efficacy, safety and overall benefit-risk during the procedure were considered to be a potential serious risk to public health and no agreement could be reached during the CMDh procedure, the procedure was referred to the CHMP under Article 29(4) of Directive 2001/83/EC by the RMS Austria.

Overall summary of the scientific evaluation by the CHMP

The results of the submitted efficacy studies cannot be considered to provide sufficiently robust evidence to establish the efficacy of Alcover (sodium oxybate) granules in the maintenance of alcohol abstinence and treatment of alcohol withdrawal syndrome (AWS). There were several drawbacks in the design of these studies, including small sample size, choice of patient population and absence of clearly defined, statistically significant outcomes, and although some of the studies showed trends to positive results, there were also some that were clearly failed studies.

With regard to the indication for the maintenance of alcohol abstinence, none of these studies can be seen as being in line with the scientific requirements for a clinical efficacy/safety study that would provide clear evidence of efficacy in the aimed at Very High DRL patient group. In order to demonstrate the efficacy of sodium oxybate granules in Very High DRL patients – the target population that was identified *post-hoc*, the applicant performed several post-hoc subgroup

analyses and meta-analyses of the data obtained in clinical trials in medium and long-term maintenance of abstinence. However these data were considered too sparse, not consistent or sufficiently robust to support the indication maintenance of alcohol abstinence in this Very High DRL patient population. As none of the subgroup analyses had been pre-specified, these are inherently weakened by their *post-hoc* derived nature. Referring to the results in abstinence rate from study SMO032/10/03, Gallimberti 1992, GATE 2 and Di Bello 1995, apart from different study designs, *post-hoc* chosen patient groups, different study duration, it cannot be concluded whether continuous abstinence was measured, and whether responders (*a posteriori* defined as completers with a DRL<high or who did not relapse to heavy drinking) are actually the group of people aimed at with full abstinence in mind. Furthermore, the number of patients included was quite small, and only Gallimberti showed positive results, whereas the results on abstinence rate in Very High DRL patients from study SMO032/10/03 and Di Bello 1995 are deemed inconclusive.

The meta-analysis that included GATE 2, SMO032/10/03, Gallimberti 1992 and Di Bello 1995 have several methodological flaws and quality concerns such as GATE 2 did not evaluate the population of interest; SMO032/10/03 trial included only a subset of High/Very High DRL patients and failed to meet its primary endpoint; Gallimberti trial did not report primary endpoint or follow-up time; Di Bello had a very small sample size (total n=17) and failed to specify the primary endpoint.

The applicant performed a subpopulation analysis (meta-analysis of seven RCTs and observational studies), which was not sufficiently robust to establish efficacy of the medicinal product in the claimed indication. Furthermore, reference to other existing marketing authorisations is not relevant due to different targets populations and/or safety profile.

Furthermore, it was noted by the CHMP that, despite the limited sample size in the clinical trials, this patient population cannot be considered as a 'small population' as defined by the EMA Guideline on Clinical Trials in Small Populations (CHMP/EWP/83561/2005).

With regards to the indication alcohol withdrawal syndrome (AWS), the efficacy of sodium oxybate granules in Very High DRL patients has also not been established. The Gallimberti 1989 trial was the only placebo-controlled RCT to evaluate sodium oxybate in the treatment of AWS, which had a small sample (n=11 oxybate vs n= 12 placebo), that evaluated the first 7 hours of treatment, showing favourable results for the active arm. The trials submitted with active arm comparators (Gate 1, Nava 2007, Addolorato 1999 and Nimmerrichter 2002) had several methodological flaws such as open label, small sample size, heterogeneity in the studies' population, lack of protocol or defined primary endpoints, assessment of large number of outcomes, and long enrolment period, which lead to conclusions based on post-hoc analysis that do not provide sufficient evidence to establish the efficacy for the use of sodium oxybate granules in the treatment of AWS.

The applicant has proposed two prospective Post-Authorisation Efficacy Studies (PAES) to confirm the efficacy of sodium oxybate in the treatment of AWS in alcohol dependent patients and its long-term benefits in the maintenance of alcohol abstinence. Whilst such studies could confirm or further characterise the efficacy of a medicinal product, they cannot replace the demonstration of efficacy in the claimed indications, which is a requirement of a marketing authorisation.

Regarding the safety of Alcover granules, the risk of Abuse / Misuse / Diversion / Overdose / Dependence / CNS / Respiratory Depression in Very High HDRL patients is well-recognized. Risks of abuse / misuse are higher in polymedication users (cocaine or heroin) and/or patients with severe psychiatric comorbidities. The applicant has proposed to further reduce them by contraindicating the use of Alcover granules specifically in patients with severe psychiatric disorders and patients with past or present co-addiction to opiates or cocaine.

In order to further mitigate these risks in the clinical practice, the applicant has proposed

additional risk minimization measures in addition to the warnings/guidance in the product information; dose reduction at the end of treatment to prevent risk of withdrawal; inpatient setting in the treatment of AWS; warnings and guidance in case of concomitant alcohol consumption, and implementation of a restricted prescribing, controlled distribution system and a packaging containing only 4 days treatment. As the efficacy of the medicinal product is not established, the relevance of the risk minimization measures could not be confirmed.

Taking into account all the available evidence submitted by the applicant and at the oral explanation before the CHMP, it was concluded that the data does not establish the efficacy of Alcover granules in the claimed indications. Considering the modest responder rates in the post-hoc subgroup analyses in the short-term, there is a potential risk that Very High DRL patients will not sufficiently respond to Alcover, but would still have the potential to become dependent on sodium oxybate in the longer term. In light of the above and the identified risks related to the product, the CHMP was of the opinion that the benefit-risk balance for Alcover granules in sachets, and associated names is not favourable.

Re-examination procedure

Following the adoption of the CHMP Opinion during the June 2017 CHMP meeting, the applicant Debrégeas & Associés (D&A) requested a re-examination of the Opinion.

CHMP discussion on grounds for re-examination

The CHMP thoroughly assessed the detailed grounds for re-examination submitted by the applicant for the use of Alcover granules in the long-term maintenance of alcohol abstinence in AD patients with a very high Drinking Risk Level (VH-DRL) and the treatment of acute alcohol withdrawal syndrome (AWS) and took into consideration the outcome of the consultation of an ad-hoc expert group on 4 October 2017.

Overall, the CHMP maintains its initial opinion that the results of the submitted clinical studies are not sufficient to establish the efficacy of Alcover (sodium oxybate) granules in the maintenance of alcohol abstinence and treatment of alcohol withdrawal syndrome (AWS) as there are several drawbacks in the design of these clinical studies, including open-label designs, small sample size, choice of patient population and absence of clearly defined, statistically significant outcomes, DRL not being recorded at baseline, low dose of comparator, and lack of assessment of effects on seizures or delirium as the most concerning events in alcohol withdrawal. The Committee also carefully considered the proposal from the applicant to perform a post-authorisation efficacy study. However, the conduct of the proposed post-authorisation study would not impact or change the Committee's conclusion that the efficacy of the medicinal product is not established. In absence of a positive benefit-risk balance established, the Committee is not in position to recommend grant of the marketing authorisation and the proposed post-authorisation study is not relevant. It is also highlighted that post-authorisation efficacy studies, as governed by Commission Delegated Regulation (EU) No 357/2014, should not be used as a justification for the premature granting of a marketing authorisation or for granting a marketing authorisation for medicinal products for which the risk-benefit balance is not considered positive.

With regards to the identified and potential risks related to the use of Alcover granules, in particular the risks of diversion, abuse, switch of addiction and toxicity if co-administered with alcohol, the Committee considered that the feasibility, proportionality and effectiveness of the proposed risk minimisation measures cannot be deemed evident in the absence of a demonstrated

efficacy in the claimed indications. Based on the above, the Committee concluded to maintain its previous opinion that the benefit-risk balance of this medicinal product is negative for both proposed indications.

Expert consultation

The CHMP consulted an ad-hoc expert meeting on some of the aspects that formed part of the detailed grounds submitted by Debrégeas & Associés (D&A).

There was a consensus among the experts on the clinical unmet need in the management of maintenance of abstinence from alcohol, and the need for more pharmacological treatment alternatives in this setting. The experts noted that only a minority of those patients receive indeed a pharmacotherapy and usually only a limited proportion of them respond to these treatments. The experts considered that sodium oxybate could potentially be a valuable addition to the current therapeutic armamentarium in the maintenance of abstinence from alcohol, if supported by adequate data. With regards to the treatment of acute withdrawal syndrome, the experts shared the views that there are well-established, evidence-based pharmacological treatments currently available, namely benzodiazepines, which are used throughout the European Union. However, it was recognised that it could be useful from the clinical perspective to have a product that could be used in both settings (acute withdrawal and maintenance of abstinence). In particular, there could be an advantage, for pragmatic reasons, to have a medicine which has a favourable impact on the craving process and thereby allow in-patient to become out-patient. The comment was also made with regards to the fact that for patients with benzodiazepines, dependence sodium oxybate could have a role.

The experts agreed that while the data currently available support a plausible effect and is encouraging, the strength of efficacy evidence is insufficient. A stronger signal of efficacy was found in the most severe population which was a promising result as those patients are less prone to placebo response and have limited therapeutic options. The experts considered that the company has generated an interesting hypothesis which requires confirmation in a prospective, well designed trial in the target population. As an additional point, the experts commented on the potential place of this medicine as substitution treatment or reduction of craving and prolongation of abstinence. It was underlined, however, that the pharmacokinetics properties of the product may be unfavourable for substitution due to short half-life and from clinical perspective the complete abstinence may not always be achievable. One of the experts with extensive experience with the use of marketed Alcover liquid considered the efficacy of sodium oxybate to be clinically shown and suggested to perform a study in the post-approval setting.

While the methodological challenges to run a randomised clinical trial in this field were acknowledged by the experts, they recommended the conduction of a prospective, multicentre placebo-controlled, feasible study in order to confirm the results in the subpopulation of interest. The target population expected to benefit most should be refined based on the data available and expert advice. The study duration should enable to conclude on efficacy and include at least 3 months of treatment and a predefined follow-up period. Regarding the outcome measures, the experts considered that data should be collected both on continuous abstinence and harm reduction. However the experts acknowledged that it may be difficult to evaluate and to have successful results for both endpoints within the same trial design. A design focusing on either of these endpoints with only supplementary data on the other might be acceptable. Craving and cognitive aspects may also be considered as secondary outcome measures. Evaluation of patients' compliance was regarded as important. The experts agreed that psychiatric comorbidities in

stabilised patients should not be an exclusion criterion, considering the high medical need in this patient group.

With regards the risk minimisation measures proposed by the applicant, the experts considered them generally welcome although some may be less realistic, notably the measure restricting the packaging to 4 days of treatment which may be difficult to handle in the clinical practice, and the contraindications about severe psychiatric disorders and poly-addicts which was not considered appropriate given the target population. Overall, whilst the experts considered that conditions of taking the medication are well-controlled and that no major safety issues have been reported so far, concerns were raised regarding the use of the product in patients of high risk groups, e.g. with renal impairment, liver dysfunction and/or electrolytes imbalance. Further investigation is also needed to assess the risk of abuse in the sub-population of interest with psychiatric comorbidities. Also experts were in favor of further monitoring the risk of seizures, particularly without convulsions. Finally, it was noticed that it could be anticipated that long-term use of sodium oxybate might have effects on cognitive function. Therefore, it would be advisable to monitor the cognitive adverse effects of sodium oxybate, particularly in patients with pre-existing cognitive impairments.

CHMP conclusions

In conclusion, further to the initial assessment and the re-examination procedure, the CHMP maintains its initial opinion that the benefit-risk balance of this medicinal product is not favourable in both of the proposed indications.

Grounds for the CHMP opinion following the re-examination procedure

Whereas

- The Committee considered the notification of the referral initiated by Austria under Article 29(4) of Directive 2001/83/EC, where Denmark, Spain, Finland, France, Ireland, the Netherlands, Portugal, Sweden and the United Kingdom raised objections to the marketing authorisation application for Alcover and associated names, 750 mg, 1250 mg, 1750 mg granules in sachets, which were considered to be a potential serious risk to public health;
- The Committee reviewed the totality of the data provided by the applicant in writing and in the oral explanations and related to the efficacy and safety of Alcover and associated names, 750 mg, 1250 mg, 1750 mg granules in sachets in the proposed indications for the maintenance of alcohol abstinence and the treatment of alcohol withdrawal syndrome; The Committee also considered the grounds submitted by the applicant within the re-examination procedure, and the views from an ad-hoc expert group.
- The Committee was of the view that the data submitted in support of the efficacy of Alcover granules in sachets in the claimed indications suffers from relevant methodological limitations relating to the design of the studies (such as insufficient sample size, selection of the patient population, post-hoc analyses). These data are therefore considered insufficient to establish the efficacy of Alcover, granules in sachets, in the proposed indications;
- With regards to the identified and potential risks related to the use of Alcover granules in sachets, the Committee considered the proposed risk minimisation measures, mainly to mitigate the potential risk of abuse, switch of addiction/ dependence and withdrawal in the light of the proposed indications;

The Committee concluded that in the absence of demonstration of efficacy for Alcover granules in sachets, the benefit-risk balance of this medicinal product is not favourable in the proposed indications.

Therefore, the Committee recommends the refusal of the marketing authorisation for Alcover and associated names, 750 mg, 1250 mg, 1750 mg granules in sachets.