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EMA/833636/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 29(4) of Directive 2001/83/EC

Alcover (granules in sachet) and associated names

INN: Sodium oxybate

Procedure number: EMEA/H/A-29(4)/1451

Note:

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

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1. Background Information

On 23 December 2014, an application was submitted under Article 8(3) of Directive 2001/83/EC, as a full-mixed application in the decentralised procedure (DCP) for Alcover and associated names, 750 mg, 1250 mg, 1750 mg granules in sachet.

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 The application in Germany was withdrawn during the DCP.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 decentralised procedure (DCP) AT/H/0552/01-03/DC, started on 2 February 2015.

On day 210, major issues on efficacy, safety and overall risk-benefit raised by Denmark, Spain, France, Ireland, The Netherlands, Sweden and United Kingdom, remained unresolved. 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. Hence, the procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), under Article 29(1) of Directive 2001/83/EC, by the RMS Austria on 21 October 2016. The CMDh 60 day procedure was initiated on 24 October 2016.

At Day 60 of the CMDh procedure (22 December 2016) no agreement could be reached and, therefore, the procedure was referred to the CHMP under Article 29(4) of Directive 2001/83/EC triggered by Austria.

2. Scientific discussion

2.1. Introduction

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) in accordance with 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 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 demonstrated. Furthermore, safety was considered to be acceptable by Austria taking into account the proposed risk minimisation measures (RMM).

However, the objecting 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.

It is to be noted that Alcover is approved in Austria and Italy, as an oral administration (syrup) used for alcoholism management to suppress the alcohol withdrawal syndrome (AWS) and the following craving. The administration of sodium oxybate reduces the alcohol craving and contributes to support the long-term weaning in alcohol-dependant patients.

2.2. Assessment of the issues raised as a potential serious risk to public health

Clinical aspects

Pharmacokinetics

The clinical module for Alcover (sodium oxybate) immediate release granules (SMO.IR) included several pharmacokinetic studies, which are summarised below:

- Study SMO032/10/01 was planned to determine the relative bioavailability and the safety profile of the granules formulation of sodium oxybate (SMO.IR) and the approved Alcover oral solution. C_{max} , AUC_t and AUC_{∞} lie well within the predefined acceptance limits between 80.00-125.00. Therefore, bioequivalence of SMO.IR and Alcover oral solution can be regarded as sufficiently proven by the study.
- Study SMO212/09/01 was planned to compare the PK profile of 4 different oral formulations of sodium oxybate in 12 healthy volunteers. The compared formulations were: Alcover oral solution (A), Xyrem oral solution (B), SMO.IR (sodium oxybate) immediate release granules (C), SMO.SR (sodium oxybate) slow release granules (D). Bioequivalence could be demonstrated between Xyrem and SMO.IR for C_{max} , AUC_t and AUC_{∞} . Bioequivalence could not be demonstrated between Alcover and SMO.IR; neither for C_{max} , nor for AUC_t nor for AUC_{∞} . Bioequivalence could be demonstrated between Alcover oral solution and Xyrem for AUC_t and AUC_{∞} , but could not be demonstrated for C_{max} . The inconclusive results of this pilot BE study were likely to be attributed to the low number of subjects included.
- Study SMO032/10/04, was planned to determine PK and PD interactions of sodium oxybate (SMO.IR granules) with alcohol. The study resulted in a significant interaction between SMO.IR and alcohol, namely an increase in alertness and stimulation and a decrease in sedation (after 15 minutes), which was interpreted as SMO.IR granules partially antagonizing the subjective sedative effects of alcohol.

Clinical efficacy

The clinical studies and bibliographic publications submitted in support of the application for the indications: long term maintenance of alcohol abstinence and treatment of alcohol withdrawal syndrome (AWS) are summarised below:

Maintenance of alcohol abstinence

- Study SMO032/10/03

Study SMO032/10/03 was planned as a randomised, multicentre (68 centres in 9 EU countries), double blind, placebo-controlled phase IIb study of the safety and efficacy of 4 dose regimens of SMO.IR (sodium oxybate granules) in the maintenance of alcohol abstinence during 84 days (12 weeks) + one

week of follow up without treatment. Responders were patients who completed the treatment phase and who were fully abstinent or with a Low or Medium drinking risk level (DRL).

The study failed to meet the primary endpoint: Percentage of Days Abstinent (PDA). Nevertheless, several secondary efficacy analyses were supportive during the treatment period and the follow-up period.

An interaction could be identified *a posteriori* between the treatment group and the patient DRL at baseline meaning that the treatment effect could be dependent upon the DRL at baseline, with very high placebo responses observed in patients presenting with a Low or Medium DRL at baseline and increased efficacy shown in the subgroup of patients with a High or Very High DRL at baseline. (According to the WHO-categorisation, high DRL means 61-100 g of pure alcohol per day for males, and 41-60 g of pure alcohol per day for females; very high DRL means ≥ 101 g/d for males and ≥ 61 g/d for females.)

The *post-hoc* analysis performed in the subgroup of patients with a High or Very High DRL at baseline, showed results that were significantly in favour of sodium oxybate (pooled active doses) for the PDA ($p = 0.022$), in the abstinence rate ($p = 0.044$) in the proportion of patients with a controlled drinking at Month 3 (as defined in Gallimberti et al, 1992¹; $p = 0.027$), in the change from baseline in TAC ($p = 0.027$) and in the change from baseline in HDD ($p = 0.015$).

The one-week follow-up period in study SMO032/10/03 to detect any withdrawal syndrome at treatment discontinuation was considered too short to support the sustainability of the treatment effect.

▪ GATE 2 Study

GATE 2 was a phase IV study, multicentre, multinational, randomised, double-blind, placebo-controlled, with parallel groups evaluating the efficacy of GHB (sodium oxybate, oral solution) versus placebo in the long-term maintenance in 314 patients (250 of them males), lasting 11 years (July 2001 till January 2012). Treatment duration was 180 days, with an untreated follow-up period up to day 360. Responders were defined as patients who completed the treatment phase in full abstinence. The DRL population at entry is unknown.

The primary endpoint was CAD (cumulative abstinence duration) during the treatment period of 180 days (6 months), showing borderline significance ($p = 0.0495$) between GHB [90.40 (SD 73.523) days] and placebo [73.92 (SD 74.499) days]. The effect size is modest which may be due to the heterogeneity of the patient population with insufficient DRL at entry.

▪ Gallimberti et al (1992)¹

A randomised, double-blind, placebo controlled trial over a 3 month treatment period ($n = 82$; 41 active vs 41 Placebo). Although no pre-defined primary endpoint or follow-up period were reported, the results are in favour of sodium oxybate with statistical significance for a number of endpoints: Percentage of Days Abstinent (PDA: the mean difference was 17.5 [95% CI: 10.5 to 24.5], $p < 0.01$), Total Alcohol Consumption (TAC: the mean difference was -4.6 drinks/day [95% CI: -6.2 to -3.0], $p < 0.01$), uninterrupted abstinence (Abstinence Rate: 26.8% of subjects in sodium oxybate group compared with 4.9% in placebo group, RR = 5.50 [95% CI: 1.30 to 23.29]), uninterrupted abstinence or controlled drinking (63.4% of subjects in sodium oxybate group compared with 19.5% in placebo group, RR = 3.25 [95% CI: 1.67 to 6.31]) as well as craving for alcohol. This study enrolled a population of Very High DRL. However, alcohol reduction was described in terms of number drinks without definition of grams of alcohol per drink.

¹ Gallimberti L, Ferri M, Ferrara SD, et al. (1992). γ -Hydroxybutyric acid in the treatment of alcohol dependence: a double-blind study. *Alcoholism, Clinical And Experimental Research*; 16(4):673-676.

- Di Bello et al (1995)²

This was a small trial over a 6 month treatment period (n= 17; 9 active vs 8 placebo). The effect of GHB on craving for alcohol and relapse into drinking (n=17) was examined under double blind conditions. The publication does not specify which endpoint was the primary endpoint. At the end of the 6-month treatment period, the percentage of subjects with continuous abstinence was higher in the sodium oxybate group (66.6%) than in the placebo arm (50%), but not statistically significant (Risk Ratio: 1.33 [95% CI: 0.58 to 3.07]; Excess Relative Risk: 16.6%; NNT = 6).

It is worth mentioning that according to the EMA guideline on the Development of Medicinal Products for the Treatment of Alcohol Dependence (EMA/CHMP/EWP/20097/2008)³, in order to establish long-term maintenance of abstinence, the overall outcome measurement including follow-up period should be of at least 12, but preferably 15 months after randomisation, which is a condition that was not fulfilled in any of the above submitted randomised trials.

- Caputo et al (2003)⁴ and Caputo et al (2007)⁵

These were open randomized comparative studies over 3 months. Sodium oxybate was shown to be superior to naltrexone in the abstinence rate with statistically significant results in Caputo et al., 2003 (n=35) and Caputo et al., 2007 (n=55). However, no statistical difference has been found in the number of patients with no relapse to heavy drinking between the groups.

- Nava et al (2006)⁶

The design of the study (N=86) was not reported in the publication. Sodium oxybate showed to be superior to disulfiram in the abstinence rate in this study with results close to statistical significance.

No statistical difference was found in the number of patients with no relapse to heavy drinking between sodium oxybate and naltrexone or disulfiram.

None of the above active comparator-controlled studies have been performed in patients with High or Very High DRL at baseline and a short abstinence period prior to randomization. In view of the high placebo response generally observed in AD trials the clinical relevance of active comparator trials not including a placebo arm is questioned.

Apart from the level of alcohol consumption at baseline, further factors such as the duration of treatment and the length of the abstinence period prior to randomization were identified as potential factors explaining the heterogeneous placebo response, with higher placebo response in shorter trials (Litten et al., 2013⁷) and in patients who had longer durations of abstinence prior to treatment (Gueorguieva et al., 2012⁸). Therefore, the applicant also carried out a meta-analysis in the abstinence rate and in the PDA by subpopulation of DRL at baseline, by duration of treatment and by duration of abstinence prior to randomisation, to show the consistency of the results in the two main endpoints (i.e. Abstinence rate and PDA) supporting the maintenance of abstinence as defined in the EMA

² Di Bello MG, Gambassi F, Mugnai L, et al. 'Gamma-hydroxybutyric acid induced suppression and prevention of alcohol withdrawal syndrome and relief of craving in alcohol-dependent patients', *Alcologia*, Vol. 7(2), 1995, 9-16.

³ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003473.pdf

⁴ Caputo F, Addolorato G, Lorenzini F, et al. 'Gamma-hydroxybutyric acid versus naltrexone in maintaining alcohol abstinence: an open randomized comparative study', *Drug and Alcohol Dependence*, Vol. 70(1), 2003, 85-91.

⁵ Caputo F, Addolorato G, Stoppo M, et al., 'Comparing and combining gamma-hydroxybutyric acid (GHB) and naltrexone in maintaining abstinence from alcohol: an open randomized comparative study', *European Neuropsychopharmacology*, Vol. 17, 2007, 781-789.

⁶ Nava F, Premi S, Manzato E, et al., 'Comparing treatments of alcoholism on craving and biochemical measures of alcohol consumptions' *Journal of Psychoactive Drugs*, Vol. 38(3), 2006, 211-217.

⁷ Litten RZ, Castle IJ, Falk D, et al., 'The placebo effect in clinical trials for alcohol dependence: an exploratory analysis of 51 naltrexone and acamprosate studies', *Alcoholism, Clinical and Experimental Research*, Vol. 37(12), 2013, 2128-2137.

⁸ Gueorguieva R, Wu R, Donovan D, et al. 'Baseline trajectories of heavy drinking and their effects on post-randomization drinking in the COMBINE Study: empirically derived predictors of drinking outcomes during treatment' *Alcohol*, Vol. 46(2), 2012, 121-131.

Guideline on the development of medicinal products for the treatment of alcohol dependence (EMA/CHMP/EWP/20097/2008)³. The target population for sodium oxybate was restricted to patients with a Very High DRL at baseline and an abstinence period prior to randomization shorter than 2 weeks for the placebo—controlled studies. However no active comparator –controlled study has been performed in patients with High or Very High DRL at baseline and a short abstinence period prior to randomisation.

The meta-analysis in the abstinence rate in the post-hoc defined population with VH-DRL showed a statistically significant treatment effect vs placebo in the target population. Similarly, the meta-analysis in the PDA showed a statistically significant treatment effect vs placebo in the target population. However the results from meta-analyses from RCTs with active comparator arms must be interpreted with caution as currently available treatments for this indication have shown only inconsistent, modest treatment effects.

In addition, the applicant replicated a subpopulation analysis based on the *post hoc* analyses of patient subgroups in small populations as carried out for another centrally approved product with a similar indication, which indicated beneficial effects.

Conclusion on the clinical efficacy for the indication: Maintenance of alcohol abstinence

In summary, the results of the submitted efficacy studies cannot be considered sufficient to provide robust evidence to establish the efficacy of Alcover (sodium oxybate) granules in the maintenance of alcohol abstinence. There are several drawbacks in the design of the 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.

Several post-hoc subgroup analyses and meta-analyses of the data obtained in clinical trials in medium and long-term maintenance of abstinence were also performed by the applicant. However these data were considered too sparse, not consistent and not sufficiently robust to support an indication in this Very High DRL patient population.

Acute withdrawal syndrome (AWS)

- Gallimberti et al (1989)⁹

A small randomised, double blind study consisting of 23 patients (11 on one single oral dose of 50 mg/kg sodium oxybate vs 12 on placebo syrup), in which 6 main AWS symptoms (tremors, sweating, nausea, depression, anxiety, and restlessness) scored on a 4 point scale, measured over 7 hours led to a highly significant decrease in the measured total score in the treatment group.

- GATE 1 Study

GATE 1 was a Phase IV, multicentre, randomized (1:1), parallel group, double-blind, double-dummy active drug-controlled study evaluating the efficacy of GHB (Alcover oral solution) versus a short acting benzodiazepine (oxazepam), in patients with moderate to severe alcohol withdrawal syndrome Clinical Institute Withdrawal Assessment for Alcohol revised version (CIWA-Ar ≥ 20 , CIWA-Ar short scale ≥ 12). The objective was to confirm the equivalence in the change from baseline in CIWA-Ar between sodium oxybate and oxazepam. Only 126 patients were included in the analyses (61 GHB, 65 Oxazepam) after 7 years of enrolment.

⁹ Gallimberti L, Gentile N, Cibir M, et al., 'Gamma-hydroxybutyric acid for the treatment of alcohol withdrawal syndrome', The Lancet, Vol. 2(8666), 1989, 787-789.

The primary endpoint was the time course of symptom intensity assessed by a CIWA-Ar scale subscore/short scale consisting of 3 items, namely tremor, hyperhidrosis (sweats), and anxiety/nervousness, evaluated during 10 days of treatment and 10 days of follow-up.

There was no statistically significant difference in the relative mean changes of the primary endpoint from screening to end of study between the two treatment groups but a tendency towards better results for Oxazepam could be seen.

- Addolorato et al (1999)¹⁰

The study was a small randomized, single-blind and diazepam-controlled study. Main criteria were evolution of CIWA-Ar, STAY-y1, and SDS Zung test. There was no significant difference between the two groups of patients at baseline and at the different times of observation. Both treatments were effective in reducing AWS physical symptoms. Enrolled patients were representative of a Very High DRL at baseline.

- Nimmerrichter et al (2002)¹¹

The study was a randomised, double-blind, clomethiazole-controlled study. The primary efficacy variable was the reduction of the CIWA-Ar compared to the individual baseline level. Patients of all groups achieved a clinically relevant and statistically significant improvement of their withdrawal symptoms on CIWA-Ar at Day 2. There was no statistically significant difference between treatment groups.

- Nava et al (2007)¹²

This was a randomized, diazepam-controlled study that was not blinded. Sodium oxybate was statistically more effective than diazepam in reducing both CIWA-Ar total score and CIWA-Ar mean sub-scores (tremor, paroxysmal sweats, anxiety and agitation) and in reducing cortisol levels at different times of observation, showing a superiority of sodium oxybate over diazepam in AWS control.

- GHB-Use and Misuse (GUM) study

The GUM study was an observational study (retrospective survey) in Italian alcohol-dependent patients. No dosage recommendation is clearly deducible from GUM, besides the information that patients obviously took between 50 and 100 mg/kg/d of sodium oxybate.

The treatments were not in accordance with the summary of product characteristics (SmPC) recommended treatment duration of Alcover (neither with the AT SmPC: 7 days for acute AWS treatment, nor with the IT SmPC: 7-10 days for AWS). Clear conclusions on the applied dosage or the drinking habits of the included patients, were impossible to draw.

A meta-analysis of RCTs vs. benzodiazepines or clomethiazole was provided indicating that CIWA-Ar score at the end of treatment was not statistically different to benzodiazepine and slightly in favour of sodium oxybate.

Conclusion on the clinical efficacy for the indication: Acute withdrawal syndrome

¹⁰ Addolorato G, Balducci G, Capristo E, et al., 'Gamma-hydroxybutyric acid (GHB) in the treatment of alcohol withdrawal syndrome: A randomized comparative study versus benzodiazepine' *Alcoholism, Clinical And Experimental Research* Vol. 23(10), 1999, 1596-1604.

¹¹ Nimmerrichter AA, Walter H, Gutierrez-Lobos KE, et al. 'Double blind controlled trial of γ- hydroxybutyrate and clomethiazole in the treatment of alcohol withdrawal', *Alcohol & Alcoholism* (Oxford, Oxfordshire), Vol. 37(1), 2002, 67-73.

¹² Nava F, Premi S, Manzato E, et al. 'Gamma-hydroxybutyrate reduces both withdrawal syndrome and hypercortisolism in severe abstinent alcoholics: an open study vs. diazepam', *The American Journal of Drug and Alcohol Abuse*, Vol. 33(3), 2007, 379-392.

In summary the results of the submitted efficacy studies cannot be considered sufficient to provide robust evidence to establish the efficacy of Alcover (sodium oxybate) granules in the treatment of alcohol withdrawal syndrome (AWS), as the studies submitted with active arm comparators (Gate 1, Nava 2007¹², Addolorato 1999¹⁰ and Nimmerrichter 2002¹¹) had several methodological limitations 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, chosen low doses in the fixed-dose active comparator arms, the chosen subset of withdrawal symptoms not covering the clinically most concerning events like seizures and delirious states and long enrolment period.

The CHMP therefore considers that these studies do not allow demonstration of efficacy in this therapeutic indication.

Clinical safety

Safety data has been collected from clinical trials sponsored by D&A PHARMA or Laboratorio Farmaceutico C.T. (707 patients exposed) to investigate alcohol-dependent patients with Very High DRL exposed to sodium oxybate based on their polymedication (the use of two or more psychoactive drugs) or psychiatric comorbidity status, 36 clinical trials from literature (2106 patients exposed), 2 observational studies (623 patients exposed) and the pharmacovigilance data notified for the Alcover syrup authorised (260,000 patients exposed).

The main risks identified are:

- **CNS depression and respiratory depression**

Nineteen (2.2%) adverse drug reactions (ADRs) of CNS depression events were reported from the clinical database in Very High DRL patients with no polymedication drug use or psychiatric comorbidity. During the post-marketing experience of Alcover syrup, 14 cases (0.01%) of CNS depression were reported, with an average dose of 15 g of sodium oxybate intake in a context of polydrug use for the majority of them. Main symptoms were sopor, coma, loss of consciousness, restlessness and confusional state, dysphagia, delirium.

There is published literature informing about a few cases of CNS depression, respiratory depression and death following administration of Gammahydroxybutyrate (GHB), but it seems that this information refers for the most part to illicit/street GHB where purity and concentration, where the excipients as well as the dose used are unknown. Furthermore, this medicinal product is often taken concomitantly with other drugs in this context. No cases of death have been reported due to Alcover syrup.

- **Risk of abuse/misuse/diversion**

Table: risk of abuse /misuse in Very High DRL patients across clinical database

Risk: ABUSE / MISUSE	Alcohol-dependent VH DRL patients			L/M/H DRL (n=343)	Unknown DRL (n=1464)	Healthy volunteers (n=231)
	Alcohol dependent only (n=846)	Poly-drug users (n=326)	Severe psychiatric comorbidities (n=226)			
Clinical data - Trials carried out by the Applicant	0	na	na	0	0	0
Clinical data – Trials from literature	0	11 (3.4%)	6 (2.7%)	0	18 (1.2%)	-
Observational studies	11 (1.3%)	25 (7.7%)	22 (9.7%)	0	7 (0.5%)	na

Source: [Applicant's response document to CHMP List of Questions – Supplementary information](#)

Grey shaded cells mean that population outside of the proposed indication or population where the treatment is contraindicated

A higher incidence of abuse/misuse can be observed in patients with severe psychiatric comorbidities or in past or present cocaine or heroin dependent patients (Caputo et al, 2009; GUM). The 11 cases of abuse in Very High DRL patients were observed in GUM study.

During more than 20 years of post-marketing experience of Alcover in its syrup formulation (260,000 patients treated), 6 cases of drug abuse were reported, with an average dose of 20g of sodium oxybate intake in a context of polymedication use for most of them. Symptoms were sopor, vomiting, vertigo, somnolence, agitation and mydriasis.

Risks of abuse / misuse are higher in polymedication users (cocaine or heroin) and/or patients with severe psychiatric comorbidities.

Regarding the risk of abuse the applicant has proposed restricted prescription and dispensing and the inclusion of a special warning in section 4.4 of SmPC as well as a contraindication in patients with polymedication use or severe psychiatric comorbidities.

▪ Risk of dependence/switch of addiction/withdrawal

The applicant has conducted a search in the clinical and pharmacovigilance database using the preferred terms: "Dependence" and "Withdrawal" to the study drug. In addition, in clinical trials sponsored by the applicant, the craving to study drug was measured as an indicator of a switch of addiction.

One case (0.1%) of dependence/withdrawal was reported from the clinical database in a Very High DRL patient with no history of polymedication use or severe psychiatric comorbidity. The case was not considered as serious. Three cases of drug withdrawal were reported from observational studies in Very High DRL patients (GUM) without any information on the presence of a history of polymedication use or psychiatric comorbidity. The cases occurred only when patients voluntarily decided to prematurely and abruptly stop treatment, suggesting that drug tapering should be medically supervised.

During the post-marketing period of over 20 years of Alcover syrup (260,000 patients treated), 2 cases of drug dependence were reported, with an average dose of 12g per day of sodium oxybate intake in a context of polymedication use and illicit / street drugs.

Overall craving for sodium oxybate was mild, with no statistically significant difference versus placebo observed at the end of active treatment in GATE 2. In study SMO032/10/03 craving for the medication increased during the week of follow-up without treatment but the score remained at the lower end of the scale, indicating a mild craving for study medication. CHMP noted that substances with addiction potential are not recommended in the treatment of alcohol dependence due to the switch of addiction

as per EMA Guideline on the development of medicinal products for the treatment of alcohol dependence (EMA/CHMP/EWP/20097/2008)³.

Risk minimisation measures

Regarding the overall safety of Alcover granules, the risk of Abuse / Misuse / Diversion / Overdose / Dependence / CNS / Respiratory Depression in Very High HDRL patients is well-recognized. The applicant has proposed to further reduce these risks 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 as well as other additional 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.

Additional risk minimization measures such as the implementation of a restricted prescribing and controlled distribution system and a packaging containing only 4 days treatment were also proposed. As the efficacy of the medicinal product is not established, the relevance of the risk minimization measures could not be confirmed.

3. Benefit-risk assessment

3.1. Initial benefit-risk balance assessment

The results of the submitted efficacy studies cannot be considered sufficient to provide 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 1992¹, GATE 2 and Di Bello 1995², 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)¹³.

With regards to the indication alcohol withdrawal syndrome (AWS), the efficacy of sodium oxybate granules has also not been established. The Gallimberti 1989 trial⁹ 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 2007¹², Addolorato 1999¹⁰ and Nimmerrichter 2002¹¹) 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 such as chosen low fixed doses in the active comparator arms, the chosen subset of withdrawal symptoms not covering the clinically most concerning events like seizures and delirium, 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 (in particular their feasibility, proportionality and effectiveness) 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 granules, 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

¹³ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf

opinion that the benefit-risk balance for Alcover granules in sachets, and associated names is not favourable.

3.2. Re-examination procedure

Following the adoption of the CHMP Opinion in June 2017, the applicant requested a re-examination of this initial Opinion on 30 June 2017. The detailed grounds for re-examination were received on the 18th August 2017.

Detailed grounds for re-examination submitted by the applicant Debrégeas & Associés Pharma are summarised below:

- **Evidence in support of the indication of “maintenance of abstinence”**

The applicant claimed that the seriousness of the disease alcohol dependence and the unmet clinical need have not been given the appropriate weight. In addition the applicant does not agree with the assessment and the issues raised on the design and the results from the analysis in broad alcohol dependent (AD) population and the validity of the meta-analysis in broad alcohol dependent population and the validity of the subpopulation analysis. Moreover, the applicant does not agree with the CHMP statement that the sample size included in target population was small and provides clarification for such inclusion. Another point of argumentation concerns the consistency, robustness and clinical relevance of the results. With the regards to the safety concerns the applicant provides argumentation for the safety profile of sodium oxybate based previous PRAC assessment for PSUR and experience from the countries where the medicinal product is authorised. The applicant concludes that the benefit/risk balance of the medicinal product for the maintenance of abstinence is positive.

- **Evidence in support of the indication of “treatment of alcohol withdrawal syndrome (AWS)”**

With regards to the treatment of alcohol withdrawal syndrome (AWS), the grounds of the re-examination included clarification that the proposed indication is not limited to very high drinking risk level (VH-DRL) patients. In addition, the applicant provides argumentation for the limited efficacy from the placebo-controlled trials and the active comparator-controlled trials (cf. clinical efficacy section in 2.2).

3.2.1. CHMP discussion on grounds for re-examination

Clinical efficacy

Indication of “maintenance of abstinence”

The applicant claimed the following indication: *“support in the medium to long-term maintenance of alcohol abstinence in alcohol dependent adult patients with a very high drinking risk level (consumption of more than 60g alcohol/day for women and of more than 100g alcohol/day for men) under careful medical supervision along with psychotherapy and social rehabilitation. Treatment should be initiated only to patients whose duration of abstinence prior to treatment does not exceed 2 weeks.”*

The above indication is summarised hereinafter as ‘maintenance of abstinence’.

In order to support the demonstration of efficacy and safety of Alcover granules in the maintenance of abstinence the applicant submitted the two following clinical trials: SMO032/10/03 and GATE-2, two

literature reports, a meta-analysis and a subpopulation analysis of seven randomised controlled clinical trials.

The applicant's grounds on the indication "maintenance of abstinence" have been addressed below discussing each study separately.

Study SMO032/10/03

The SMO032/10/03 study was a randomised, multicentre, double blind, placebo-controlled phase IIb study in 496 patients evaluating the safety and efficacy of 4 dose regimens (0.75 g tid, 1.25 g tid, 1.75 g tid, 2.25 g tid) of SMO.IR (sodium oxybate granules) versus placebo in the maintenance of alcohol abstinence during 12 weeks plus one week of follow-up without treatment. Responders were patients who completed the treatment phase and who were fully abstinent or with a low or medium drinking risk level (DRL).

Although there were several supportive secondary endpoints (such as abstinence rate, number of HDD, percentage of HDD), the primary efficacy endpoint PDA (percentage of days abstinent) compared to placebo was not met for any of the four doses (p value of 0.547 [-6.49; 12.24] 95 CI% in the 0.75g tid active group, p value of 0.871 [-8.66; 10.22] 95 CI% in the 1.25g tid active group, p value of 0.856 [-10.16; 8.43] 95 CI% in the 1.75g tid active group, p value of 0.749 [-7.83; 10.88] 95 CI% in the 2.25g tid active group) or across doses over the 12-week double-blind treatment period in the intention to treat (ITT) population. Moreover, the chosen primary endpoint allows interruptions of days with drinking and, therefore, is not in line with the primary endpoint as defined in the EMA guideline (EMA/CHMP/EWP/20097/2008)³ for full abstinence-oriented treatment settings.

The study results were also highly compromised by the high drop-out rate of 38% of the ITT population (189 patients out of 496 did not complete the 12-week treatment period).

An interaction could be identified *a posteriori* between the treatment group and the patient DRL at baseline meaning that the treatment effect could be dependent upon the DRL at baseline. Very high placebo responses observed in patients presenting with a low or medium DRL at baseline and increased efficacy shown in the subgroup of patients with a High or VH-DRL at baseline. It is noted that according to the WHO definition of the DRL, the majority (68.8%) of included subjects, although being formally diagnosed as alcohol dependent, presented with medium or even low DRL. Only 16.1% were in the category VH-DRL and therefore representing the proposed target population.

In view of the overall design-related shortcomings, the high drop-out rate and the failure to meet the primary endpoint of the phase IIb study SMO032/10/03, the results of this study do not provide sufficient evidence to establish the efficacy of the medicinal product in the maintenance of abstinence setting.

Study GATE 2

The GATE 2 study was a phase IV study, multicentre, multinational, randomised, double-blind, placebo-controlled, with parallel groups evaluating the efficacy of GHB versus placebo in the long-term maintenance in 314 patients (250 of them males), lasted 11 years. The treatment duration was 180 days, with an untreated follow-up period up to day 360. Responders were defined as patients who completed the treatment phase in full abstinence.

At study inclusion, subjects were recruited according to their assignment to so-called Lesch typology (type I-IV). The DRL at entry was not recorded. The applicant performed retrospective back-calculation for baseline assumed alcohol consumption based on biomarkers (GGT, MCV) and concluded on a mild

DRL. However, the CHMP did not consider that it could satisfactorily address the lack of recording of DLR at baseline. Therefore, it is questionable in how far the data obtained from the study population can support the label claim in the VH-DRL AD patients.

The drop-out rate was high for the 180 day double blind period (58%) and for the entire study (360 days) leading to overall drop-out rate of 77.8%; 74% in the GHB group and 80.6% in the placebo group and questioning the robustness of the study results.

The primary endpoint cumulative abstinence duration (CAD) during the treatment period of 180 days reached borderline statistical significance ($p = 0.0495$) between GHB [90.40 (SD 73.523) days] and placebo [73.92 (SD 74.499) days]. The effect size is modest possibly due to the heterogeneity of the patient population with insufficient DRL at entry. This endpoint does not capture the continued duration of abstinence achieved within 180 day double blind treatment period but is calculated per 30-day interval in between 2 study visits (visits were conducted every 30 days until day 180 of the double-blind treatment period). The sensitivity of this endpoint is questioned by CHMP and is not in line with the primary endpoint as defined in the EMA guideline (EMA/CHMP/EWP/20097/2008)³ for full abstinence-oriented treatment settings.

Continued abstinence was assessed at the end of the treatment period (day 180) and the end of the observation period (day 360) as secondary endpoint. However, this secondary endpoint failed to reach statistical significance both at the end of the treatment period at day 180 (25.3% in GHB group versus 20% in the placebo group, $p = 0.259$) and at the end of the observation period at day 360 (15.6% in the GHB group and 10.6% in the placebo group, $p = 0.192$).

In summary, this clinical study suffers from methodological limitations such as study population chosen according to criteria (Lesch's typology as defined in *Lesch et al.*, 1988) other than the population of the claimed indication, the lack of recording of DRL, the high drop-out rate and the inconsistent outcome with borderline significant and non-significant results. The limitations of this study do not allow demonstrating the efficacy in the maintenance of abstinence in patients with VH-DRL.

Subpopulation analysis

In addition, the applicant conducted *a posteriori*, a subpopulation analysis in patients presenting with VH-DRL, including 7 RCTs (GATE 2, SMO032/10/03, Gallimberti 1992¹, Di Bello 1995², Caputo 2003⁴, Caputo 2007⁵, Nava 2006⁶) and claims similarity of this analysis with the analysis conducted for nalmefene.

The CHMP noted that the benefit-risk assessment is made on the merits of each application, in particular based on the strength of the evidence submitted. Comparison with nalmefene dossier is not relevant due to the fact that Nalmefene dossier included two phase III RCTs and the primary parameters recommended by the AD guideline were measured. Secondly the included study population was representative of the therapeutic indication; hence the subgroup analysis was not undertaken because the study population was *a priori* inadequately chosen. Thirdly unlike GHB, nalmefene is an opioid receptor antagonist without any inherent addictive properties. Furthermore, the safety concerns related to reported cases of fatal outcome in case of mixing alcohol with GHB are not comparable with nalmefene.

This subpopulation analysis was conducted in support of the applicant's claim to narrow the proposed indication of Alcover granules to the sub-population of patients presenting with VH-DRL (16.1% of the ITT population of SMO032/10/03).

The CHMP questioned the significance of the pooled doses data based on study SMO032/10/03 as this phase II dose finding study was not powered for comparisons per baseline DRL of included subjects

and as the subpopulation VH-DRL represents only 16.1% of ITT (80 on 496 patients). In this *post-hoc* analysis of the pooled very severe population VH-DRL subgroup of study SMO032/10/03, no statistical significance in comparison to placebo could be reached. In addition, a very high rate of drop-out rate (61%, 11 out of 18 patients) was observed in the highest dose group (2.25g).

It was also noted by CHMP that none of the three open label studies (Caputo 2003⁴, Caputo 2007⁵, Nava 2006⁶) was placebo controlled and GHB was compared with active comparators. As such these studies do not provide confirmatory evidence to the demonstration of GHB's efficacy in abstinence-oriented treatment of AD.

Based on the above, the CHMP confirmed its previous conclusions that the subpopulation analysis was not sufficiently robust to support the efficacy of the medicinal product in a therapeutic indication narrowed to the VH-DRL population.

Literature reports

Two literature reports were submitted as part of this procedure: Gallimberti et al. 1992¹ and Di Bello² et al. 1995².

The Gallimberti study (1992) was a randomised, double-blind, placebo controlled trial over a 3 month treatment period (n= 82; 41 active vs 41 Placebo).

The primary endpoint or follow-up period was not reported. The evaluated endpoints were in favour of sodium oxybate with statistical significance for a number of endpoints: Percentage of Days Abstinent (PDA: the mean difference was 17.5 [95% CI: 10.5 to 24.5], $p < 0.01$), Total Alcohol Consumption (TAC: the mean difference was -4.6 drinks/day [95% CI: -6.2 to -3.0], $p < 0.01$), uninterrupted abstinence (Abstinence Rate: 26.8% of subjects in sodium oxybate group compared with 4.9% in placebo group, RR = 5.50 [95% CI: 1.30 to 23.29]), uninterrupted abstinence or controlled drinking (63.4% of subjects in sodium oxybate group compared with 19.5% in placebo group, RR = 3.25 [95% CI: 1.67 to 6.31]) as well as craving for alcohol. The major drawback was the failure to define *a priori* the primary study endpoints and the missing follow-up. The CHMP considered that this study as hypothesis generating but not confirmatory.

In view of the major drawbacks, notably primary endpoints not pre-specified and missing follow-up data, the CHMP considered that this study can not be seen as confirmatory.

In the Di Bello study (1995)² which included only 17 patients, the abstinence rate was in favour of sodium oxybate but with a small effect size and not statistically significant (Risk Ratio: 1.33 [95% CI: 0.58 to 3.07]; Excess Relative Risk: 16.6%; NNT = 6). Furthermore, the primary endpoint was not pre-specified, small sample size and the follow up after the 6-month treatment was missing. These methodological limitations combines with a small sample size do not allow CHMP to consider this study as confirmatory.

Meta-analysis

The applicant also conducted a meta-analysis of SMO032/10/03, GATE-2 and the two clinical trials referenced in Gallimberti (1992)¹ and Di Bello (1995)² with the aim to confirm efficacy in the general alcohol-dependent population regarding the abstinence rate.

According to the EMA guideline "Points to consider on Application with 1. Meta-Analyses; 2. One Pivotal Study" CPMP/EWP/2330/99¹⁴, it is outlined that a meta-analysis cannot reconcile the conflicting results

¹⁴ EMA guideline "Points to consider on Application with 1. Meta-Analyses; 2. One Pivotal Study" CPMP/EWP/2330/99 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003657.pdf

of one positive and one inconclusive study. In this meta-analysis, the included studies were not clearly positive. In particular, the two applicant-sponsored clinical trials (SMO032/10/03, GATE-2) do not provide a clearly significant result for the broad population or are inconsistent. In addition, both studies failed to define a primary endpoint for abstinence in line with the above-mentioned EMA guideline, i.e. reflecting continued abstinence. These two studies have also other methodological limitations detailed in the discussion in the previous ground. The two literature reports (Gallimberti et al. 1992, Di Bello et al. 1995) have major drawbacks (no primary endpoint pre-specified, small sample size etc.) and cannot be taken as positive confirmatory studies but only hypothesis-generating.

The applicant provided further clarification but it was not considered sufficient to address the shortcomings of the meta-analysis.

In conclusion, the CHMP confirmed its previous position that the meta-analysis performed does not provide sufficient evidence to establish the efficacy of Alcover granules in the claimed indication.

Treatment of alcohol withdrawal syndrome (AWS)

With regards to the indication for the treatment of alcohol withdrawal syndrome (AWS), the applicant highlighted that the proposed indication "Treatment of acute alcohol withdrawal syndrome in alcohol dependent adult patients." covers alcohol dependent adult patients with an acute alcohol withdrawal syndrome. The indication is not limited to VH DRL patients. The CHMP acknowledges this confirmation and agreed that AWS arises in alcohol-dependent individuals after reducing or interrupting ethanol consumption and requires treatment.

The applicant's grounds on the indication "Treatment of alcohol withdrawal syndrome" have been addressed below discussing each study separately.

Literature report

The applicant presented one literature report (Gallimberti 1989⁹) which was the only placebo-controlled RCT to evaluate sodium oxybate in the treatment of AWS. The clinical trial showed favourable results for the active arm in reducing alcohol withdrawal symptoms during the double-blind treatment phase (7 hours) but the sample size was too small (n=11 sodium oxybate vs. n= 12 placebo) to conclude on the efficacy in the treatment of AWS.

Based on the baseline score of 6 withdrawal symptoms (4-pt scale, type of scale not reported), patients presented with a score of 11.8 – 12.6, hence pointing to moderate AWS. Patients were excluded if presenting with a history of convulsions or delirium tremens. The scores of 6 pre-defined symptoms significantly improved in the GHB arm and remained the same (or even worsened) in the placebo arm over a 7-hour treatment/observation period. Seven subjects in the GHB arm (63%) experienced transient dizziness and none in the placebo group.

It is noted that alcohol withdrawal symptoms usually appear within 4 to 12 hours after the last drink, peak within 24 to 48 hours and diminish markedly within 4 to 5 days¹⁵. Hence, the 7-hour period described in the literature report does not cover a representative time span. In addition, Leone MA and co-workers conclude in their Cochrane Review that "*There is insufficient randomised evidence to be confident of a difference between GHB and placebo, or to determine reliably if GHB is more or less effective than other drugs for the treatment of alcohol withdrawal or the prevention of relapse*"¹⁶.

¹⁵ Claassen CA & Adinoff B (1999). Alcohol Withdrawal Syndrome. CNS Drugs; 12(6)279-291)

¹⁶ Leone MA et al. Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses (Review) The Cochrane Collaboration 2011.

The CHMP acknowledged the ethical concern of including a placebo patient group with AWS as the disease can be life-threatening and as there is available effective treatment.

The other clinical trials from the literature with active arm comparators (Nava 2007¹², Addolorato 1999¹⁰ and Nimmerrichter 2002¹¹) have also serious methodological flaws (e.g small sample size, heterogeneity in the studies' population, lack of protocol or defined primary endpoints, assessment of large number of outcomes such as chosen low fixed doses in the active comparator arms, the chosen subset of withdrawal symptoms not covering the clinically most concerning events like seizures and delirium,) which lead to conclusions based on post-hoc analysis not allowing to conclude on the efficacy of Alcover granules in the treatment of AWS.

GATE 1

The double-blind phase IV clinical study GATE 1 was initially intended to recruit 208 patients but the recruitment stopped after 7 years where 127 patients were recruited and randomized. With this recruitment rate, the study reached a statistical power of only 64%. The objective was to confirm the equivalence in the change from baseline in Clinical Institute Withdrawal Assessment for Alcohol revised version (CIWA-Ar) between sodium oxybate and oxazepam. The primary endpoint was the time course of symptom intensity assessed by a CIWA-Ar scale sub-score/short scale consisting of 3 items, namely tremor, hyperhidrosis (sweats), and anxiety/nervousness, evaluated during 10 days of treatment and 10 days of follow-up. There was no statistically significant difference in the relative mean changes of the primary endpoint from screening to end of study between the two treatment groups but a tendency towards better results for Oxazepam could be seen.

In addition, it is noted that the major clinical concern in patients requiring pharmacological treatment of AWS is occurrence of seizures and development of potentially life-threatening delirious states. However, these symptoms are not captured by the outcome criteria (tremor, sweating, anxiety-nervousness).

Overall, it is concluded that due to design features (e.g. choice of efficacy outcome), the lack of sufficient statistical power and observed protocol violations, GATE-1 study does not provide confirmatory evidence for establishing the efficacy of Alcover granules in the treatment of AWS.

Conclusion on efficacy

The CHMP acknowledged the great burden of alcohol dependence to public health and the limitations of the available therapeutic options in the claimed indication. However, the efficacy and safety of the medicinal product in the claimed indications and a positive benefit-risk balance should be demonstrated.

The CHMP also acknowledged the methodological challenges of clinical trials for medications for the treatment of AD and withdrawal. However, the CHMP took into consideration the overall high prevalence of AD. The CHMP did not agree with the estimation on the number of eligible patients provided by the applicant. All exclusion criteria were subtracted consecutively from the initially assumed subject number potentially in need of treatment for AD leading to an artificially low number.

The CHMP confirmed its previous opinion that the presented data were considered too sparse, not consistent or sufficiently robust to support the efficacy of Alcover granules in the claimed indications.

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 thus far established. In the absence of a positive benefit-risk balance being established, the Committee is not in position to recommend the granting of the marketing authorisation nor to consider the proposed post-authorisation study. Indeed, 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.

Clinical Safety

Within the submitted grounds, the applicant refers to the PRAC report of 2016 and 2017 on the PSUR for sodium oxybate regarding the lack of serious safety concerns in relation to sodium oxybate in liquid formulation. The CHMP acknowledged the significant exposure to Alcover syrup in 3,493 patients in the applicant's clinical database and 260,000 patients in the applicant's pharmacovigilance database, among which no deaths attributable to sodium oxybate have been reported.

The CHMP noted that despite this exposure, the addictive properties of GHB cannot be ignored and maintains its previous position that there is a significant risk of abuse, misuse, overdose and dependence in VH-DRL patients.

With regards to the applicant's position that the abuse was not reported for the granules, the CHMP noted that GHB as a substance and due to its pharmacokinetic/pharmacodynamic profile has a potential for abuse and that the granule formulation would not change this.

Evidence from literature Abandes (2007)¹⁷ suggests "*a high abuse liability of GHB and flunitrazepam in club drug users*". It is noted that the doses of GHB tested by Abandes are exactly in the same range as proposed for the indications of Alcover granules.

In a recent small pilot study to examine the use of sodium oxybate (SO) in maintaining abstinence in alcohol-dependant patients according to Lesch typology considerable craving rates resp. abuse was noticed: (Craving for SO: Lesch I 18.2% [2/11], Lesch II 25% [3/12], Lesch III 35.7% [5/14], Lesch IV 9.1% [1/11], Abuse of SO: Lesch II 8.3% [1/12], Lesch III 14.2% [2/14]) (Caputo F et al. 2014¹⁸).

A publication from Barker (2007)¹⁹ showed a peculiar time course of GHB effects with an extremely fast onset and short duration, rendering GHB particularly liable to abuse. In a publication by Abandes (2007)¹⁷, recreational drug users rated GHB higher in terms of euphoria (measures "high" and "stimulated") than ethanol or flunitrazepam.

Of note, the respective EMA guideline requires the assessment of reinforcing/addition potential to rule out switch of addiction.

There is also a safety concern regarding the co-ingestion with alcohol, these alerts were given by non-alcohol dependent recreational users (Barker 2007). In 2012, FDA issued a Drug Safety Communication and a contraindication for use of sodium oxybate in combination with sedative hypnotics or alcohol after cases of severe CNS depression leading to coma and death had occurred. Similar warnings are included in the EU SmPC of products contain sodium oxybate. Although it is acknowledged that the doses recommended for these products are higher than those for Alcover, concomitant intake of alcohol and/or sedatives is more likely in the proposed target population for

¹⁷ Abandes S et al. (2007). Relative Abuse Liability of γ -Hydroxybutyric Acid, Flunitrazepam and Ethanol in Club Drug Users. J Clin Psychopharmacol; 27(6):625-638).

¹⁸ Caputo F et al., 'Sodium oxybate in maintaining alcohol abstinence in alcoholic patients according to Lesch typologies: A pilot study', J Psychopharmacol, Vol. 28(1), 2014, 23-30.

¹⁹ (Barker JC et al. (2007). Experiences of Gamma Hydroxybutyrate (GHB) Ingestion: A Focus Group Study. J Psychoactive Drugs; 39(2):115-129))

Alcover. Alcohol dependence is a life-long, in many cases chronically relapsing condition. In the AD population co-ingestion with alcohol cannot be ruled out, apart from the risk of illicit diversion.

The CHMP confirmed its previous opinion that there is a risk of a significant risk of abuse, misuse, overdose and dependence in VH-DRL patients with sodium oxybate. Cases of CNS depression have been reported both in clinical trials and in post-marketing.

The CHMP also considered the proposed risk minimisation measures by the applicant to mitigate the risks related to the use of Alcover granules but could not conclude on their suitability in view of the lack of demonstration of the efficacy in the claimed 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.

3.2.2. Final conclusion on the benefit risk

The CHMP thoroughly assessed all the data submitted within this procedure, both at the initial phase and within the re-examination procedure, as well as the additional explanations provided during the oral explanation, 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 conclusions of an *ad-hoc* expert group.

The CHMP maintains its initial opinion that the results of the submitted efficacy studies do not provide robust evidence to establish the efficacy of Alcover granules in the claimed indications as there are major limitations in the design of these studies, including open-label design small sample size, choice of patient population, absence of clearly defined and consistent 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 CHMP carefully considered the proposal from the applicant to conduct 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 thus far not established. In absence of a positive benefit-risk balance established, the Committee is not in position to recommend grant of the marketing authorisation nor to consider the proposed post-authorisation study. 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..

In the absence of demonstration of the efficacy for Alcover granules, the CHMP concluded that the benefit-risk balance of this medicinal product is not favourable for the proposed indications and confirms its previous conclusions that the marketing authorisation for Alcover and associated names, 750 mg, 1250 mg, 1750 mg granules in sachet for the claimed therapeutic indications should not be granted.

4. Grounds for 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.