NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
E-mail: [redacted]

This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by France:

Product/application name(s) in the Referring Member State	[redacted]
Active substance(s)	Sodium oxybate
Pharmaceutical form(s)	All
Strength(s)	175 mg/mL
Route(s) of Administration	All
Applicant in the referring Member State	[redacted]

Background

Sodium oxybate (SMO), which is the sodium salt of gamma-hydroxybutyric acid (GHB), a derivative of gamma-aminobutyric acid (GABA), is a partial agonist on both GABAA and GABAB receptors and also binds with high affinity to GHB-specific receptors. SMO has an alcohol-mimicking effect on the central nervous system (CNS). Like GABA, it exerts an overall inhibiting effect on the CNS.

In 1999, Austria granted a national marketing authorisation (MA) for Alcover - syrup in accordance with Article 10a of Directive 2001/83/EC on the basis of well-established use. It is indicated for "*the treatment of alcohol withdrawal syndrome (AWS) in chronic alcohol abuse and for the maintenance of abstinence in alcohol dependent (AD) patients under careful medical supervision, in conjunction with psychotherapy and social rehabilitation*". Of note in 1991, Italy had also granted a national MA for Alcover 175mg/mL oral solution in accordance with Article 8(3) of Directive 2001/83/EC, which is currently only indicated as "*adjuvant in the control of acute AWS*".

In 2022, [redacted] submitted to the French medicines agency (ANSM), according to Article 10(1) of Directive 2001/83/EC, an application for a national marketing authorisation for [redacted], a generic medicinal product of the reference medicinal product Alcover - syrup. In the context of the assessment of the MA application for [redacted], certain doubts were raised in connection with the benefit-risk balance of the reference medicinal product.

Issues to be considered

- **Efficacy**

During the course of the assessment of the above-mentioned national application in France, clinical studies in the claimed indications were submitted as part of the clinical dossier. The most recent ones are summarised below.

In the treatment of AWS, SMO efficacy was studied in two clinical trials versus a benzodiazepine (Nimmerrichter et al, 2002: GHB/GP 29-96; Caputo et al, 2014: GATE 1). [1,2]

Study GHB/GP 29-96 was a double-blind, double-dummy clomethiazole-controlled trial in 98 AD patients with moderately severe AWS at baseline. SMO 50mg/kg/day and 100mg/kg/day and clomethiazole 1000 mg/day were tested. All groups showed improvement in their withdrawal symptoms (tremor, sweating and anxiety) as measured in the CIWA-Ar short scale. The mean sums (± standard deviation (SD)) were 13.0 ± 1.1 in the SMO 50 group, 13.4 ± 1.7 in the SMO 100 group and 13.1 ± 1.3 in the clomethiazole group. There was no statistically significant difference between the three treatment groups.

Study GATE 1 was an international, double-blind, double-dummy study to evaluate the efficacy of SMO (suspension for oral use) in comparison with oxazepam in the treatment of patients with moderate to severe AWS at baseline (CIWA-Ar scores of ≥20 and CIWA-Ar-short scale ≥ 12). The SMO dose regimen of GATE 1 with its fixed dose of 10 mL (1750 mg) tid for <75 kg patients, and 12 mL (2100 mg) tid for >75 kg patients is not in line with Alcover syrup recommendations. 127 AD patients with mean CIWA-Ar scores of 18 and CIWA-Ar-short scale of 10 were included. 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. The decrease of the mean total CIWA-Ar score from the baseline to the end of the study in the SMO group was of -15.62 ± 0.38 (adjusted mean change from baseline) and of -16.27 ± 0.38 in the oxazepam group (adjusted mean change from baseline) with no significant differences between the two treatments estimated point 0.65 (95 % confidence interval [CI] -0.37 to 1.66; p = 0.210).

In the maintenance of abstinence in AD patients, efficacy data was obtained from one double-blind placebo controlled study (Guiraud *et al*, 2022: GATE 2).[3] GATE 2 was a phase IV, multicentre, multinational, randomised, double-blind, placebo-controlled study, with parallel groups evaluating the efficacy of SMO versus placebo in the long-term maintenance in 314 patients. Treatment duration was 180 days, with an untreated follow-up period up to day 360. The primary endpoint was the cumulative abstinence duration (CAD) during the treatment period of 180 days (6 months), showing borderline significance (p= 0.0495) between SMO and placebo. The secondary endpoints did not show any statistically significant difference between the two groups after 6 months of treatment. This initial analysis shows a treatment effect at the limit of statistical significance with a great heterogeneity of the responses to the treatments and a treatment effect which loses its clinical relevance).
A new final post-hoc analysis in accordance with different versions of the protocol, SAP, and CSR, between 2000 and 2018 was proposed by the authors, including in the model the interaction between treatment and study centre factors. This analysis shows more favourable results, with a treatment effect of at least 43 days and a statistically significant interaction at the threshold proposed by the authors. Meta-analysis-type sensitivity analyses, including centre as a random effect, also show a favourable overall treatment effect of around thirty days but highlight significant heterogeneity in treatment effects between centres. These analyses show that 4 centres with small patient numbers, representing a total of 33 subjects (11% of the

total number), concentrate extreme effects (CAD between 82 and 130 days). Even when including a centre of 28 subjects which presents a weaker treatment effect (42 days), the majority of the treatment effect remains concentrated on less than 20% of the subjects in the study. In the remaining 6 centres, representing 80% of the total number of subjects, the treatment effect is negative to modest.

Thus, these results from recent post-marketing clinical data cast aspersions on the efficacy in both indications.

- **Safety**

Regarding safety, the risks associated with sodium oxybate are known, in particular, the risks of abuse, misuse, diversion and/or use for criminal purposes. Moreover, these risks are of particular concern in the broad population of alcohol-dependent patients, who may have multiple addictions and have a high-risk profile for abuse and dependence.

In 2016, following a fatal case of drug diversion in Italy, a reassessment of the risk-benefit balance of Alcover 175mg/mL oral solution was performed in that Member State. This led to:
- restriction of the *"treatment of acute and chronic alcohol withdrawal"* indications to *"adjuvant in the control of acute AWS"*;
- limiting the duration of treatment (maximum of 10 days);
- restriction of the supply regime: medicinal product subject to medical prescription limited to specialists in the hospital setting or similar facilities (public centres for the treatment of addictions);
- introduction of a RMP at national level;
- changes to the composition of the excipients with the addition of an excipient (black cherry flavoring) that modified the color and flavor of the medicinal product (originally Alcover 175mg/mL oral solution was a colorless, odorless and tasteless solution).

Since 2003 chemical submission has been monitored in France via an on-going national survey. The latest annual survey, published in September 2024, showed that the medicinal products most frequently incriminated in drug-facilitated crimes are the psychoactive drugs (56.7% of mentions of substances in 2022).[4] Actions to reduce the use of medicinal products in drug-facilitated crimes are on-going in France and concerned MAHs were requested to propose measures to reduce the risk of chemical submission (e.g. feasibility of changes in the composition of the finished product; introduction of a colouring agent or an excipient with organoleptic properties to arouse the victim's vigilance). Communication to the general public was also made at the end of December 2024.[5]

Consequently, ANSM is of the view that, the pharmaceutical form and characteristics of Alcover syrup and the application for a generic of that medicinal product (colourless solution, highly soluble, with a cherry flavour, same excipients) could facilitate these risks, especially when used outside hospital setting, as they cannot easily be detected in the case of dilution in solutions.

The syrup is classified as a "risk" formulation, as it may encourage both abuse and diversion. Notably, Alcover syrup (and Alcover oral solution) contains a sour cherry flavour, which could increase its attractiveness. A sensory metrology study was included in the dossier of the application, which aimed to assess whether the presence of 10 mL of syrup could be detected (conducted with only four types of beverages). It showed that this cherry flavour, does not alert consumers to criminal use. Furthermore, the flavour was less detectable in mixed drinks, particularly in cola-based beverages, compared to wine.

Thus, the most appropriate measure to reduce the risks of abuse, misuse, and drug facilitated crimes could be a change of the galenic formulation (e.g. addition of excipients in order to colour the solution and/or to create poorly soluble residues (floats or gelling agents), especially in the context of authorisation for use in a non-hospital setting.

Therefore, in this context, ANSM considers that the risks associated with SMO in the treatment of alcohol dependence are insufficiently mitigated to-date and they pose a potential serious risk to public health.

Conclusion

Overall, considering the data from several recent post marketing authorisation clinical trials, ANSM has concerns regarding the clinical pertinence of the effect of SMO in both indications (treatment of AWS and maintenance of abstinence) in the context of the insufficiently mitigated risks of abuse, misuse, diversion and/or use for criminal purposes. Consequently, the efficacy no longer outweighs the risks, and thus France considers that the benefit-risk balance of Alcover medicinal products is negative.

In view of the above and the necessity to take action at EU level, France considers that it is in the interest of the Union to refer the matter to the CHMP and requests that the CHMP assesses the impact of the findings mentioned above on the benefit-risk balance of Alcover medicinal products, and of sodium oxybate 175 mg/mL pending application(s). The CHMP is requested to give its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of Alcover (sodium oxybate 175 mg/mL) medicinal products should be maintained, varied, suspended, or revoked, and whether the issues raised affect the criteria for the granting of marketing authorisation(s) for pending application(s).

Signed Date

Alexandre DE LA COLOMBE DE LA VOLPILIERE
Signature numérique de Alexandre DE LA COLOMBE DE LA VOLPILIERE
Date : 2025.06.06 14:41:56 +02'00'

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3. Guiraud J, Addolorato G, Antonelli M, et al. Sodium oxybate for the maintenance of abstinence in alcohol-dependent patients: An international, multicenter, randomized, double-blind, placebo-controlled trial. J Psychopharmacol. 2022 Oct;36(10):1136-1145.
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