

## CSST “Evaluation of the benefit/risk ratio of the use of baclofen in alcohol-dependent patients”

### Statement of opinion - 17/04/2018

- Regarding the efficacy of Baclofen in the reduction of alcohol consumption in adult patients with alcohol dependence and high drinking risk level, the decrease in consumption attributed to Baclofen compared to placebo (6 months) was estimated at 11g/day (secondary endpoint not significant in the ALPADIR study) and at 6g/day (primary endpoint significant in the BACLOVILLE study), which represents about 7% of the average initial consumption.

Given the important methodological limitations of both studies, including their low statistical power, the high proportion of missing data and withdrawals from the trials, the robustness of these results cannot be taken for granted. Therefore and taking into account the modest size effect the clinical relevance of these findings appears to be questionable.

Furthermore, no dose response relationship has been established to conclude on an optimal therapeutic range. Among the other efficacy outcomes, no difference compared to placebo could be established, in particular for continuous abstinence (the primary endpoint in the ALPADIR study) after 6 months of treatment.

The obsessive/compulsive component of the drinking habit (craving) was the only outcome that showed a significant improvement with baclofen in both studies.

- Regarding the safety of baclofen, the frequency of adverse events is higher with baclofen than placebo and is related to the main adverse effects usually associated with its use: nervous system and psychiatric disorders, asthenia, gastrointestinal disorders. The proportion of patients with at least one adverse event considered serious was twice as high with Baclofen compared to placebo in the BACLOVILLE trial but not in the ALPADIR trial in which they were similar in both groups. The same is true for the proportion of subjects who dropped out prematurely because of side effects.

No firm conclusion can be drawn on the association between adverse events and baclofen dose with the data available, which were collected in a flexible dose setting. However, for instance, the observed proportion of serious adverse events among all the adverse events appears to increase according to the dose of baclofen received.

In the BACLOVILLE study, 6 deaths in the baclofen arm were recorded and 3 deaths in the placebo arm (one deceased patient received marketed baclofen after the study treatment period). Five deaths in the baclofen arm were considered by the sponsor as related to the treatment.

A pharmaco-epidemiological study was conducted in “real life” by CNAMTS/ANSM/INSERM, independently from the marketing authorization submission dossier. Results show that baclofen use was strongly associated with a dose-related increased risk of hospitalization and death compared to approved treatments for alcohol dependence.

- In summary, the efficacy of Baclofen in the reduction of alcohol consumption in adult patients with alcohol dependence and high drinking risk level, as demonstrated in the present application, was judged clinically insufficient. This, in addition to a potentially increased risk of developing serious adverse events (including death) especially at high doses, leads to consider that the benefit risk balance is negative.