Canadian Expert Drug Advisory Committee (CEDAC)
Summary of Discussion

Acamprosate calcium (Campral®—Prempharm Inc.)
Indication – Maintenance of Alcohol Abstinence

Canadian Expert Drug Advisory Committee (CEDAC) Members Participating
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Regrets
None.

Conflicts of interest
CEDAC members reported no conflicts of interest related to this submission.

Description of Drug
Acamprosate calcium is approved for the maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation. Acamprosate modulates glutamatergic and GABAergic neurotransmission and modifies neuronal excitability; however, its mechanism of action in alcohol dependence is not completely understood.

Discussion of Clinical and Pharmacoeconomic Reviews
CEDAC considered a systematic review of published and unpublished clinical studies prepared by CDR and a CDR review of a pharmacoeconomic evaluation supplied by the manufacturer. An overview of these reviews and the complete CEDAC Final Recommendation and Reasons for Recommendation (technical and plain language versions) are available in the CDR Drug Database on the CADTH web site (www.cadth.ca).

The following is a summary of presentations by CEDAC members and discussions regarding this drug at the CEDAC meetings held on January 23, 2008 and March 19, 2008.

Therapeutic Rationale and Need
Alcoholism is a very common and debilitating condition from both an individual and societal perspective. In Canada, approximately 18,000 deaths occur annually from related disease and injuries. Alcohol abuse accounts for $7.52 billion in lost productivity, law enforcement and direct health care costs. Both physical and psychiatric co-morbidities cause deterioration, isolation, substance addiction and violence in patients with this disease. Interventions that reduce alcohol intake and/or assist in maintenance of abstinence would be expected to reduce alcohol-related morbidity and mortality.

Clinical trials
One methodologically sound systematic review evaluating 17 double-blind randomized controlled trials (DB RCTs) and 4 additional individual DB RCTs (one which was also included in the systematic review) were considered. In total, approximately 4900 alcohol-dependent patients (mostly male) who were newly abstinent were included in the trials. Individual study sample sizes ranged from 10 to 581 participants and

treatment durations ranged from 2 to 12 months. Follow-up ranged from 2 months to 2 years. There was considerable heterogeneity among the trials with respect to treatment site (recruitment site, availability of inpatient detoxification, specialized outpatient clinic setting), patient population (family history, average daily alcohol consumption) and behavioural intervention.

Comparators or Other Available Treatment Options

Comparators included placebo and naltrexone with or without behavioural intervention. The combination of acamprosate and naltrexone was assessed in one trial. The comparison with naltrexone is complicated by the fact that naltrexone is used for both maintaining abstinence from alcohol, and also for reducing alcohol intake in heavy drinkers.

Outcomes

The primary outcome of the systematic review was continuous abstinence at 6 months; other outcomes included continuous abstinence at 3 months, continuous abstinence to study end, cumulative abstinence duration, time to first drink, and time to heavy drinking. The validity of such self report measures in alcoholism treatment studies is a subject of debate. The majority of the literature suggests that it is reliable when used with objective corroborating data reports to allow assessment of biases. Important clinical outcomes such as mortality, social-role functioning and quality of life were not assessed.

Efficacy or Effectiveness

A meta analysis of the trials in the systematic review reported a statistically significant difference in continuous abstinence at 6 months between acamprosate (36.1%) and placebo (23.4%). Individually, approximately half of the trials reported non-statistically significant results and three trials reported large treatment effects; however, all but one of the trials reported at least a trend towards improvement with acamprosate. Three of the individually reviewed trials reported mixed results in time to first drink, and time to heavy drinking; two studies reported mixed results for continuous abstinence; others did not report on these measures. Cumulative abstinence was not affected in the one individual study that reported results. No DB RCTs, comparing acamprosate with naltrexone, provide evidence of superiority of one over the other in maintaining abstinence. High attrition rates were noted in the individual trials. While withdrawals were considered non-abstinent, an assumption that can lead to falsely low estimates of efficacy, documented relapse was often cited as a reason for withdrawal in the individually reviewed trials. Additional limitations included short trial duration/follow-up, self-report for abstinence (with a lack of objective corroborating data reported), and lack of data addressing important clinical outcomes such as mortality, social functioning, and quality of life.

Two trials which did not meet the eligibility requirements of the CDR systematic review but were summarized in the review report were also discussed given that they were both large trials conducted in North America treatment settings that may be more relevant to the Canadian setting compared to the large number of European based trials in the systematic review. One trial in which higher than approved doses of acamprosate and naltrexone were used, acamprosate did not demonstrate improved drinking outcomes compared to placebo, either by itself or with any combination of naltrexone, combined behavioural intervention or both. However, naltrexone was shown better than placebo in patients not receiving combined behavioural intervention. Another study also showed no advantage of acamprosate over placebo, although participants in this trial were not abstinent at the beginning of the trial.

Harms (Safety and Tolerability)

There were no statistically significant differences in mortality or serious adverse effects; however, a statistically significant increase in adverse events of a suicidal nature (suicidal ideation, attempts and intentional overdose) was reported. It was noted that this group of patients is already at a high risk of such events. While gastrointestinal adverse events (e.g., diarrhea) were more common with acamprosate than placebo, the overall incidence of adverse events was not different.

Cost and Pharmacoeconomic Evaluation

The daily cost of acamprosate is similar to that of naltrexone (approximately $5 daily). However, the cost analysis provided by the manufacturer had a number of limitations. These include an unproven assumption of equal efficacy and safety compared to naltrexone, lack of inclusion of comprehensive management programs that include counselling, use of clinical study results that may not be generalizable to the Canadian setting.

Other Discussion Points

- Treatment efficacy may be affected by treatment setting. The evidence related to the superior efficacy of acamprosate was mainly from European-based studies where inpatient detoxification and specialized alcohol or psychiatric treatment programs are extensively used. These results may not be generalizable to the more common less specialized settings, like those in Canada.
- The considerable heterogeneity among the studies with regard to patient characteristics, treatment setting and the intensity of behavioural intervention may have impacted the large differences in treatment effect that were demonstrated.
- The adherence to a regimen of three times daily dosing of a medication by this patient population in an outpatient setting was questioned.
- The Committee noted that acamprosate is indicated for maintenance of abstinence while naltrexone can be used to reduce excessive drinking and to maintain abstinence.
- The Committee recognized the relative lack of treatment options for alcohol dependency, the withdrawal of disulfiram from the market, and considered the need for an option for patients unable to take naltrexone.

CEDAC Recommendation

The Canadian Expert Drug Advisory Committee (CEDAC) recommended that acamprosate be listed in patients who have been abstinent from alcohol for at least four days and who have contraindications to naltrexone (currently receiving opioids, acute hepatitis or liver failure). The maximum treatment duration should be one year.

CEDAC Reasons for the Recommendation

- Acamprosate has been shown to be better than placebo in improving measures of abstinence from alcohol in some randomized controlled trials (RCTs) and in a large meta analysis of clinical trials.
- Aside from patients with contraindications to naltrexone, there is insufficient evidence for a therapeutic advantage of acamprosate compared to naltrexone. One large RCT reported that acamprosate, with or without combined behavioural intervention, had no evidence of beneficial effect on alcohol drinking outcomes while the same study did report a benefit with naltrexone therapy.
- Acamprosate costs $4.80 per day which is similar in cost to naltrexone ($5.00 per day). The manufacturer submitted an economic evaluation which assumed that the effectiveness of acamprosate was equivalent to naltrexone. As there was insufficient evidence to support this assumption, the Committee felt that acamprosate should be reserved for use in patients with contraindications to naltrexone.

The Summary of CEDAC Discussion

This document contains a summary of the relevant discussion by CEDAC members in making the formulary listing recommendation to participating public drug plans regarding this drug. This summary is not a complete record of the proceedings of the CEDAC meeting at which the drug was considered.

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The manufacturer has reviewed this document and has not requested the deletion of any confidential information.