CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

ACAMPROSATE CALCIUM (Campral® – Prempharm Inc.)

Description:

Acamprosate calcium modulates glutamatergic and GABAergic neurotransmission and modifies neuronal excitability, although the mechanism of action of acamprosate calcium in maintenance of alcohol abstinence is not well established. Acamprosate calcium is approved for the maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation. Treatment with acamprosate calcium should be part of a comprehensive management program that includes counselling.

Dosage Forms:

333 mg tablets. The recommended dose is 666 mg taken three times daily. The recommended duration of treatment is up to one year.

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends 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.

Reasons for the Recommendation:

1. 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.

2. 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.

3. 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.

Summary of Committee Considerations:

The Committee considered a published systematic review of 17 double-blind, placebo controlled RCTs of acamprosate in adults with alcohol dependency, plus an additional four RCTs not included in the systematic review.

A meta-analysis of all trials in the systematic review found that, compared to placebo, acamprosate resulted in a statistically significant improvement in the duration of abstinence and continuous abstinence from alcohol for up to 12 months. However, there was considerable variability in the treatment results with approximately half of trials reporting no statistically significant difference between acamprosate and placebo while three trials reported a relatively large treatment effect in favour of acamprosate. Many of these studies were conducted in hospitals or specialized treatment centres. The three trials which included a high proportion of patients undergoing outpatient detoxification reported no statistically significant differences between acamprosate and placebo. Subject withdrawal rates were 30 – 50 % in many of the trials.

The Committee reviewed two RCTs of 12 weeks duration comparing the approved doses of acamprosate and naltrexone with placebo. One trial reported that the acamprosate and naltrexone arms were associated with statistically significant improvements in the time to first drink and time to heavy drinking compared to placebo. The other trial reported no statistically significant difference between acamprosate, naltrexone and placebo on continuous abstinence from alcohol at 12 weeks, time to first drink or time to heavy drinking.

The Committee also considered a trial that evaluated acamprosate at doses higher than that approved in Canada (3 g versus 2g daily) and naltrexone (100 mg versus 50 mg daily). This 16 week RCT, with up to one year of follow-up in 1383 recently abstinent outpatients in the United States compared nine treatments groups - eight groups of patients received medical management with naltrexone or acamprosate, both, and/or both placebos, with or without a combined behavioural intervention. Only 6% of patients in this trial were lost to follow-up. Acamprosate demonstrated no statistically significant effect on drinking outcomes compared to placebo, either by itself or with any combination of naltrexone, combined behavioural intervention, or both.

None of the trials reported on the effect of acamprosate on the consequences of alcohol consumption such as alcohol-related mortality, social role functioning, and quality of life.

While acamprosate appears to be generally well tolerated, adverse events of a suicidal nature (suicidal ideation, suicide attempts, completed suicides) were more common in acamprosate-treated patients than in patients treated with placebo (1.4% vs. 0.5% in studies of 6 months or less; 2.4% vs. 0.8% in 12 month studies). There was no statistically significant difference in the rate of death due to suicide.

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.

Background:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.