



## Therapeutic Class Review<sup>SM</sup>

### Acamprosate calcium (Campral<sup>®</sup>) Delayed-Release Tablets

July 2006 Update

**Product for Review:**

Acamprosate (Campral<sup>®</sup>) [Forest]

**Dossier Provided by Manufacturer:** yes

**Quality of Dossier:** 3

- 1 - Low quality (dossier w/missing components)
- 2 - Medium quality (all components, except pharmacoeconomic model)
- 3 - High quality (all components, well done)

#### Executive Summary

- Alcohol abuse and dependence:
  - Ranks among the top 3 psychiatric disorders in the U.S.
  - Is associated with significant medical and economic consequences.
- Successful treatment of alcohol addiction involves a combination of pharmacologic and psychological interventions, and behavioral modification.
- The proportion of patients remaining continuously abstinent throughout treatment represents the best indicator of clinical benefit.
- Acamprosate (Campral) and naltrexone (ReVia) are approved for maintenance of abstinence from alcohol in recently weaned alcoholics when used as part of a comprehensive management program that includes psychosocial support.
- Disulfiram (Antabuse) acts as a deterrent to drinking alcohol. However, its efficacy is not supported by controlled trials, and is directly affected by patient compliance and motivation to stop drinking alcohol.

#### Evidence

- There is inconsistent evidence that acamprosate (Campral) increases the duration of abstinence, reduces the relapse rate, and reduces the quantity of alcohol consumed in patients with alcohol dependence.
  - European trials have demonstrated clinical benefit with acamprosate (Campral); however, U.S. trials have shown inconsistent benefit.
  - Variable and inconsistent treatment effects may result from:
    - \* Differences in trial design and baseline populations between studies.

- \* Large numbers of dropouts from trials of this nature (reported treatment effects depend on assumptions made regarding missing data).
- \* Differences in psychosocial support.
- Current evidence does not support the efficacy of acamprosate (Campral) in patients with:
  - Severe alcohol dependence (even with psychosocial support).
  - Patients who are not abstinent when initiating acamprosate (Campral).
  - Concurrent drug abuse.
- Three trials compare acamprosate (Campral) and naltrexone (ReVia) in the treatment of alcohol dependence. There is no consistent evidence that:
  - One product is superior over the other.
  - Concomitant administration of both agents is superior to either agent alone.
- There are no head-to-head trials that compare the efficacy of acamprosate (Campral) or naltrexone (ReVia) to disulfiram (Antabuse) in the maintenance of abstinence in recently weaned alcoholics.
- There is no evidence that acamprosate (Campral) is safer than naltrexone (ReVia) or disulfiram (Antabuse) when used in the treatment of alcohol dependence.

## Decision

- Acamprosate (Campral) is non-preferred/non-formulary because:
  - Evidence regarding its efficacy is inconsistent.
  - Newest information from the COMBINE trial does not provide evidence of additional clinical value with acamprosate (Campral) over currently available preferred/formulary products.

## Products

| Drug Product                  | FDA Approval <sup>a</sup> | FDA Approved Indications  | Dose Route                             | Potential Off-Label Uses <sup>c</sup>   |
|-------------------------------|---------------------------|---|--|---|
| acamprosate calcium (Campral) | 7/29/2004                 | <ul style="list-style-type: none"> <li>▪ Maintenance of abstinence from alcohol in patients with alcohol dependence that is abstinent at treatment initiation. Treatment with acamprosate should be part of a comprehensive management program that includes psychosocial support.</li> </ul>                                 | 666mg po (2 x 333mg) three times daily | No information.   |
| naltrexone (generic)          | 11/20/1984                | <ul style="list-style-type: none"> <li>▪ Treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids. Naltrexone has not been shown to provide any therapeutic benefit except as part of an appropriate plan of management for the addictions.</li> <li>▪ Opioid Abuse</li> </ul> | 50mg po daily                          | bulimia, Tourette's syndrome, nicotine dependence, exogenous obesity, polycystic ovary syndrome, premenstrual syndrome, prevention of morphine adverse reaction |

|                          |            |   |                           |                    |
|--------------------------|------------|---|---------------------------|--------------------|
| disulfiram<br>(Antabuse) | 12/08/1983 | <ul style="list-style-type: none"> <li>▪ Approved as an aid in the management of selected chronic alcohol patients who want to remain in a state of enforced sobriety so that supportive and psychotherapeutic treatment may be applied to best advantage.</li> </ul> | 250mg - 500mg<br>po daily | Cocaine dependence |
|--------------------------|------------|---|---------------------------|--------------------|

<sup>a</sup> Date applies to approval date for the original brand name medication where there are now generics available.

<sup>c</sup> As listed in © 1974 - 2006 Thomson MICROMEDEX database or as referenced.

## References

1. Paille M, Guelfi JD, Perkins AC, Royer RJ, Steru L, Parot P. Randomized multicenter trial of acamprosate in a maintenance program of abstinence after alcohol detoxification. *Alcohol Alcoholism* 1995;30: 239–247.
2. Pelc I, Verbanck P, Le Bon M, Gavrilovic M, Lion K, Lehert PH. Efficacy and safety of acamprosate in the treatment of detoxified alcohol-dependent patients: a 90-day dose finding study. *Br J Psychiatry* 1997;171: 73–77.
3. Sass H, Soyka M, Mann K, Zieglansberger W. Relapse prevention by acamprosate: results from a placebo controlled study on alcohol dependence. *Arch Gen Psychiatry* 1996; 53: 673–680.
4. Tempesta E, Janiri L, Bignamini A, Chabac S, Potgieter A. Acamprosate and relapse prevention in the treatment of alcohol dependence: a placebo-controlled study. *Alcohol Alcoholism*. 2000;35:202-9.
5. Gual A, Lehert P. Acamprosate during and after acute alcohol withdrawal: a double-blind placebo-controlled study in Spain. *Alcohol Alcoholism* 2001;36(5):413-18.
6. Wang S-J. NDA 21-431-acamprosate (Campral<sup>®</sup>): Statistical review and evaluation. Center for Drug Evaluation and Research. ([http://www.fda.gov/cder/foi/nda/2004/21-431\\_Campral\\_Statr.pdf](http://www.fda.gov/cder/foi/nda/2004/21-431_Campral_Statr.pdf)) May 10, 2002.
7. Winchell CM. NDA 21-431-acamprosate (Campral<sup>®</sup>): Review and evaluation of clinical data. Center for Drug Evaluation and Research. [http://www.fda.gov/cder/foi/nda/2004/21-431\\_Campral\\_Medr\\_P1.pdf](http://www.fda.gov/cder/foi/nda/2004/21-431_Campral_Medr_P1.pdf) (Vol.1-8).
8. Chick J, Howlett H, Morgan MY, Ritson B. United Kingdom multicenter Acamprosate Study (UKMAS): a 6-month prospective study of acamprosate versus placebo in preventing relapse after withdrawal from alcohol. *Alcohol Alcoholism*. 2000;35:176-87.
9. Rubio G, Jimenez-Arriero MA, Ponce G, Palomo T. Naltrexone versus acamprosate: one-year follow-up of alcohol dependence treatment. *Alcohol Alcoholism* 2001;36:419-25.
10. Kiefer F, Jahn H, Tarnaske T, Helwig H, Briken P, Holzbach R, et al. Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo-controlled study. *Arch Gen Psychiatry* 2003;60:92-99.
11. Garbutt JC, West SL, Carey TS, Lohr KN, Crews PT. Pharmacological treatment of alcohol dependence; a review of evidence. *JAMA* 1999;281:1318-1325.
12. Fuller RK, Branchey L, Brightwell DR, Derman RM, Emrick CD, Iber FL, James KE, Lacoursiere RB, Lee KK, Lowenstam I, et al. Disulfiram treatment of alcoholism. A Veterans Administration cooperative study. *JAMA* 1986;256:1449-55.
13. Fuller RK, Gordis E. Does disulfiram have a role in alcoholism treatment today? *Addiction* 2004;99:21-24.
14. Fuller RK, Roth HP. Disulfiram for the treatment of alcoholism. An evaluation in 128 men. *Ann Intern Med* 1979;90:901-4.
15. Powell BJ, Penick EC, Read MR, Ludwig AM. Comparison of three outpatient treatment interventions: a twelve-month follow-up of men alcoholics. *J Stud Alcohol* 1985;46:309-12.
16. Besson J, Aeby F, Kasas A, Lehert P, Potgieter A. Combined efficacy of acamprosate and disulfiram in the treatment of alcoholism: a controlled study. *Alcohol Clin Exp Res* 1998;22:573-79.
17. Cook PJ, Moore MJ. The economics of alcohol abuse and alcohol-control policies. Price levels, including excise taxes, are effective at controlling alcohol consumption. Raising excise taxes would be in the public interest. *Health Affairs (Millwood)* 2002;21(2):120-33.
18. Rice DP. Economic costs of substance abuse, 1995. *Proc Assoc Am Physicians* 1999;111:119-25.

19. U.S. Preventive Services Task Force. Screening and behavioral counseling interventions in primary care to reduce alcohol misuse: recommendation statement. *Ann Intern Med* 2004;140:554-6.
20. Mayo-Smith MF. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. *JAMA* 1997;278:144-51.
21. Mayo-Smith MF, Beecher LH, Fischer TL, Gorelick DA, Guillaume JL, Hill A, et al. For the Working Group on the Management of Alcohol Withdrawal Delirium, Practice Guidelines Committee, American Society of Addiction Medicine. Management of alcohol withdrawal delirium. An evidence-based practice guideline. *Arch Intern Med* 2004;164:1405-12.
22. Apodaca TR, Miller WR. A meta-analysis of the effectiveness of bibliotherapy for alcohol problems. *J Clin Psychol* 2003;59:289-304.
23. Palmer AJ, Neeser K, Weiss C, Brandt A, Comte S, Fox M. The long-term cost-effectiveness of improving alcohol abstinence with adjuvant acamprosate. *Alcohol Alcoholism*. 2000;35:478-92.
24. Schadlich PK, Brecht JG. The cost effectiveness of acamprosate in the treatment of alcoholism in Germany. Economic evaluation of the Prevention of Relapse with Acamprosate in the Management of Alcoholism (PRAMA) Study. *Pharmacoeconomics* 1998;13:719-30.
25. U.S. Preventive Services Task Force. Screening and behavioral counseling interventions in primary care to reduce alcohol misuse: recommendation statement. *Ann Intern Med* 2004;140:554-6.  
([http://www.guideline.gov/summary/summary.aspx?doc\\_id=4618&nbr=3399&string=Alcoholism](http://www.guideline.gov/summary/summary.aspx?doc_id=4618&nbr=3399&string=Alcoholism))
26. Behavioral counseling interventions in primary care to reduce risky/harmful alcohol use. Rockville (MD); Agency for Healthcare Research and Quality; 2004 Mar (Systematic Evidence Review No. 30).
27. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
28. Grant BF, Dawson DA, Hasin DS. The Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version. Bethesda, Md: National Institute on Alcohol Abuse and Alcoholism; 2001.
29. Stanton Peele. Ten Radical Things NIAAA Research Shows About Alcoholism. *The Addictions Newsletter* (The American Psychological Association, Division 50), Spring, 1998 (Vol. 5, No. 2), pp. 6; 17-19.
30. Pharmacological and behavioral treatment guidelines for alcohol addiction:  
<http://www.aafp.org/afp/980700ap/miller.html> <http://www.hosprract.com/issues/1999/04/cekick.htm>  
<http://www.ahcpr.gov/clinic/epcsums/alcosumm.htm> <http://www.ahcpr.gov/clinic/epcsums/alcosumm.htm>  
<http://www.asam.org/publ/pg.htm>.
31. Lingford-Hughes AR, Welch S, Nutt DJ. Evidence-based guidelines for the pharmacological management of substance misuse, addiction comorbidity: recommendations from the British Association of Psychopharmacology. *J Psychopharmacol* 2004;18:293-335.
32. O'Connor PG, Schottenfeld RS. Patients with alcohol problems. *New Engl J Med* 1998; 338:592-602.
33. Martin SE. The links between alcohol, crime and the criminal justice system: explanations, evidence and interventions. *Am J Addict*. 2001;10:136-58.
34. Hasin DS, Grant BF. The co-occurrence of DSM-IV alcohol abuse in DSM-IV alcohol dependence: results of the National Epidemiologic Survey on Alcohol and Related Conditions on heterogeneity that differ by population subgroup. *Arch Gen Psychiatry* 2004;61:891-96.
35. Grant BF, Dawson DA, Stinson FS, Chou SP, Dufour MC, Pickering RP. The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991-1992 and 2001-2002. *Drug Alcohol Depend* 2004;74:223-34.
36. Volpicelli JR. Alcohol abuse and alcoholism: an overview. *J Clin Psychiatry*. 2001;62 Suppl 20:4-10.
37. Agosti V. The efficacy of controlled trials of alcohol misuse treatments in maintaining abstinence: a meta-analysis. *Int J Addict* 1994;29:759-69.
38. Wilk AI, Jensen NM, Havighurst TC. Meta-analysis of randomized control trials addressing brief interventions in heavy alcohol drinkers. *J Gen Intern Med* 1997;12:274-83.
39. Mayo-Smith MF, Beecher LH, Fischer TL, Gorelick DA, Guillaume JL, Hill A, Jara G, Kasser C, Melbourne J; Working Group on the Management of Alcohol Withdrawal Delirium, Practice Guidelines Committee, American Society of Addiction Medicine. Management of alcohol withdrawal delirium. An evidence-based practice guideline. *Arch Intern Med* 2004;164:1405-12.

40. Mason BJ, Ownby RL. Acamprosate for the treatment of alcohol dependence: a review of double blind, placebo-controlled trials. *CNS Spectrums* 2000; 5: 58-69.
41. Mason BJ. Treatment of alcohol-dependent outpatients with acamprosate: a clinical review. *J Clin Psychiatr* 2001; 62 (Suppl 2): 42-48.
42. Annemans L, Vanoverbeke N, Tecco J, D'Hooghe D. Economic evaluation of campral (acamprosate) compared with placebo in maintaining abstinence in alcohol-dependent patients. *Eur Addict Res* 2000; 6: 71-78.
43. Pelc I, Le Bon O, Verbanck P, Lehert PH, Opsomer L. Calcium acetyl homotaurine for maintaining abstinence in weaned alcoholic patients; a placebo controlled double blind multicenter study. *In Novel Pharmacological Interventions for Alcoholism*. Naranjo C, Sellers EM. Eds, pp. 348-352. Springer-Verlag, New York 1992.
44. Ladewig D, Knecht T, Leher P, Fendl A. Acamprosate--a stabilizing factor in long-term withdrawal of alcoholic patients. *Ther Umsch* 1993;50:182-88.
45. Roussaux JP, Hers D, Ferauge M. Does acamprosate diminish the appetite for alcohol in weaned alcoholics? *Pharm Belg* 1996;51:65-68.
46. Whitworth AB, Fischer F, Lesch OM, Nimmerrichter A, Oberbauer H, Platz T, et al. Comparison of acamprosate and placebo in long-term treatment of alcohol dependence. *Lancet* 1996;347(9013):1438-42.
47. Barrias JA, Chabac S, Ferreira L, Fonte A, Potgieter A. Acamprosate: multicenter Portuguese efficacy and tolerance evaluation study. *Psiquiatria Clinica* 1997; 18:149-160.
48. Geerlings PJ, Ansoms C, van den Brink W. Acamprosate and prevention of relapse in alcoholics. *Eur Addict Res* 1997;3: 129-137.
49. Poldrugo F. Acamprosate treatment in a long-term community-based alcohol rehabilitation program. *Addiction* 1997;92:1537-46.
50. Besson J, Aeby F, Kasas A, Lehert P, Potgieter A. Combined efficacy of acamprosate and disulfiram in the treatment of alcoholism: a controlled study. *Alcohol Clin Exp Res* 1998;22:573-79.
51. Namkoong K, Lee B-O, Lee P-G, Choi M-J, Lee E. Acamprosate in Korean alcohol-dependent patients: a multi-center, randomized, double-blind, placebo-controlled study. *Alcohol Alcoholism* 2003;38: 135-141.
52. Mann K, Lehert P, Morgan MY. The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis. *Alcohol Clin Exp Res* 2004;28:51-63.
53. Chick J, Lehert P, Landron F, for the Plinius Maior Society. Does acamprosate improve reduction of drinking as well as aiding abstinence? *J Psychopharm* 2004;17:397-402.
54. The Bandolier: <http://www.jr2.ox.ac.uk/bandolier/painres/download/Bando126.pdf>.
55. Lhuintre JP, Daoust M, Moore ND, Chretien P, Saligaut C, Tran G, et al. Ability of calcium bis acetyl homotaurine, a GABA agonist, to prevent relapse in weaned alcoholics. *Lancet* 1985;1(8436):1014-6.
56. Lhuintre JP, Moore N, Tran G, Steru L, Langrenon S, Daoust M, et al. Acamprosate appears to decrease alcohol intake in weaned alcoholics. *Alcohol Alcoholism* 1990;25:613-22.
57. Hunt WA. Neuroscience research: how has it contributed to our understanding of alcohol abuse and alcoholism? A review. *Alcohol Clin Exp Res* 1993;17:1055-1065.
58. Littleton J. Acamprosate in alcohol dependence: how does it work? *Addiction* 1995; 90:1179-1188.
59. Acamprosate calcium (Campral®). Prescribing information (July 29, 2004). <http://www.fda.gov/cder/foi/label/2004/21431lbl.pdf>.
60. Anton RF, O'Malley SS, Ciraulo DA, et al. Combined Pharmacotherapies and behavioral interventions for alcohol dependence. The COMBINE study: a randomized controlled trial. *JAMA*. 2006;295(17):2003-17.
61. The COMBINE study research group. Testing combined pharmacotherapies and behavioral interventions in alcohol dependence: rationale and methods. *Alcohol Clin Exp Res*. 2003;27(7):1107-22.