1. NAME OF THE MEDICINE

Acamprosate calcium

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains acamprosate calcium 333 mg as the active ingredient.

For a full list of excipients, see Section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Acamprosate calcium is a white, odourless or practically odourless powder with a bitter taste. It is freely soluble in water, practically insoluble in absolute ethanol and dichloromethane.

Acamprosate calcium is presented as enteric coated tablets which are round, white and, marked "333" on one side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Campral is indicated as therapy to maintain abstinence in alcohol dependent patients. It should be combined with counselling.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with acamprosate calcium should be initiated as soon as possible after the withdrawal period and should be maintained if the patient relapses. The recommended period of treatment is 1 year.

Campral tablets should be taken with meals, and swallowed whole.

Based on the clinical results the daily dose is fixed according to body weight:

For adults weighing 60 kg or more, the dose is 2 tablets taken three times daily (i.e. 2 tablets in the morning, at midday and at night).

In adults weighing less than 60 kg, the dose is 2 tablets in the morning, 1 tablet at midday and 1 tablet at night.

Lower doses might be ineffective. The efficacy and safety of higher doses have not been established.

4.3 CONTRAINDICATIONS

Campral is contraindicated in:

- patients with a known hypersensitivity to the medicine
- pregnant or breastfeeding women
- renal insufficiency (serum creatinine >120 micromol/L)
- severe hepatic failure (Child-Pugh Classification C)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Acamprosate does not constitute treatment for the withdrawal period.

Because the interrelationship between alcohol dependence, depression and suicidality is well recognised and complex, it is recommended that alcohol-dependent patients, including those treated with acamprosate, be monitored for respective symptoms.

Each tablet contains 33.3 mg of calcium. In preclinical studies, various signs of toxicity were observed, including diarrhoea, hyperkeratosis and dysplasia of the stomach, soft tissue calcification, and increased deaths due to renal and cardiac lesions in the rat.

Use in Hepatic Impairment

The safety and efficacy of Campral has not been established in patients with severe hepatic failure (Child-Pugh Classification C).

Use in the Elderly

The safety and efficacy of Campral has not been established in patients older than 65 years. Campral should not be administered to the elderly.

Paediatric Use

The safety and efficacy of Campral has not been established in patients younger than 18 years. Campral should not be administered to children.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The concomitant intake of alcohol and acamprosate calcium does not affect the pharmacokinetics of either alcohol or acamprosate.

Administering acamprosate calcium with food diminishes the bioavailability of the medicine compared with its administration in the fasting state.

Pharmacokinetic studies show no interaction between acamprosate calcium and diazepam, disulfiram or imipramine.

Since pharmaco-interaction studies have not been performed with all psychotropic medicines, when acamprosate is administered simultaneously with such medicines, it is advisable to monitor the patient carefully for possible interactions.

Co-administration of naltrexone with acamprosate produced a 25% increase in AUC and a 33% increase in Cmax of acamprosate; however, this finding has limited clinical impact so that no adjustment of dosage is necessary in such patients. The pharmacokinetics of naltrexone and its major metabolite 6-beta-naltrexol were unaffected following co-administration with acamprosate.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No adverse effects on fertility or reproduction were observed in male or female mice administered acamprosate at oral doses up to 2400 mg/kg daily (approximately 6 times human exposure at the maximum recommended clinical dose, based on BSA), prior to and throughout mating and gestation. In an equivalent study in rats, no

effects were seen at daily oral doses up to 1000 mg/kg (approximately 5 times human exposure at the maximum recommended clinical dose, based on BSA).

Use in Pregnancy

Pregnancy category: B2

Acamprosate crosses the placenta and is distributed into fetal tissue following oral administration to pregnant rats. Acamprosate administered during organogenesis was not teratogenic in mice, rats or rabbits at daily oral doses up to 2400 mg/kg, 2000 mg/kg and 1000 mg/kg, respectively (approximately 6, 10 and 9 times human exposure at the maximum recommended clinical dose, based on BSA). The safety of acamprosate calcium has not been established in pregnant women. Campral should not be administered to pregnant women (see Contraindications).

Use in Lactation

Acamprosate calcium is excreted in the milk of lactating animals. Safe use of acamprosate calcium has not been demonstrated in lactating women. Campral must not be administered to breastfeeding women (see Contraindications).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Acamprosate should not impair the patient's ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following definitions apply to the frequency terminology used hereafter: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000, including isolated cases), frequency not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Gastrointestinal disorders:

Very common: Diarrhoea

Common: Abdominal pain, nausea, vomiting, flatulence

Skin and subcutaneous tissue disorders:

Common: Pruritus, maculo-papular rash

Immune system disorders:

Very rare: Hypersensitivity reactions including urticaria, angio-oedema or anaphylactic reactions.

Reproductive system and breast disorders:

Common: Frigidity or impotence.

Psychiatric disorders:

Common: Decreased libido

Uncommon: Increased libido

Reporting Suspected Adverse Reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Acute overdosage with acamprosate is usually benign. In all reported cases, the only symptom which could be reasonably ascribed to acamprosate overdose was diarrhoea. A risk of hypercalcaemia should be considered in chronic overdosage only. Treatment of overdosage should be symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Acamprosate calcium has a chemical structure similar to that of amino acid neuromediators, such as taurine or gamma-aminobutyric acid (GABA), including an acetylation to facilitate passage across the blood brain barrier. Pharmacodynamic studies have been unable to confirm any specific neuromodulatory effect via amino acid receptors. If acamprosate is administered to rats during the induction of ethanol-dependence, the elevation of extracellular brain glutamate concentrations seen during ethanol withdrawal is decreased. In studies in rats and dogs, there was inconclusive evidence of significant distribution of acamprosate into the brain following oral administration of radiolabelled medicine.

Animal experimental studies have demonstrated that acamprosate calcium decreases the voluntary intake of drinking water containing alcohol without affecting food and total fluid intake. The mechanism for this effect in rats is unclear.

Clinical Trials

In an extensive clinical research programme, acamprosate proved its efficacy as an adjuvant to psycho-social therapy over long treatment periods of up to one year, independent of the country where the trial was performed and the type of psycho-social programme applied.

The primary outcome criteria was abstinence, defined as no alcohol intake whatsoever. In the combined efficacy analysis which pooled data from 3338 weaned alcohol dependent patients, despite this very stringent definition (more reliable from a standardisation point of view), the clinical data demonstrated that:

- there is a doubling of the absolute abstinence rate after one year treatment when compared to placebo with 22% of the acamprosate treated patients remaining completely abstinent for one year compared to 12% in the placebo group.

- patient compliance to remain in the treatment was statistically significantly different from Day 90 onwards with 50% retention rate in patients on acamprosate compared with 40% on placebo at the end of the one year treatment period.

- the drink-free periods (Cumulative Abstinent Duration calculated as a fraction of the total abstinent days over the total duration of exposure to treatment) were much longer in the active treatment group in 11 of 12 comparative studies: 53.3 ± 38.5% in acamprosate group compared to 40 ± 35.4% in the placebo group.

- there is no overt rebound drinking after termination of treatment and no signs of medicine withdrawal.

5.2 PHARMACOKINETIC PROPERTIES

Absorption and Distribution

Acamprosate calcium absorption across the gastrointestinal tract is moderate, slow and sustained and varies substantially from person to person. Food reduces the oral absorption of acamprosate calcium. Steady-state levels of acamprosate calcium are achieved by the seventh day of dosing. Acamprosate calcium is not protein bound.

Oral absorption shows considerable variability and is usually less than 10% of the ingested medicine in the first 24 hours. After a single acamprosate dose of 2 x 333 mg tablets, peak plasma concentrations of approximately 200 ng/mL are reached after 5 to 7 hours and longer. After a 15 minute infusion of 666 mg of acamprosate, the volume of distribution is on average 72 ± 3 L.

Metabolism and Excretion

The medicine is excreted in the urine and is not metabolised significantly. There is a linear relationship between creatinine clearance values and total apparent plasma clearance, renal clearance and plasma half-life of acamprosate calcium. After oral dosing of 666 mg of acamprosate, the apparent elimination half life ranged from 13 to 28.4 hours. The pharmacokinetics of acamprosate calcium are not altered by hepatic dysfunction.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Acamprosate showed no evidence of genotoxicity in a series of assays for gene mutations (bacterial and mammalian cells) and chromosomal damage (human lymphocytes in vitro and micronucleus formation in vivo).

Carcinogenicity

In carcinogenicity studies, mice and rats were administered acamprosate in the diet for 91 and 104 weeks, respectively. In mice, there was no evidence of an increased incidence of tumours at doses up to 400 mg/kg/day, a dose which approximates the human exposure at the maximum recommended clinical dose, based on body surface area (BSA). In male rats, there was an increased incidence of adrenal phaeochromocytomas at 400 mg/kg/day (approximately twice human exposure at the maximum recommended clinical dose, based on BSA). Dietary calcium can lead to adrenal medullary proliferative disease in rats but there is no evidence that increased dietary calcium poses a risk of increased adrenal medullary lesions in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Campral enteric coated tablets contain the following inactive excipients: crospovidone, microcrystalline cellulose, magnesium silicate dihydrate, sodium starch glycollate, colloidal anhydrous silica, magnesium stearate, purified talc, propylene glycol and Eudragit L 30 D-55.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: PVC/PVDC/Aluminium blister packs.

Pack sizes: 18, 48, 54, 60, 84, 90, 168 and 180 tablets*

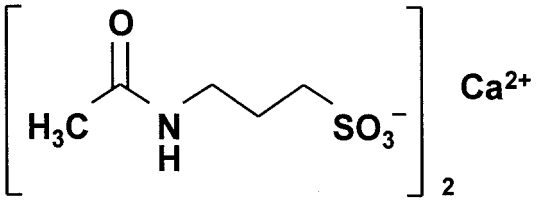
* Not all presentations are marketed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Molecular formula: $C_{10}H_{20}N_2O_8S_2Ca$

Molecular weight: 400.48

CAS Number

77337-76-9 (acamprosate)

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8. SPONSOR

Alphapharm Pty Limited

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

ABN 93 002 359 739

www.mylan.com.au

9. DATE OF FIRST APPROVAL

02/08/1999

10. DATE OF REVISION

15/11/2016

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information
All.	Reformat.

campral_pi\Mar18/00