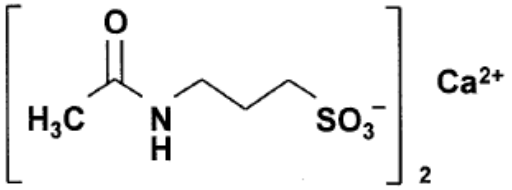
APO-ACAMPROSATE ENTERIC COATED TABLETS

NAME OF THE MEDICINE

Acamprosate Calcium.

Chemical Name: Calcium bis[3-(acetylamino)propane-1-sulphonate]

Structural Formula:



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

Molecular Weight: 400.5

CAS Registry Number: 77337-76-9

DESCRIPTION

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. The parameters such as Log P / Partition coefficient is -3.57 and pKa value is 1.8.

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

In addition, each enteric coated tablet contains the following inactive ingredients: methylcellulose, hyprolose, crospovidone, magnesium stearate, methacrylic acid copolymer, triethyl citrate, purified talc and sodium hydroxide.

PHARMACOLOGY

Pharmacological Actions

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.

Pharmacokinetics

Absorption

Oral absorption shows considerable variability and is usually less than 10% of the ingested medicine in the first 24 hours.

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.

Distribution

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.

Steady-state levels of acamprosate calcium are achieved by the seventh day of dosing. Acamprosate calcium is not protein bound.

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.

Hepatic Dysfunction

The pharmacokinetics of acamprosate calcium are not altered by hepatic dysfunction.

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.

INDICATIONS

APO-Acamprosate, is indicated as therapy to maintain abstinence in alcohol dependent patients. It should be combined with counselling.

CONTRAINDICATIONS

Acamprosate calcium enteric coated tablets are contraindicated in:

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

PRECAUTIONS

The safety and efficacy of acamprosate calcium enteric coated tablets has not been established in patients with severe hepatic failure (Childs-Pugh Classification C).

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 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. Acamprosate calcium enteric coated tablets 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. Acamprosate calcium enteric coated tablets must not be administered to breastfeeding women (see **CONTRAINDICATIONS**).

Paediatric Use

The safety and efficacy of Acamprosate calcium enteric coated tablets has not been established in patients younger than 18 years. Acamprosate calcium enteric coated tablets should not be administered to children.

Use in the Elderly

The safety and efficacy of Acamprosate calcium enteric coated tablets has not been established in patients older than 65 years. Acamprosate calcium enteric coated tablets should not be administered to the elderly.

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.

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*).

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).

Effect on Ability to drive or Operate Machinery

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

INTERACTIONS WITH OTHER MEDICINES

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 C_{max} 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.

ADVERSE 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

DOSAGE AND 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.

Acamprosate calcium enteric coated 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.

OVERDOSAGE

Symptoms

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

Treatment of overdosage should be symptomatic and supportive.

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

PRESENTATION AND STORAGE CONDITIONS

APO-Acamprosate Tablets are intended for oral administration.

Each enteric coated tablet contains 333 mg Acamprosate calcium, as the active ingredient.

333 mg tablets:

White to off-white coloured, round-shaped, biconvex enteric coated tablets engraved “APO” on one side and “300” on the other side.

Blister (ALU/PVC) of 180 tablets (AUST R 286652).

Storage

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
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Macquarie Park NSW 2113

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POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

21 Dec 2017