PRESCRIBING INFORMATION : For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

ACAMPTAS 333

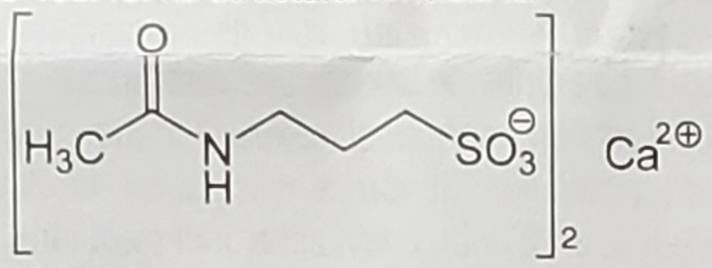
(Acamprosate Calcium Tablets 333 mg)

COMPOSITION

Each enteric coated tablet contains:
Acamprosate calcium IP 333 mg
Colour: Ferric Oxide Yellow, Ferric Oxide Red & Titanium Dioxide IP
Excipients : Q.S.

DESCRIPTION

Pharmaceutically active component of ACAMPTAS 333 is acamprosate calcium which is a synthetic compound with a chemical structure similar to that of the endogenous amino acid homotaurine, which is a structural analogue of the amino acid neurotransmitter γ-aminobutyric acid (GABA) and the amino acid neuromodulator taurine. Its chemical name is calcium acetylaminopropane sulfonate. Its chemical formula is $C_{10}H_{20}N_2O_8S_2Ca$ and molecular weight is 400.48. Its structural formula is:



CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The mechanism of action of acamprosate in maintenance of alcohol abstinence is not completely understood. It is hypothesized that chronic alcohol exposure alters the normal balance between neuronal excitation and inhibition. The evidence from the results of *In vitro* and *in vivo* studies in animals suggests that acamprosate may interact with glutamate and GABA neurotransmitter systems centrally, and has led to the hypothesis that acamprosate restores this balance.

Pharmacodynamic studies have shown that acamprosate reduces alcohol intake in alcohol-dependent animals in a dose-dependent manner and that this effect appears to be specific to alcohol and the mechanisms of alcohol dependence.

Acamprosate has negligible observable central nervous system activity in animals outside of its effects on alcohol dependence, exhibiting no anticonvulsant, antidepressant, or anxiolytic activity.

Acamprosate is not known to cause alcohol aversion and doesn't cause a disulfiram-like reaction after ethanol ingestion.

The administration of acamprosate calcium is not associated with the development of tolerance or dependence in animal studies.

PHARMACOKINETICS

Absorption

The absolute bioavailability of acamprosate after oral administration is about 11%. Steady state plasma concentrations of acamprosate are reached within 5 days of dosing. Steady state peak plasma concentrations after acamprosate doses of 2 x 333 mg tablets three times daily average 350 ng/mL and occur at 3-8 hours post-dose. Coadministration of acamprosate with food decreases bioavailability as measured by C_{max} and AUC, by approximately 42% and 23%, respectively. The food effect on absorption is not clinically significant and no adjustment of dose is necessary.

Distribution

The volume of distribution for acamprosate following intravenous administration is estimated to be 72-109 liters (approximately 1 L/kg). Plasma protein binding of acamprosate is negligible.

Metabolism

Acamprosate does not undergo metabolism.

Elimination

After oral dosing of 2 x 333 mg of acamprosate, the terminal half-life ranges from approximately 20 - 33 hours. Following oral administration of acamprosate, the major route of excretion is via the kidneys as acamprosate.

Special Populations

Gender: Acamprosate does not exhibit any significant pharmacokinetic differences between male and female subjects.

Age: The pharmacokinetics of acamprosate has not been evaluated in a geriatric population. However, since renal function diminishes in elderly patients and acamprosate is excreted unchanged in urine, acamprosate plasma concentrations are likely to be higher in the elderly population compared to younger adults.

Pediatrics: The pharmacokinetics of acamprosate has not been evaluated in a pediatric population.

Renal Impairment: Peak plasma concentrations after administration of a single dose of 2 x 333 mg acamprosate tablets to patients with moderate or severe renal impairment were about 2-fold and 4-fold higher, respectively, compared to healthy subjects. Similarly, elimination half-life was about 1.8-fold and 2.6-fold longer, respectively, compared to healthy subjects. There is a linear relationship between creatinine clearance values and total apparent plasma clearance, renal clearance and plasma half-life of acamprosate. A dose of 1 x 333 mg acamprosate, three times daily, is recommended in patients with moderate renal impairment (creatinine clearance of 30-50 mL/min).

Patients with severe renal impairment (creatinine clearance ≤30 mL/min) should not be given acamprosate.

Hepatic Impairment: Acamprosate is not metabolized by the liver and the pharmacokinetics of acamprosate is not altered in patients with mild to moderate hepatic impairment (groups A and B of the Child-Pugh classification). No adjustment of dosage is recommended in such patients.

Alcohol-dependent subjects: A cross-study comparison of acamprosate at doses of 2 x 333 mg three times daily indicated similar pharmacokinetics between alcohol-dependent subjects and healthy subjects.

Drug-Drug Interactions

Acamprosate had no inducing potential on the cytochrome CYP1A2 and 3A4 systems, and *in vitro* inhibition studies suggest that acamprosate does not inhibit *in vivo* metabolism mediated by cytochrome CYP1A2, 2C9, 2C19, 2D6, 2E1, or 3A4. The pharmacokinetics of acamprosate was unaffected when co-administered with alcohol, disulfiram or diazepam. Similarly, the pharmacokinetics of ethanol, diazepam and nordiazepam, imipramine and desipramine, naltrexone and 6-beta naltrexol were unaffected following co-administration with acamprosate. However, co-administration of acamprosate with naltrexone led to a 33% increase in the C_{max} and a 25% increase in the AUC of acamprosate. No adjustment of dosage is recommended in such patients.

INDICATIONS

ACAMPTAS 333 is indicated for the maintenance of abstinence from alcohol in patients with alcohol dependence that is abstinent at treatment initiation. Treatment with ACAMPTAS 333 should be part of a comprehensive management program that includes psychosocial support.

The efficacy of ACAMPTAS 333 in promoting abstinence has not been demonstrated in subjects who have not undergone detoxification and not achieved alcohol abstinence prior to beginning ACAMPTAS 333 treatment.

The efficacy of ACAMPTAS 333 in promoting abstinence from alcohol in polysubstance abusers has not been adequately assessed.

DOSAGE AND ADMINISTRATION

The recommended dose of ACAMPTAS 333 is two tablets taken orally three times daily.

Treatment with ACAMPTAS 333 should be started once the period of alcohol withdrawal is over, when the patient has achieved abstinence. The therapy should be maintained if the patient relapses. ACAMPTAS 333 should be used as part of a comprehensive psychosocial treatment program.

In Renal Impairment: if creatinine clearance is between 50 and 30 mL/min, recommended starting dose is one tablet of ACAMPTAS 333 three times daily. In patients having severe renal impairment (creatinine clearance ◘ 30 mL/min), ACAMPTAS 333 should not be used.

CONTRAINDICATIONS

ACAMPTAS 333 is contraindicated in patients who previously have exhibited hypersensitivity to acamprosate calcium or any of the components of ACAMPTAS 333.

ACAMPTAS 333 is also contraindicated in patients with severe renal impairment (creatinine clearance ◘30 mL/min).

PRECAUTIONS

Use of ACAMPTAS 333 does not eliminate or diminish withdrawal symptoms. This is to be used to maintain abstinence from alcohol in alcohol dependent patients once they are abstinent of alcohol and it is to be accompanied by comprehensive psychosocial program.

Renal Impairment: Treatment with ACAMPTAS 333 in patients with moderate renal impairment (creatinine clearance of 30-50 mL/min) requires a dose reduction. Patients with severe renal impairment (creatinine clearance of ◘30 mL/min) should not be given ACAMPTAS 333.

Suicidality: The interrelationship between alcohol dependence, depression and suicidality is well-recognized and complex. Alcohol dependent patients,

including those patients being treated with ACAMPTAS 333 should be monitored for the development of symptoms of depression or suicidal thinking. Families and caregivers of patients being treated with ACAMPTAS 333 should be alerted to the need to monitor patients for the emergence of symptoms of depression or suicidality, and to report such symptoms to the patient's health care provider.

Drug Interactions:

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

Pharmacokinetic studies indicate that administration of disulfiram or diazepam does not affect the pharmacokinetics of acamprosate. Co-administration of naltrexone with acamprosate produced a 25% increase in AUC and a 33% increase in the C_{max} of acamprosate. No adjustment of dosage is recommended in such patients.

The pharmacokinetics of naltrexone and its major metabolite 6-beta-naltrexol were unaffected following co-administration with acamprosate.

Pregnancy: Category C

Teratogenic effects: Acamprosate calcium has been shown to be teratogenic in rats when given in doses that are approximately equal to the human dose (on a mg/m² basis) and in rabbits when given in doses that are approximately 3 times the human dose (on a mg/m² basis). The findings in animals should be considered in relation to known adverse developmental effects of ethyl alcohol, which include the characteristics of fetal alcohol syndrome (craniofacial dysmorphism, intrauterine and postnatal growth retardation, retarded psychomotor and intellectual development) and milder forms of neurological and behavioral disorders in humans. There are no adequate and well controlled studies in pregnant women. So, ACAMPTAS 333 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation:

In animal studies, acamprosate was excreted in the milk of lactating rats dosed orally with acamprosate calcium. The concentration of acamprosate in milk compared to blood was 1.3:1. It is not known whether acamprosate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACAMPTAS 333 is administered to a nursing woman.

Pediatric Use:

The safety and efficacy of acamprosate have not been established in the pediatric population.

Geriatric Use:

Acamprosate is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

Below mentioned are the system wise adverse events reported during the clinical trials of acamprosate.

Body as a Whole – frequently reported ones are: headache, abdominal pain, back pain, infection, flu syndrome, chest pain, chills, suicide attempt; infrequent and rare ones are: fever, malaise, allergic reaction, abscess, neck pain, hernia, intentional injury, ascites, face edema, photosensitivity reaction, enlarged abdomen, sudden death.

Cardiovascular System – Palpitation and syncope are reported frequently. Other infrequent and rare ones are: hypotension, tachycardia, hemorrhage, angina pectoris, varicose vein, myocardial infarct, phlebitis, postural hypotension, heart failure, mesenteric arterial occlusion, cardiomyopathy, deep thrombophlebitis, shock.

Digestive System – Nausea, vomiting, diarrhea, anorexia, flatulence, dyspepsia, constipation and increased appetite are reported frequently. Infrequent and rare events reported are abnormal liver function tests, gastroenteritis, gastritis, dysphagia, eructation, gastrointestinal hemorrhage, pancreatitis, rectal hemorrhage, liver cirrhosis, esophagitis, hematemesis, hepatitis, melena, stomach ulcer, cholecystitis, colitis, duodenal ulcer, mouth ulceration, carcinoma of liver.

Endocrine System – Rarely goiter and hypothyroidism are reported.

Blood and Lymphatic System – Infrequent and rare adverse events reported are anemia, ecchymosis, eosinophilia, lymphocytosis, thrombocytopenia, leukopenia, lymphadenopathy, and monocytosis.

Metabolic and Nutritional Disorders – Peripheral edema and weight gain are reported frequently. Infrequent and rare ones are hyperglycemia, increased SGOT & SGPT, gout, thirst, hyperuricemia, diabetes mellitus, avitaminosis, bilirubinemia, increased ALP, creatinine increased, hyponatremia and increased LDH.

Musculoskeletal System – Myalgia and arthralgia are frequent. Leg cramps, rheumatoid arthritis and myopathy are reported infrequently.

Nervous System – Somnolence, decreased libido, amnesia, abnormal thinking, tremor, anxiety, depression, dizziness, dry mouth, insomnia, paresthesia, vasodilatation are frequently reported. Infrequent and rare events are convulsion, confusion, vertigo, withdrawal syndrome, apathy, suicidal ideation, neuralgia, hostility, agitation, neurosis, abnormal dreams, hallucinations, hypesthesia, alcohol craving, psychosis, hyperkinesia, twitching, depersonalization, increased salivation, paranoid reaction, torticollis, encephalopathy, manic reaction.

Respiratory System – Rhinitis, increased cough, dyspnea, pharyngitis and bronchitis are frequent. Infrequently/rarely reported events are asthma, epistaxis, pneumonia, laryngismus, and pulmonary embolus.

Skin and Appendages – Rash is frequently reported. Pruritus, sweating, acne, eczema, alopecia, maculopapular rash, dry skin, urticaria, exfoliative dermatitis and vesiculo-bullous rash are infrequent

Urogenital System – Frequently reported adverse event is impotence. Infrequent and rare adverse events are metrorrhagia, urinary frequency, urinary tract infection, abnormal sexual function, urinary incontinence, vaginitis, kidney calculus, abnormal ejaculation, hematuria, menorrhagia, nocturia, polyuria, urinary urgency, acute kidney failure.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Acamprosate calcium is not a controlled substance.

OVERDOSAGE

In all reported cases of acute overdosage, total reported doses of up to 56 grams of acamprosate calcium, the only symptom that could be reasonably associated with acamprosate calcium was diarrhea. Hypercalcemia has not been reported in cases of acute overdose. A risk of hypercalcemia should be considered in chronic overdosage only. Treatment of overdose should be symptomatic and supportive.

STORAGE

Store below 25°C. Protect from sunlight & moisture.

PRESENTATION

ACAMPTAS 333 is available in a pack of 6's Tablets.

Manufactured by :

INTAS

INTAS PHARMACEUTICALS LTD.

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