For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

ESPERAL
(Disulfiram 250mg Tablet)

COMPOSITION
ESPERAL TAB
Each uncoated tablet contains:
Disulfiram I.P. 250mg

INDICATION
Alcohol deterrent compound. Disulfiram may be indicated as an adjuvant in the treatment of carefully selected and co-operative patients with drinking problems. Its use must be accompanied by appropriate supportive treatment.

DOSAGE FORM
Uncoated tablet

POSOLOGY AND METHOD OF ADMINISTRATION
Disulfiram should never be administered until the patient has abstained from alcohol for at least 12 hours. Initial Dosage Schedule: In the first phase of treatment, a maximum of 500 mg daily is given in a single dose for one to two weeks. Although usually taken in the morning, disulfiram may be taken on retiring by patients who experience a sedative effect. Alternatively, to minimize, or eliminate, the sedative effect, dosage may be adjusted downward.
Maintenance Regimen: The average maintenance dose is 250 mg daily (range, 125 to 500 mg), it should not exceed 500 mg daily.
Note: Occasionally patients, while seemingly on adequate maintenance doses of disulfiram, report that they are able to drink alcoholic beverages with impunity and without any symptomatology. All appearances to the contrary, such patients must be presumed to be disposing of their tablets in some manner without actually taking them. Until such patients have been observed reliably taking their daily disulfiram tablets (preferably crushed and well mixed with liquid), it cannot be concluded that disulfiram is ineffective.
Duration of Therapy: The daily, uninterrupted administration of disulfiram must be continued until the patient is fully recovered socially and a basis for permanent self-control is established. Depending on the individual patient, maintenance therapy may be required for months or even years.

CONTRAINDICATIONS
Disulfiram is contraindicated in below conditions: -
- Presence of cardiac failure
- coronary artery disease
- previous history of CVA
- hypertension
- severe personality disorder
- suicidal risk or psychosis
- consumption of alcohol
- hypersensitivity to disulfiram or to any of the excipients

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Caution should be exercised in the presence of renal failure, hepatic or respiratory disease, diabetes mellitus, hypothyroidism, cerebral damage and epilepsy.

Alcohol must not be consumed during treatment and for up to 14 days after discontinuation, as disulfiram prevents the metabolism of ethanol, causing acetaldehyde to accumulate in the body. This can result in a "disulfiram-alcohol reaction" causing adverse effects.

Before initiating treatment, it is advised that appropriate examinations should be carried out to establish the suitability of the patient for treatment. Patients must be warned of the unpredictable and potentially severe nature of a Disulfiram-alcohol reaction as, in rare cases deaths have been reported following the drinking of alcohol by patients receiving Disulfiram. Certain foods, liquid medicines, remedies, tonics, toiletries, perfumes and aerosol sprays may contain sufficient alcohol to elicit a Disulfiram-alcohol reaction and patients should be made aware of this. Caution should also be exercised with low alcohol and "non-alcohol" or "alcohol-free" beers and wines, which may provoke a reaction when consumed in sufficient quantities. All personnel involved in the administration of Disulfiram to the patient know that Disulfiram should not be given during a drinking episode.

DRUG-INTERACTION

Disulfiram blocks the metabolism of alcohol and leads to an accumulation of acetaldehyde in the blood stream.

The intensity of the Disulfiram-alcohol reaction may be increased by amitriptyline. Chlorpromazine while decreasing certain components of the Disulfiram-alcohol reaction may increase the overall intensity of the reaction.

Disulfiram inhibits the metabolism of certain benzodiazepines such as chlordiazepoxide and diazepam enhancing their sedative effect. The interaction is not indicated for oxazepam. Benzodiazepines may reduce the disulfiram-alcohol reaction.

Disulfiram inhibits the metabolism of many drugs which are converted in the liver (such as phenytoin, theophylline and warfarin) and thereby enhances efficacy. Dose adjustment may be necessary.

Animal studies have indicated similar inhibition of metabolism of pethidine, morphine and amphetamines.

A few case reports of increase in confusion and changes in affective behaviour have been noted with the concurrent administration of metronidazole, isoniazid or paraldehyde.

Potentiation of organic brain syndrome and choreoatphetosis following pimozide have occurred very rarely.

Disulfiram inhibits the oxidation and renal excretion of rifampicin.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy: The use of Disulfiram in the first trimester of pregnancy is not advised. The risk/benefit ratio in assessing adverse effects of alcoholism in pregnancy should be taken into account when considering the use of Disulfiram in pregnant patients.

There have been rare reports of congenital abnormalities in infants whose mothers have received Disulfiram in conjunction with other medicines.

Lactation: Should not be used. No information is available on whether Disulfiram is excreted in breast milk. Its use during breast feeding is not advised especially where there is a possibility of interaction with medicines that the baby may be taking.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Disulfiram may cause side effects such as drowsiness or fatigue. Patients should make sure they are not affected before driving or operating machinery.

UNDESIRABLE EFFECTS

Psychiatric disorders

- psychotic reactions; depression, paranoia, schizophrenia, mania.
- reduction in libido
- Nervous system disorders
- drowsiness (during initial treatment)
- peripheral neuritis
- optic neuritis
- encephalopathy
- Gastrointestinal disorders
- nausea
- vomiting
- Hepatobiliary disorders
- hepatic cell damage
- Skin and subcutaneous tissue disorders
- allergic dermatitis
- General disorders and administration site conditions
- fatigue (during initial treatment)
- halitosis
- Disulfiram-alcohol reaction:

Disulfiram irreversibly inhibits acetaldehyde dehydrogenase. Intake of ethanol during disulfiram therapy will lead to accumulation of acetaldehyde, which is considered the main contributing factor to the disulfiram-alcohol reaction

Disulfiram-ethanol reactions often develop within 15 minutes after exposure to ethanol; symptoms usually peak within 30 minutes to 1 hour, and then gradually subside over the next few hours. Symptoms may be severe and life-threatening.

The disulfiram- alcohol reaction is characterised by:

- Intense vasodilation of the face and neck causing flushing, increased body temperature, sweating, nausea, vomiting, pruritis, urticaria, anxiety, dizziness, headache, blurred vision, dyspnoea, palpitations and hyperventilation.
- In severe cases tachycardia, hypotension, respiratory depression, chest pain, QT prolongation, ST depression, arrhythmias, coma and convulsions may occur.
- Rare complications include hypertension, bronchospasm and methaemoglobinaemia.

OVERDOSE

Disulfiram alone has low toxicity. Although most patients will develop symptoms within the first 12 hours, there are case reports of clinical deterioration days after an overdose, with slow recovery and long-term sequel.

Symptoms include:

- Nausea, vomiting, abdominal pain, diarrhoea, drowsiness, delirium, hallucinations and lethargy may occur.
- Tachycardia, tachypnoea, hyperthermia and hypotension. Hypotonia may be prominent, especially in children and tendon reflexes may be reduced. Hyperglycaemia, leukocytosis, ketosis (often disproportionate to the degree of dehydration) and methaemoglobinaemia have been reported.
- In severe cases there may be cardiovascular collapse, coma and convulsions.
- Rare complications include sensorimotor neuropathy, EEG abnormalities, encephalopathy, psychosis and catatonia, which may appear several days after

overdose. Dysarthria, myoclonus, ataxia, dystonia and akinesia may also occur. Movement disorders may be related to direct toxic effects on the basal ganglia.

Treatment:

Treatment should be symptomatic and observation is recommended. Supportive therapy should be available and measures may be necessary to counteract hypotension.

Gastric lavage and/or activated charcoal may be considered in cases of disulfiram overdose. Severe vomiting might occur requiring administration of intravenous fluids.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

The effect of Disulfiram is primarily due to irreversible inactivation of liver ALDH. In the absence of this enzyme, the metabolism of ethanol is blocked and the intracellular acetaldehyde concentration rises. The symptoms of the Disulfiram-alcohol reaction (DAR) are due partly to the high levels of acetaldehyde. The conversion of dopamine to noradrenaline is also inhibited and the depletion of noradrenaline in the heart and blood vessels allows acetaldehyde to act directly on these tissues to cause flushing, tachycardia and hypotension.
In addition to its effect on acetaldehyde dehydrogenase, disulfiram inhibits other enzyme systems including dopamine-beta-hydroxylase (which converts dopamine and noradrenaline) and hepatic microsomal mixed function oxidases (which are responsible for the metabolism of many drugs). Disulfiram may thus potentiate the action of drugs which are metabolised by these enzymes.

Pharmacokinetic properties

Following oral administration, absorption is variable, distribution is primarily to the kidney, pancreas, liver, intestines and fat. Disulfiram is rapidly metabolised to diethyldithiocarbamic acid (DDC), is conjugated with glucuronic acid, oxidised to sulphate, methylated and decomposed to diethylamine and carbon disulphide. Excretion is primarily through the kidneys.

PRECLINICAL SAFETY DATA

None.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Keep in dry place, protected from light.

PRESENTATION

ESPERAL is available in blister strip of 10 Tablets.

MARKETED BY

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