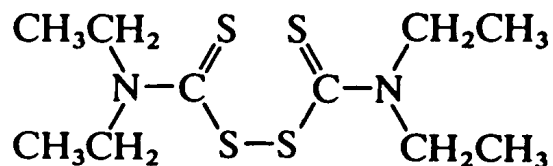


**PRODUCT INFORMATION****ANTABUSE® (Disulfiram) 200 mg  
Effervescent Tablets****Description**

Disulfiram is tetraethylthiuram disulphide, which occurs as a cream-white, almost odourless, slightly bitter crystalline powder, practically insoluble in water (0.02 g/100 mL), soluble in ethanol and chloroform.



C10H20N2S4

mw 296.5

CAS 97-77-8

ANTABUSE 200 mg Effervescent Tablets are white, flat tablets, scored and engraved CDC.

The tablets also contain maize starch, povidone, tartaric acid, sodium bicarbonate (equivalent to 6.6 mg sodium per tablet), microcrystalline cellulose, silica colloidal anhydrous, magnesium stearate and talc.

**Pharmacology**

ANTABUSE Tablets are designed to act as a deterrent to alcohol consumption in patients as an aid in the overall management of chronic alcoholism. Disulfiram is relatively pharmacologically inert when taken in small doses. Disulfiram produces irreversible inhibition of the enzyme responsible for oxidation of the ethanol metabolite acetaldehyde. The accumulation of acetaldehyde contributes to the reaction occurring after alcohol ingestion in disulfiram-treated patients. (see "CONTRAINDICATIONS", "WARNINGS", "The Disulfiram-Ethanol Reaction"). Blockage of the enzyme leads to accumulation of acetaldehyde, which is an important factor for the clinical disulfiram-alcohol reaction. Re-establishment of the enzymatic activity is dependent on new synthesis which occurs gradually during the course of 1 week or more. Disulfiram and its chief metabolite, diethyldithiocarbamide (DDC) also inhibit the enzyme, dopamine-beta-hydroxylase. This results in reduced synthesis of noradrenaline, which may contribute to the reaction.

The disulfiram-alcohol reaction provokes a number of unpleasant symptoms: intense flushing of the face, a feeling of difficulty in breathing, palpitations, a throbbing headache, nausea, and vomiting. Ingestion of large amounts of alcohol may cause the blood pressure to fall, with fainting and the risk of collapse. In patients receiving maintenance treatment with ANTABUSE the ingestion of alcohol may bring about a typical reaction as quickly as within 5-10 minutes.

Disulfiram is a sulphydryl (-SH, thiol) group reagent and inhibits enzymes concerned with oxidation of active (-SH group) sites on enzyme protein molecules. The pharmacological action of disulfiram is based on its inhibition of enzymes involved in ethanol catabolism. Normally, ethanol is metabolised to carbon dioxide and water but, in the presence of disulfiram, the enzyme aldehyde dehydrogenase is inhibited and the metabolic chain of reactions stop after the production of acetaldehyde. Although it is accepted that acetaldehyde accumulation produces the disulfiram-ethanol reaction, it is also believed that the reaction may be caused by a toxic quaternary compound.

Disulfiram also diffuses readily into cells and raises intracellular -SH levels, and, therefore, can act on intracellular oxidation-reduction reactions. Notably, disulfiram has been shown to inhibit the enzymes xanthine oxidase and succinoxidase. Disulfiram has been shown to possess an antithyroid action attributable to the presence of the NCS grouping, common to many antithyroid compounds, presumably reacting with free iodine to form a stable complex substance.

### **Pharmacokinetics**

Disulfiram is a prodrug.

Absorption of disulfiram from the gastrointestinal tract is rapid but incomplete and approximately 20% is excreted in the faeces. Because of its high lipid solubility disulfiram is widely distributed and accumulated in various fat depots. Disulfiram is rapidly metabolised to diethyldithiocarbamate (DDC), which is partly excreted as carbon disulphide in the expired air and is partly metabolised in the liver to Me-DDC. Me-DDC is metabolised further to the active metabolite MeDTC (diethylthiocarbaminic acid methyl ester). The concentration of Me-DTC reaches its maximum after about 4 hours, but the maximum enzyme-inhibiting effect (ALDH) is first reached after 3 daily doses. The plasma half-life for Me-DTC is about 10 hours, but the enzyme inhibiting effect of ALDH lasts considerably longer. The effect can thus persist for 7-14 days after discontinuation. In patients receiving disulfiram maintenance treatment, the ingestion of alcohol brings about a typical disulfiram-alcohol reaction within the course of 5-10 minutes. Metabolism is not appreciably affected by a mild to moderate decrease in liver function. Conversely, in the presence of liver cirrhosis an increased concentration of the metabolites is seen in the blood. The metabolites are chiefly excreted with the urine. Part is recovered in the expired air as carbon disulphide.

Up to 20% of a dose may remain in the body for one week or longer.

It is possible that ANTABUSE tablets may be more bioavailable when given with food. It is also possible that ANTABUSE 200 mg effervescent tablets are more bioavailable than the previously marketed 250 mg ANTABUSE tablet.

### **Indications**

ANTABUSE Tablets are indicated to act as a deterrent to alcohol consumption and an aid in the overall management of selected chronic alcoholic patients involved in an integrated programme of counselling and psychiatry. Only alcoholic patients who are motivated to abstain from drinking and who are undergoing supportive psychotherapeutic treatment, ancillary to a total programme of rehabilitation, should be selected for ANTABUSE administration.

### **Contraindications**

ANTABUSE Tablets are contraindicated in individuals who are hypersensitive to this drug or to other thiuram derivatives used in pesticides and rubber vulcanization.

ANTABUSE Tablets are contraindicated in patients with severe myocardial disease, or ischaemic heart disease, in pregnancy, advanced liver and renal disease, and in psychotic states.

Under all circumstances, patients receiving ANTABUSE Tablets must not take alcohol or alcohol-containing preparations, e.g. certain cough syrups, sauces, vinegar, tonics, foods prepared with wine, and even should avoid the use of after shave lotions and alcoholic back rubs.

ANTABUSE Tablets should not be administered to patients receiving paraldehyde or metronidazole (see "PRECAUTIONS" - "Interactions with Other Drugs").

ANTABUSE Tablets should never be administered to a patient who is taking alcohol or is in a state of alcoholic intoxication.

ANTABUSE Tablets should never be administered to patients without their consent and full explanation, and the physician should caution the relatives accordingly. The patient should be fully informed of the disulfiram-ethanol reaction and cautioned against the possible consequences of taking alcohol either surreptitiously or unwittingly.

## Precautions

DO NOT ADMINISTER ANTABUSE DISULFIRAM TABLETS UNTIL THE PATIENT HAS ABSTAINED FROM ALCOHOL FOR AT LEAST 24 HOURS.

Patients who stop taking ANTABUSE Tablets should be advised to wait at least one week before taking alcohol and that reactions with alcohol may occur for up to three weeks after ingesting disulfiram.

**The Disulfiram-Ethanol Reaction** - Disulfiram inhibits the enzyme system responsible for the conversion of acetaldehyde to acetate. The ingestion of ethanol subsequent to the administration of disulfiram results in raised blood acetaldehyde levels with accumulation in the tissues producing the so-called "aldehyde-reaction". Note that the "aldehyde reaction" can occur 10-14 days after discontinuation of disulfiram, and possibly up to three weeks after discontinuation.

A disulfiram-ethanol toxic reaction is heralded by an intense cutaneous flushing from the head downwards, involving the face, sclera, upper limbs, and chest. The cutaneous flushing is caused by vasodilation and is accompanied by a sensation of heat and sweating, palpitations, with tachycardia, dyspnoea, hyperventilation and the patient develops a pounding headache. There is a feeling of constriction and irritation of the throat and trachea, resulting in spasms of coughing. Chest pains may occur simulating coronary spasm. Restlessness or a sense of uneasiness and fear of dying may develop. These symptoms are accompanied by a steep rise in blood pressure, followed by hypotension if vasodilation is significant. Flushing is then replaced by pallor, weakness, vertigo, and nausea develops that turns into violent vomiting with abdominal cramps. Other symptoms reported include thirst, dizziness, blurred vision, numbness of hands and feet, and insomnia. Severe reactions may affect the heart, and there may be convulsions, loss of consciousness, and death from cardio-respiratory failure.

The intensity of the reaction varies with each individual, but is generally proportional, albeit in a non-linear fashion, to the amounts of disulfiram and ethanol ingested. Mild reactions may occur in the sensitive individual when the blood ethanol concentration is increased to as little as 5 to 10 mg per 100 mL. Symptoms are fully developed at 50 mg per 100 mL, and unconsciousness usually results when the blood ethanol level reaches 125 to 150 mg per 100 mL.

The duration of the reaction varies from 2-4 hours to several hours in the more severe cases, or as long as there is ethanol in the blood. Confusion, drowsiness and sleep usually follow. Frequently, there are transient ECG changes, such as flattening of T waves, depression of S-T segment, and Q-T prolongation in a pattern suggestive of right ventricular strain.

**Management of Disulfiram-Ethanol Reaction** - In the event of an "aldehyde reaction" as a consequence of a disulfiram-treated patient receiving alcohol, supportive measures should be undertaken.

Generous amounts of ascorbic acid (1 g) should be administered intravenously.

It is possible that serotonin, histamine, and various catecholamines which are released play some part in the reaction, and the administration of intravenous or intramuscular antihistamines have been used in treatment. In uncomplicated reactions, chlorpromazine 5-100 mg intramuscularly has been found to be useful.

Maintenance care of a patient with an "aldehyde-reaction" includes routine nursing care, intensive supportive therapy, and standard cardio-respiratory resuscitation measures, involving the treatment of hypotension, circulatory failure, correction of hypoxia, and fluid and electrolyte imbalance to restore haemodynamic equilibrium, all of which are determined by monitoring examinations. The foot of the bed should be elevated raising the patient's feet by about 20-25 cm. Other measures include an adequate patent airway, adequate ventilation with oxygen, if necessary, the correction of arterial pCO<sub>2</sub> and pO<sub>2</sub>, pG, and the intravenous infusion of standard bicarbonate, if there is obvious acidemia. An infusion of plasma to counteract shock and fluid therapy should be administered according to monitoring of central venous pressure.

### **Other Precautions**

Strict caution is advised in patients with diabetes mellitus, hypothyroidism, epilepsy, renal function impairment, advanced liver disease, cardiovascular disorder, pregnancy, allergic eczematous contact dermatitis, asthma and psychosis. Although disulfiram may be taken without harm in these conditions, strict medical supervision is necessary.

In prolonged use, cautious monitoring of hepatic dysfunction as a result of disulfiram therapy should be carried out. It is also recommended that full blood counts and sequential multiple analysis (SMA-12) should be made regularly.

\*Hepatic toxicity including hepatic failure resulting in transplantation or death have been reported. Severe and sometimes fatal hepatitis associated with disulfiram therapy may develop even after many months of therapy. Hepatic toxicity has occurred in patients with or without prior history of abnormal liver function. Patients should be advised to immediately notify their physician of any early symptoms of hepatitis such as fatigue, weakness, malaise, anorexia, nausea, vomiting, jaundice or dark urine.

Careful clinical monitoring with discontinuation of disulfiram and laboratory (bilirubin and hepatic enzyme) determinations is recommended when hepatitis is suspected.

**Use in Pregnancy** Category (B2) - The safe use of this drug in pregnancy has not been established and ANTABUSE Tablets should not be used. Therefore, the administration of ANTABUSE Tablets in women of childbearing potential, requires that the benefits of the drug be weighed against the possible hazards.

**Use during Lactation** - The safe use of this drug during lactation has not been established and use during lactation requires that benefits be weighed against possible hazards to the infant.

**Interactions with Other Drugs** - Disulfiram may retard the metabolism of certain drugs and thus prolong the duration of action or increase the possibility of clinical toxicity of drugs given concomitantly. The drugs include phenytoin and its congeners, and isoniazid.

**Isoniazid** - The adverse reactions associated with concurrent use of isoniazid include ataxia and changes in mental state.

**Phenytoin** - Concurrent use with phenytoin may increase serum levels of phenytoin and possibly lead to phenytoin intoxication. Phenytoin serum levels should be carried out and dosage adjustments of phenytoin may have to be made during concurrent therapy with ANTABUSE Tablets. There is evidence that phenobarbitone is not affected by disulfiram.

**Benzodiazepines** - The effects of chlordiazepoxide and diazepam, but not oxazepam are increased and prolonged by the concurrent use of disulfiram.

**Anticoagulants** - Since disulfiram may prolong prothrombin time, it may be necessary to adjust dosage of oral anticoagulants, e.g. warfarin, in patients receiving these drugs.

**Metronidazole** - Acute psychotic reaction and confusion can result.

**Paraldehyde** - Theoretically, concurrent use may cause a modified “disulfiram-ethanol reaction” and is not recommended.

**Miscellaneous** - The toxicity of certain centrally-acting drugs has been increased by disulfiram in rats. These drugs include morphine, pethidine, amphetamine and barbiturates.

## **Adverse Reactions**

The principal toxic clinical effects to disulfiram administration alone are drowsiness, lassitude (psychotic reactions), and sensorimotor peripheral neuropathy. Some of these reactions have been known to occur in dosages ranging from 200 mg to 400 mg daily and in associated combined toxicity, e.g. with metronidazole or isoniazid.

The following adverse reactions have been reported. Numbness, tingling, pain or weakness in hands or feet (peripheral neuritis, polyneuritis). Patients who are maintained on disulfiram 500 mg daily tend to develop peripheral neuropathy. This neuropathy improves when disulfiram is discontinued.

Eye pain or tenderness and changes in vision (optic neuritis), mood and mental changes [psychotic (including manic) reactions], jaundice, hepatitis, hepatic necrosis, cirrhosis and

altered liver function tests have been reported with the administration of ANTABUSE Tablets, although rarely.

In addition, impotence, headache, fatigue, acneiform eruption, allergic dermatitis, rashes, stomach upset, seizures, have been reported and a metallic or garlic-like after taste may be experienced during the first two weeks of therapy. These complaints disappear spontaneously or by reducing dosage.

### **Overdosage**

High doses of disulfiram (up to 6 g daily) are relatively non-toxic in man. Disulfiram is toxic to animals only in large doses. The LD50 of a single dose administration in the dog is 3.5 g/kg and in the rat 8.6 g/kg. Death occurs by respiratory arrest, preceded by ascending paralysis, and pathological lesions are seen in the liver, spleen, kidney and CNS, with congestion in the adrenal gland and oedema in the heart muscle. Similar lesions have arisen in animals following chronic administration.

In overdosage situations the stomach should be emptied promptly by induced emesis or lavage. There is no specific therapy for acute overdosage with ANTABUSE Tablets and general symptomatic and supportive measures should be instituted and maintained for as long as necessary. (See "WARNINGS". The Disulfiram - Ethanol Reactions.)

### **Dosage and Administration**

ANTABUSE Tablets are administered as a single daily dose. They should be taken preferably on waking, although in patients who experience a sedative effect, ANTABUSE Tablets may be taken on retiring. Alternatively, to minimise the sedative effect, the initial dosage may be reduced.

**Initial Dosage** - One half of a tablet (100 mg) is given daily for 7-14 days, escalating the dosage after that if required, to a maximum of one and one-half tablets (300 mg).

**Maintenance Dosage** - The recommended maintenance dosage is one tablet daily, taken for 6 weeks to 6 months as required. A review of the effectiveness of therapy should be undertaken before continuation on a longer term basis. A few patients would require higher doses of disulfiram and longer duration of treatment under close supervision.

### **Presentation**

ANTABUSE 200 mg Effervescent Tablets in bottles of 30.

Distributed by:  
Orphan Australia Pty Ltd  
48 Kangan Drive  
Berwick Victoria 3806

Under license from:  
Actavis Group hf

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\* Please note change in Product Information

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