NEW ZEALAND DATA SHEET

1. PRODUCT NAME
Antabuse

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each effervescent tablet contains 200 mg disulfiram (equivalent to disulfiram hydrofile 201 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Round white, effervescent flat tablet, 11 mm diameter, engraved CDC with a breakline on one side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Deterrent to alcohol consumption and an aid in the overall management of selected chronic alcoholic patients involved in an integrated program 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 program of rehabilitation should be selected for Antabuse administration.

4.2 Dose and method of administration
Adults

Dose

Initial dosage: Four 200 mg tablets (800 mg) daily for 2 to 3 days.

Maintenance dose: Reduce by 200 mg daily until a daily dose of 100 to 200 mg is attained.

Antabuse should be taken for six weeks to six 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.

Method of administration

Add the prescribed dose to a quarter glass of water or fruit juice, until completely dispersed and drink immediately. Antabuse should be taken preferably on waking although in patients who experience a sedative effect, it may be taken on retiring. Alternatively, to minimise the sedative effect the initial dosage may be reduced.

Paediatric population

No data are available.

4.3 Contraindications
Hypersensitivity to this drug or to other thiuram derivatives used in pesticides and rubber vulcanisation; severe myocardial disease, ischaemic heart disease or uncompensated heart failure; pregnancy; advanced hepatic and renal disease; suicidal risk or psychosis; serious organic brain damage.

Under all circumstances, patients receiving Antabuse 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 aftershave lotions and back rubs containing alcohol.

Antabuse should not be administered to patients receiving paraldehyde or metronidazole (see section 4.5 Interaction with other medicines and other forms of interaction).

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

Antabuse should never be administered to patients without their consent and full explanation, and the doctor 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.

4.4 Special warnings and precautions for use

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

Patients who stop taking Antabuse 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.

Caution should be taken when hepatic function is reduced.

Disulfiram treatment may cause drug-induced liver injury. Fatal cases have been reported (see section 4.8 Undesirable effects).

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 to 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 vasodilatation and is accompanied by a sensation of heat and sweating, and palpitations, with tachycardia, dyspnoea, hyperventilation and the development of 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 vasodilatation 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 cardiorespiratory failure.

The intensity of the reaction varies with each individual, but is generally proportional 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/100 mL. Symptoms are fully developed at 50 mg/100 mL, and unconsciousness usually results when the blood ethanol level reaches 125 to 150 mg/100 mL.

The duration of the reaction varies from two to four 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 the ST segment, and QT prolongation in a pattern suggestive of right ventricular strain.

Management of the 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 to 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 cardiorespiratory 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 to 25 cm. Other measures include an adequate patent airway, adequate ventilation with oxygen, if necessary, the correction of arterial pCO_2 and pO_2, pH, and the intravenous infusion of standard bicarbonate, if there is obvious acidaemia. 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 hepatic 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.

4.5 Interaction with other medicines and other forms of interaction
Concomitant ingestion of antacids containing divalent cations may reduce absorption. Large doses of ferrous salts similarly block absorption.

Disulfiram blocks the oxidation and renal excretion of rifampicin.

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. Concurrent use, theoretically 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.

4.6 Fertility, pregnancy and lactation

Use in pregnancy (Category B2)

The safe use of this drug in pregnancy has not been established and Antabuse should not be used. Therefore, the administration of Antabuse in women of childbearing potential requires that the benefits of the drug be weighed against the possible hazards.

Use in lactation

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

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that Antabuse therapy will not adversely affect their ability to engage in such activities.

4.8 Undesirable effects

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 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 (depression, psychotic, including manic, reactions), jaundice, hepatitis, hepatic necrosis and altered liver function tests have been reported with the administration of Antabuse, although rarely.

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

List of adverse reactions

The frequencies of adverse events are ranked according to the following: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Nervous system disorders

Common: Somnolence

Hepatobiliary disorders

Not known: Drug-induced liver injury (fatal cases have been reported)

Skin and subcutaneous tissue disorders

Not known: Rash

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions (https://nzphvc.otago.ac.nz/reporting/).

4.9 Overdose
High doses of disulfiram (up to 6 g daily) are relatively nontoxic in humans. Symptoms of overdose include vomiting, headache, apathy, ataxia, motor restlessness, irritability, hallucinations, psychosis, loss of consciousness and convulsions. 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.

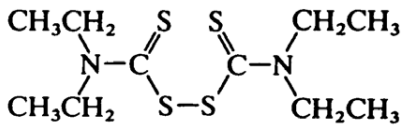
In overdosage situations, the stomach should be emptied promptly by induced emesis or lavage. There is no specific therapy for acute overdosage with Antabuse and general symptomatic and supportive measures should be instituted and maintained for as long as necessary (see section 4.4 Special warnings and precautions for use).

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Drugs used in alcohol dependence, ATC code: N07BB01

Disulfiram is tetraethylthiuram disulfide, which occurs as a cream white, almost odourless, slightly bitter crystalline powder, practically insoluble in water, soluble in ethanol and chloroform.

Chemical structure:



Molecular formula: $C_{10}H_{20}N_2S_4$
Molecular weight: 296.5
CAS number: 97-77-8

Antabuse is designed to act as a deterrent to alcohol consumption in patients as an aid in the overall management of chronic alcoholism. 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 sections 4.3 Contraindications and 4.4 Special warnings and precautions for use, 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 one 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 five to ten minutes.

Disulfiram is a sulfhydryl (-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 stops 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.

5.2 Pharmacokinetic properties

Disulfiram is a prodrug.

Absorption

Absorption of disulfiram from the gastrointestinal tract is rapid but incomplete and approximately 20% is excreted in the faeces.

Distribution

Because of its high lipid solubility, disulfiram is widely distributed and accumulated in various fat depots.

Metabolism

Disulfiram is rapidly metabolised to diethyldithiocarbamate (DDC), which is partly excreted as carbon disulfide in the expired air and is partly metabolised in the liver to Me-DDC. Me-DDC is metabolised further to the active metabolite Me-DTC (diethylthiocarbaminic acid methyl ester). The concentration of Me-DTC reaches its maximum after about four hours, but the maximum enzyme inhibiting effect (aldehyde dehydrogenase (ALDH)) is first reached after three daily doses. The plasma half-life for Me-DTC is about ten hours, but the enzyme inhibiting effect of ALDH lasts considerably longer. The effect can thus persist for 7 to 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 five to ten minutes. Metabolism is not appreciably affected by a mild to moderate decrease in hepatic function.

Excretion

The metabolites are chiefly excreted with the urine. A part is recovered in the expired air as carbon disulfide.

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.

5.3 Preclinical safety data
None.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Maize starch, povidone, tartaric acid, sodium bicarbonate (equivalent to 6.6 mg sodium per tablet), microcrystalline cellulose, anhydrous colloidal silica, magnesium stearate, talc, polysorbate 20.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
60 months

6.4 Special precautions for storage
Store below 25^{o}C.

6.5 Nature and contents of container
HDPE bottle and screw cap with desiccant: Pack size of 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements for disposal.

7. MEDICINE SCHEDULE
Prescription Medicine

8. SPONSOR
Teva Pharma (New Zealand) Limited
PO Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL
31 December 1969

10. DATE OF REVISION OF THE TEXT
29 June 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
6.1	Polysorbate 20 added to list of excipients.