PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE:

ANTABUSE® Dispergettes

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each dispergette contains 400 mg disulfiram.

Excipients with known effect: each dispergette contains 13,14 mg of sodium.

Sugar free.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Dispergettes

ANTABUSE dispergettes are white, round, flat tablets with a 15 mm diameter, cross scored on one side and marked “CJ”.

They are effervescent in water and form a palatable drink.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

As an adjunct in the treatment of chronic alcoholism.

4.2 Posology and method of administration:

Posology:

ANTABUSE treatment should only be carried out under strict medical control.

½ - 1 dispergette daily or as directed by the medical practitioner.

The dose can be given at longer intervals if desired, i.e. one **ANTABUSE** dispergette every two days instead of half dispergette daily.

Method of administration:

ANTABUSE is for oral use.

The whole or part dispergette should be dropped into a quarter glass of water or other liquid.

It will effervesce at once and, after stirring for a few seconds, will form a palatable suspension.

The suspension should be drunk before it has had time to settle. Alternatively, **ANTABUSE** dispergettes can be swallowed without chewing as normal tablets.

4.3 Contraindications:

- **ANTABUSE** should not be administered until the patient has abstained from alcohol for at least 12 hours and the blood alcohol level is zero (see **sections 4.4**, **4.5** and **4.8**).
- **ANTABUSE** is contraindicated in patients known to be hypersensitive to disulfiram or to any of the excipients listed in **section 6.**1
- in patients hypersensitive to other thiuram compounds, such as those used in rubber compounds, pesticides or fungicides, isoniazid and metronidazole.
- uncompensated cardiac failure
- coronary artery disease
- previous history of CVA
- hypertension
- pregnancy (see **section 4.6**)
- psychosis
- severe personality disorders and drug addiction
- suicidal risk
- Phenothiazine antiemetics, i.e. chlorpromazine are contraindicated in association with disulfiram-alcohol reaction.
- Cerebral damage
- Presence of cardiovascular disease.

4.4 Special warnings and precautions for use:

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 as listed in **section 4.8**.

ANTABUSE should not be given without the patient's knowledge unless the prescriber deems it fit.

Before initiating treatment it is advisable 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 disulfiram-alcohol reaction, as cases of deaths have been reported following the drinking of alcohol by patients receiving disulfiram.

Patients should not use aftershave lotions, colognes or any other toilet preparations containing alcohol.

Foods and medicines containing alcohol should also be avoided, e.g. cough syrups, fermented vinegar, sauces.

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 **ANTABUSE** to the patient know that **ANTABUSE** should not be given during a drinking episode.

The liver function of patients with liver damage should also be closely monitored. **ANTABUSE** treatment may cause drug-induced liver injury. Fatal cases have been reported (see **section 4.8**). Liver function should be monitored before initiation of treatment and periodically thereafter; caution should be taken in patients with known reduced hepatic function. Consider medicine discontinuation if symptoms or signs of liver injury associated with jaundice occur.

Concentrations of metals, particularly nickel, in the blood rise progressively during treatment with **ANTABUSE**.

Since accumulation of metals in the brain is also promoted, the use of **ANTABUSE** should be avoided in those patients who are apt to encounter them in their environment.

Caution should be exercised in administering **ANTABUSE** to patients with impaired renal or hepatic function, respiratory disorders, hypothyroidism, or diabetes mellitus and in patients with a history of epilepsy or other

seizure disorders.

No information is available on the relationship of age to the effects of disulfiram as in **ANTABUSE**. Safety and efficacy in children have not been established.

However, elderly patients are more likely to have age related renal function impairment.

In addition, elderly patients with cardiac or cerebrovascular disease may not tolerate the disulfiram-alcohol reaction, as well as younger patients. See **section 4.3**.

Blood cell counts and blood chemistry profiles and liver function tests should be performed every 6 months during treatment.

ANTABUSE contains less than 1 mmol sodium (23 mg) per dispergette. **ANTABUSE** contains 13,14 mg sodium per dose, equivalent to approximately 0,7 % of the WHO recommended maximum daily intake for sodium. This medicinal product is considered low in sodium.

4.5 Interaction with other medicines and other forms of interaction:

Disulfiram as in **ANTABUSE** may inhibit the metabolism of paraldehyde leading to an accumulation of acetaldehyde and these medicines should not be given concomitantly. For full details of the disulfiram-alcohol reaction please refer to **section 4.8**.

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 as contained in **ANTABUSE** 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.

The use of alcohol or alcohol-containing products within 14 days of disulfiram therapy will result in a disulfirarn-alcohol reaction.

Disulfiram as in **ANTABUSE** inhibits hepatic enzymes and may interfere with the metabolism of other medicines taken at the same time e.g. monoamine oxidase inhibitors, barbiturates and alfentanil.

Disulfuram as in **ANTABUSE** inhibits the metabolism and excretion of rifampicin and may similarly affect pethidine, morphine, amphetamines and other centrally active medicines mediated by noradrenaline or dopamine.

Cases of increase in confusion and changes in affective behaviour have been reported with the concurrent administration of metronidazole, isoniazid or paraldehyde.

There have been occasional reports of choreoathetosis in patients receiving disulfiram as in **ANTABUSE** and pimozide.

Disulfiram as in **ANTABUSE** enhances the effects of anticonvulsants.

Hydantoin, especially phenytoin and coumarin or indandione anticoagulants and their dosage may need to be reduced.

Disulfiram as in **ANTABUSE** 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.

Laboratory/physiological test values:

Serum cholesterol concentrations may be increased.

Vanillylmandelic acid (VMA) concentrations in urine may be decreased.

4.6 Fertility, pregnancy and lactation:

Use in Pregnancy and Lactation: **see section 4.3**.

Pregnancy:

There have been rare reports of congenital abnormalities in infants whose mothers have received disulfiram as in **ANTABUSE** in conjunction with other medicines. **ANTABUSE** should not be used in pregnancy.

Breast-feeding:

ANTABUSE should not be used. No information is available on whether disulfiram is excreted in breast milk. Its use during breastfeeding is not advised especially where there is a possibility of interaction with medicines that the baby may be taking.

Fertility:

No data available.

4.7 Effects on ability to drive and use machines:

ANTABUSE may cause side effects such as drowsiness or fatigue. Patients should make sure they are not drive or operate machinery until they know hot treatment with **ANTABUSE** affects them.

4.8 Undesirable effects:

MedDRA SOC	**Frequency**	**Description**
Blood and lymphatic system disorders	*Less frequent*	Blood dyscrasias
Psychiatric disorders	*Frequency unknown*	Psychotic reactions; depression, paranoia, schizophrenia, mania, reduction in libido
Nervous system disorders	*Frequent*	Somnolence
	Frequency unknown	Drowsiness (during initial treatment), peripheral neuritis, optic neuritis, encephalopathy, headache, restlessness, dizziness
Eye disorders	*Less frequent*	Optic atrophy
Gastrointestinal disorders	*Frequency unknown*	Nausea, vomiting, unpleasant taste, body odour
Hepato-biliary disorders	*Frequency unknown*	Hepatotoxicity (including hepatitis consistent with a hypersensitivity reaction), hepatic cell damage, drug induced liver injury (fatal cases have been reported)
Skin and subcutaneous tissue disorders	*Frequency unknown*	Allergic dermatitis, rash

General disorders and administration site conditions	*Frequency unknown*	Fatigue (during initial treatment), halitosis, acetonaemia

Disulfiram-alcohol reaction:

Disulfiram irreversibly inhibits acetaldehyde dehydrogenase. Intake of ethanol during **ANTABUSE** 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, dysrhythmias, coma and convulsions may occur.
- Rare complications include hypertension, bronchospasm and methaemoglobinaemia.

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. Health care provders are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose:

Treatment is symptomatic and supportive.

The syndrome of disulfiram intoxication in children, with sequelae of brain damage or death, is distinct from the disulfiram-alcohol interaction or acute disulfiram intoxication in adults.

It is characterised by lethargy or somnolence, weakness, hypotonia and vomiting, beginning approximately 12 hours after ingestion and progressing to stupor or coma.

Dehydration, moderate tachycardia and marked tachypnea occur frequently, muscle tone is greatly decreased and deep-tendon reflexes may be weak or absent.

A severe reaction is likely to occur when an overdose of **ANTABUSE** and alcohol is taken.

Psychotic reactions, such as depressive psychosis (with suicidal tendencies), paranoia, paranoid Schizophrenia, mania and Korsakoff's psychosis have been reported as well as a few fatalities.

No specific treatment for severe **ANTABUSE**-alcohol reactions has yet been developed.
In severe disulfiram-alcohol reactions, supportive measures to restore blood pressure and treat shock should be instituted.
Other recommendations include: administration of supplemental oxygen, monitoring of serum potassium levels; and monitoring of ECG tracings.

5. PHARMACOLOGICAL PROPERTIES:

A.9 Medicines against alcoholism

Pharmacotherapeutic group: Drugs used in alcohol dependence.

ATC code: N07BB01

5.1 Pharmacodynamic properties:

ANTABUSE (disulfiram) interferes with the normal metabolic degradation of alcohol in the body resulting in an increased concentration of acetaldehyde in the blood.
When a patient undergoing treatment with **ANTABUSE** drinks alcohol, marked subjective and objective symptoms will be experienced within about 10 minutes.
These symptoms are accompanied by pronounced discomfort and persist until the alcohol is eliminated. Reactions to alcohol may occur up to 14 days following withdrawal of disulfiram.

The marked unpleasantness of an **ANTABUSE**-alcohol reaction acts as a form of aversion treatment. Consequently, the regular administration of A**NTABUSE** permits the effective treatment of chronic alcoholics as outpatients.

5.2 Pharmacokinetic properties:

Absorption:

Following oral administration, absorption is variable.

Distribution:

Distribution is primarily to the kidney, pancreas, liver, intestines and fat.

Biotransformation:

Disulf Disulfiram is rapidly metabolised to diethyldithiocarbamic acid (DDC), is conjugated with glucuronic acid, oxidised to sulphate, methylated and decomposed to diethylamine and carbon disulphide.

Elimination:

Excretion is primarily through the kidneys.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Magnesium stearate

Maize starch

Microcrystalline cellulose

Polysorbate 20

Povidone

Silica, colloidal anhydrous

Sodium hydrogen carbonate

Talc

Tartaric acid

6.2 Incompatibilities:

None.

6.3 Shelf life:

5 years

6.4 Special precautions for storage:

Store at or below 25 ºC, in a well closed container and protect from light.

6.5 Nature and contents of container:

Amber glass bottles or white HDPE bottles of 50 and amber HDPE bottles of 500 dispergettes.

6.6 Special precautions for disposal and other handling:

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City, Midrand

Gauteng

2090

8. REGISTRATION NUMBER(S):

G2932 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

1 December 1974

10. DATE OF REVISION OF THE TEXT:

24 May 2022