Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Antabuse 400 mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Tablet contains 400mg Disulfiram.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent Tablets
White, flat, circular effervescent tablets, 15 mm in diameter, with a cross-score on one side and coded 'CJ'.
The cross-score allows the product to be divided into equal quarters.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Antabuse is indicated as an adjuvant for the treatment of co-operative chronic alcoholic dependents. It should be used in conjunction with appropriate psychiatric treatment.

4.2 Posology and method of administration

Posology

On the first day of treatment the patient should be given 800 mg Antabuse in one dose and told on no account to take any alcohol. The next day the patient is to take 600 mg and on the third day 400 mg. On the fourth and fifth day the patient should take 200 mg and subsequently 200 mg or 100 mg daily or 2-3 times weekly, the dosage continuing until, in the opinion of the physician, the patient is restored to the social order.

The physician, bearing in mind the potential severity, may feel that in individual cases an alcohol challenge is necessary. This may be performed from the fifth day of dosage onwards. Alcohol challenge consists initially of the administration of 5 ml ethanol (approximately 12 ml of brandy) on an empty stomach.

If there is no reaction after 20 minutes, patients may receive a further 10 ml of ethanol. At this dosage of alcohol a positive result rarely consists of more than a noticeable flushing with tachycardia and sometimes a slight fall in blood pressure. If there is no reaction the dosage of Antabuse may be increased, and the test repeated a week later until a positive result is obtained.

Method of administration

For oral use.

Disperse the tablet in water and stir immediately before intake.

4.3 Contraindications

Antabuse is contraindicated:
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- in the presence of uncompensated heart failure
- coronary artery disease
- previous history of CVA
- hypertension
- serious organic brain damage

- severe personality disorder
- suicidal risk
- psychosis
- side effect to the liver on previous exposure to disulfiram (see section 4.4)
- current hepatic disease

- medication dependency
- consumption of alcohol.

4.4 Special warnings and precautions for use

1. During initial treatment with Antabuse drowsiness and fatigue are common. Headache, nausea, vomiting, halitosis and reduction in libido can also occur. If side effects are marked the dosage should be reduced.

There have been reports of psychotic reactions, optic neuritis, peripheral neuropathy, allergic reactions and liver cell damage occurring in patients on Antabuse therapy.

2. Antabuse should be used with caution in the presence of renal, hepatic or respiratory disease, diabetes mellitus, epilepsy, peripheral neuropathy, hypothyroidism or when there is evidence of irreversible brain damage.

3. Do not give Antabuse until at least 24 hours after the last ingestion of alcohol.

4. Both patients and relative should be made aware that on no account must the patient take alcohol during treatment with Antabuse unless it is given as challenge dose by the physician.

5. Antabuse should never be administered when the patient is in a state of alcoholic intoxication.

6. Antabuse should not be given without the patient's knowledge.

7. The Antabuse/alcohol reaction may be precipitated by alcohol containing food sauces and also some medicines, cosmetics and toiletries. The patient should be instructed to avoid all such products.

8. There have been rare reports of death following the drinking of alcohol by patients receiving Antabuse.

9. Great care should be taken when the challenge dose of alcohol is given to patients taking Antabuse. The extent of the reaction is very variable. It may not appear at all on the first alcohol challenge but it may be very severe. Diazepam and chlorpromazine can reduce, and amitriptylene increase, the severity of the Antabuse/alcohol reaction.

10. It is suggested that supportive measures designed to counteract hypotension such as Trendelenberg posture, oxygen and intravenous fluid administration should be available and employed. A pressor agent such as noradrenaline may be required.

11. Alcohol should not be taken for 1 week after ceasing Antabuse therapy.

12. The disulfiram-alcohol reaction is mediated by histamine and the symptoms may thus be masked by antihistamines and other drugs with antihistamine effect.

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

The severity of liver injury can range from asymptomatic elevations in serum aminotransferase levels, to symptomatic liver injury with jaundice, acute hepatitis and even acute liver failure and death. The clinical presentation of hepatitis resembles acute viral hepatitis and the pattern of injury is typically hepatocellular. Rash, fever and eosinophilia may occur. Disulfiram hepatotoxicity with jaundice is associated with high mortality and appearance of symptoms or signs of liver injury should lead to its immediate discontinuation. It is recommended that patients and carers be advised to seek urgent medical attention should they feel unwell or develop a fever or jaundice. If stopped early, complete recovery is expected within 4 to 6 weeks. Treatment with disulfiram should not be re-introduced (see section 4.3).

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

1. In addition to its effects on acetaldehyde dehydrogenase, disulfiram inhibits other enzyme systems including dopamine-beta-hydroxylase (which converts dopamine to noradrenaline) and hepatic microsomal mixed function oxidases.

2. The latter system is involved in the metabolism of many drugs, including the following - paraldehyde, phenytoin barbiturates, amphetamines, morphine, diazepam, rifampicin, chlordiazepoxide and oral hypoglycaemics. It is possible that the enhanced activity of the courmarin anti-coagulants by disulfiram is due to inhibition of their metabolism.

3. Disulfiram inhibits the oxidation and renal excretion of rifampicin.

4. Concurrent usage with isoniazid can lead to an increase in side effects in the area of the CNS (dizziness, coordination breakdown, irritability, insomnia). Concurrent use with metronidazole can lead to confusion or psychotic reactions. Isoniazid and metronidazole can be administered at the same time only if there are compelling grounds, and the patient must be placed under observation.

5. Alcohol – Antabuse Reaction can occur within 10 minutes and may last several hours. The reaction is characterised by flushing, dyspnoea, headache, palpitations, tachycardia, hypotension, nausea and vomiting. The intensity of the reaction may be increased by amitriptyline and decreased by diazepam. Chlorpromazine may increase the overall intensity of the reaction.

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

4.6 Fertility, pregnancy and lactation

Pregnancy: Antabuse is contracindicated in pregnancy. There is inadequate evidence of the safety of disulfiram in human pregnancy. Congenital abnormalities in infants whose mothers had received disulfiram during their pregnancy have been reported.

Breast-feeding: Should not be used. No information is available on whether Disulfiram is excreted in breast milk.

4.7 Effects on ability to drive and use machines

Antabuse may cause drowsiness and fatigue (see section 4.8). Do not drive, if these side-effects are present.

4.8 Undesirable effects

The most common adverse effects are unspecific symptoms as somnolence, headache and gastrointestinal symptoms, which often can be related to the underlying disorder. If the side effects are marked, the dose may be reduced.

MedDRA system organ class	Common (≥ 1/100 and < 1/10)	Uncommon (≥ 1/1,000 and < 1/100)	Rare (≥ 1/10,000 and < 1/1,000)	Very rare (< 1/10,000)	Not known (cannot be estimated from the available data)
Gastrointestinal disorders	Abdominal pain upper Diarrhoea Nausea Vomiting Breath odour				
General disorders and administration site conditions	Drowsiness Fatigue Discomfort				

Hepatobiliary disorders	Elevations in liver enzyme levels (transaminases and S-GT)		Jaundice	Hepatitis, Hepatotoxicity, hepatocellular damage, fulminant hepatitis, and hepatic necrosis which might lead to hepatic failure, hepatic coma and death. The effects on the hepatobiliary system generally occur during the first 2 months of therapy.	Drug induced liver injury *
Immune system disorders		Hypersensitivity			
Investigations			Abnormalities of liver function tests including blood bilirubin increased, aspartate aminotransaminase increased, and alanine aminotransaminase increased		
Nervous system disorders	Somnolence Dysgeusia Headache		Peripheral neuropaty Polyneuropathy Optic neuritis Encephalopathy Tremor	Convulsion, Confusion.	
Psychiatric disorders	Depression Mania		Psychotic disorders, e.g.: Paranoia Schizophrenia	Change in behaviour, acute organic brain syndrome.	
Reproductive system and breast disorders		Libido decreased, Sexual dysfunction			
Skin and subcutaneous tissue disorders		Acne, Dermatitis allergic, Pruritus, Rashes			

* Fatal cases have been reported.

The adverse effects on the liver are not dose-dependent.

Neurological undesirable effects are probably dose-dependent and normally occur several months after initiation of treatment. Neurological effects are slowly reversible.

Smokers seem to be susceptible to optic neuritis. Psychotic disorders are mostly seen in patients with medical history of depression or schizophrenia. The symptoms are probably caused by increased dopamine activity, which is the result of inhibition of dopamine-ß-hydroxylase.

Possible side effects in the event of concurrent consumption of alcohol:

MedDRA system organ class	Adverse drug reaction
Cardiac disorders	Tachycardia Palpitations Dyspnoea Dizziness Arrhythmia Syncope
Gastrointestinal disorders	Vomiting
General disorders and administration site conditions	Fatigue
Musculoskeletal and connective tissue disorders	Muscle spasms
Nervous system disorders	Unconsciousness Headache Coordination abnormal Somnolence
Psychiatric disorders	Apathy
Skin and subcutaneous tissue	Hyperhidrosis Flushing
Vascular disorders	Hypotension Circulatory collapse

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Intensification of the undesirable effects. Antabuse itself has low toxicity. Disulfiram blocks the metabolism of alcohol and leads to an accumulation of acetaldehyde in the blood stream. The alcohol-Antabuse reaction can occur within 10 minutes of ingestion of alcohol and may last several hours. It is characterised by intense flushing, dyspnoea and vomiting. (see section 4.5). Treatment should be symptomatic, gastric lavage and observation are recommended.

Supportive measures designed to counteract hypotension, such as oxygen and intravenous fluid administration should be available and the Trendelberg position employed. A pressor agent such as noradrenaline may be required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in alcohol dependence, ATC code: N07BB01

The effect of disulfiram is primarily due to irreversible inactivation of liver Aldehyde Dehydrogenase (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 are partly due 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 produce 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 oxidises (which are responsible for the metabolism of many drugs). Disulfiram may thus potentiate the action of drugs which are metabolised by these enzymes.

5.2 Pharmacokinetic properties

Absorption & Distribution:
Following oral administration, absorption is variable, distribution is primarily to the kidney, pancreas, liver, intestines, and fatty tissue.

Biotransformation:
Disulfiram is rapidly metabolised to diethyldithiocarbamic acid, is conjugated with glucuronic acid, oxidised to sulphate, methylated and decomposed to diethylamine and carbon disulphide.

Elimination:
Excretion is primarily through the kidneys.

5.3 Preclinical safety data

None.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Povidone
Microcrystalline cellulose
Tartaric acid
Colloidal anhydrous silica
Sodium hydrogen carbonate
Magnesium stearate
Polysorbate 20
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the container tightly closed in order to protect from moisture and light.

6.5 Nature and contents of container

White polyethylene container containing 50 effervescent tablets and a desiccant capsule filled with silica gel.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem

Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1986/110/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 06 February 2010

10 DATE OF REVISION OF THE TEXT

December 2022