SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Antabus 400 mg soluble tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One soluble tablet contains 400 mg disulfiram.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablets for preparing an oral solution.
White, round (diameter 15 mm) flat tablets with a cross-shaped score line and the imprint 'CJ' on one side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

To support withdrawal therapy and maintain abstinence behavior in chronically alcohol-dependent patients. Treatment with Antabus is preferably indicated as part of a comprehensive therapeutic concept, which should also include accompanying psycho- and sociotherapeutic measures.

Antabus is used in adults (from 18 years).

4.2 Posology and method of administration

The dosage and administration schedule are fundamentally based on the individual response of the patient. After a 2 to 3 day loading phase (initial dosage), the maintenance dose is taken daily or every other day.

Adults (from 18 years)

Initial dosage (loading phase)
800 mg Disulfiram = 2 tablets of Antabus are dissolved completely in water or fruit juice and consumed daily for 2 to 3 days.

Maintenance dose (maintenance phase)
Dosage for daily intake:
100 mg–200 mg Disulfiram per day = ¼–½ tablet of Antabus per day is recommended.
Dosage for intake every 2nd day:
200 mg–400 mg Disulfiram every 2nd day = ½–1 tablet of Antabus every 2nd day is recommended.

A maximum dose of 400 mg must not be exceeded.

Elderly (over 65 years) or debilitated adults
The lowest recommended dose should be used.

Use in liver or kidney dysfunction, impaired lung function and cardiac insufficiency
In cases of severe dysfunction, Antabus must not be used (see also section 4.3), in milder organ diseases, the tablets should only be used with great caution and restraint at the lowest recommended dose (see also section 4.4).

Children and adolescents (under 18 years)
Antabus must not be used in children and adolescents (see also section 4.3).

Method and duration of use
For oral use after dissolution.

The tablets are, if necessary, divided at the score line and dissolved completely in ½ glass of water or fruit juice with stirring and consumed immediately.

To stabilize abstinent behavior, the treatment should last at least 6 months. The treatment can, if necessary, be continued for several years.

Instructions for use
Since the patient voluntarily decides to abstain from alcohol by taking Antabus, daily intake should be preferred if possible – a daily no to alcohol acts as a motivational enhancer.

Since increased fatigue can often occur at the beginning of treatment, Antabus – soluble tablets should preferably be taken in the evening during the saturation phase.

The possibilities of controlled intake (supervision, therapy support) promote compliance and should be utilized.

4.3 Contraindications

Antabus – soluble tablets must not be used in:

Hypersensitivity to the active substance (disulfiram), other thiuram compounds, or any of the excipients listed in section 6.1. Some rubber compounds contain thiuram; therefore, patients with a rubber allergy should not be treated with Antabus.
Hypersensitivity to nickel (nickel allergy), as there is an increased risk of developing liver inflammation.
Reduced serum albumin and a serum bilirubin level of > 25 mmol/l, heart and vascular diseases such as coronary heart disease, cardiomyopathies, cardiac arrhythmias
Severe hypotension
Hypertension
Diabetes mellitus
Severe liver and kidney dysfunction
Thyroid diseases
Severe lung and respiratory diseases
Organic brain diseases

Psychoses
Severe personality disorder
Epilepsy
Alcohol consumption
Acute alcohol intoxication, or if there are still traces of alcohol in the blood
Children and adolescents (under 18 years)

4.4 Special warnings and precautions for use

Initiation of treatment and determination of dosage should preferably be done in a hospital or rehabilitation facility after several days of abstinence for patient monitoring. Antabus – soluble tablets should only be taken under strict medical supervision and after a thorough clinical examination to exclude all risk factors.

Antabus – soluble tablets should only be administered after informing and with the consent of the patient. Physical alcohol detoxification must be completed. At the time of the first intake, it must be ensured that the patient no longer has residual alcohol in the blood.

The patient must be aware that any alcohol consumption – even in the smallest amounts – can lead to severe intolerance reactions. The necessity of absolute abstinence should be emphasized, as the intensity of intolerance reactions is unpredictable.

Patients must be informed that even small alcohol content in foods, sweets, medications, cosmetics, toiletries, or tonics can lead to intolerance reactions and should therefore be avoided.

Special patient groups
In patients suffering from conditions where possible intolerance reactions
(see also section 4.8 “Disulfiram-alcohol intolerance reaction”) pose an increased health risk, the tablets should be used with great caution and restraint. These include mild blood pressure regulation disorders, mild respiratory insufficiency, as well as milder lung, liver, and kidney diseases (see sections 4.2 and 4.3).

Before starting treatment, a precise internal and cardiological examination and liver and kidney function tests must be conducted.

The risk of developing toxic hepatitis is greatest within the first 3 months after starting treatment (maximum after about 60 days). In some cases, drug-induced liver damage was fatal (see section 4.8). Coagulation factors,
transaminases, and alkaline phosphatase should be checked before starting treatment. After starting treatment, transaminases should be monitored every 14 days for the first three months and then at least every 3–6 months. At the first signs of toxic hepatitis, treatment with Antabus – soluble tablets must be stopped immediately!

Severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported very rarely in connection with the use of Antabus (see section 4.8). Antabus – soluble tablets must be discontinued at the first appearance of rash, mucosal lesions, or any other signs of hypersensitivity.

Disulfiram slightly inhibits dopamine-□-hydroxylase; in patients with already reduced activity, there is an increased risk of developing acute organic brain syndrome, catatonias, and psychoses.

For prolonged, frequently repeated, or high-dose use, regular monitoring of blood count and liver and kidney function is recommended.

During and up to 14 days after the end of treatment, no alcohol should be consumed, as disulfiram prevents the breakdown of ethanol. This can lead to an accumulation of acetaldehyde with symptoms such as headache, facial flushing, tachycardia, increased breathing, nausea, vomiting, pallor, hypotension, dizziness, and collapse.

If signs of hepatitis develop (loss of appetite, fatigue, malaise, vomiting,
Fever, itching, jaundice, dark-colored urine, light stools), the intake of disulfiram must be stopped and liver function checked. The patient must be informed that they should consult a doctor immediately if the mentioned symptoms occur.

Other ingredient

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per soluble tablet, i.e., it is almost "sodium-free".

4.5 Interactions with other medicinal products and other forms of interaction

Disulfiram inhibits the microsomal enzyme system of the liver. An interaction is therefore expected with all medicinal products that are metabolized via the same pathway (e.g., paraldehyde, phenytoin, barbiturates, amphetamine, morphine, diazepam, chlordiazepoxide, isoniazid, rifampicin, and oral antidiabetics). The elimination of various medicinal products may be delayed; an enhancement or prolongation of the effects of the medications is to be expected.

Oral anticoagulants: Prolongation of prothrombin time
Phenytoin: Increase in phenytoin levels to toxic ranges
Benzodiazepines (except oxazepam, lorazepam): Prolongation of half-life
Rifampicin: Inhibition of oxidation and renal excretion
Theophylline: Increase in plasma levels
Isoniazid: Mutual increase in CNS toxicity
Metronidazole: Increased occurrence of psychoses and confusion states
Tricyclic antidepressants, e.g., clomipramine: Temporary delirious states, increase in plasma levels
Very rarely, pimozide can cause an enhancement of organic brain syndromes and choreoathetosis.

An enhancement of alcohol intolerance reactions can occur after the simultaneous administration of disulfiram with cyanamide (Colme drops), metronidazole, tricyclic antidepressants, MAO inhibitors, chlorpromazine, phenothiazine compounds, and medications with blood pressure-lowering properties (vasodilators, □- and □-receptor blockers) can occur.

Antihistamines and diazepam reduce the intensity of the Antabuse-alcohol intolerance reaction.

Disulfiram should not be administered with aldehyde-containing medications such as paraldehyde or chloral derivatives.

No interactions were observed when administered concurrently with acamprosate calcium (Campral).

The absorption of disulfiram may decrease when taken simultaneously with antacids based on bivalent cations or high-dose iron salts.

Interaction with alcohol (disulfiram-alcohol intolerance reaction):

The side effects listed in the table below are symptoms of acute acetaldehyde intoxication according to the pharmacological action of disulfiram. They occur exclusively after alcohol consumption within 5 to 15 minutes and can last for several hours.

The intensity and duration of intolerance reactions usually correlate with the level of disulfiram dose and the amount of alcohol consumed. In particularly sensitive individuals, even small amounts of alcohol can lead to severe intolerance reactions. Sudden deaths have been observed.

Intolerance reactions to alcohol can occur in individual cases up to 14 days after the last tablet intake.

Nervous system	
Constant	Throbbing head and neck pain, dizziness, confusion
Very rare after excessive alcohol consumption	Seizures and unconsciousness
Gastrointestinal tract	
Constant	Nausea, vomiting
Skin and subcutaneous tissue	
Constant	Flush and skin hyperemia, sweating
Heart and circulatory system	
Constant	Tachycardia and palpitations
Very rare after excessive alcohol consumption	Myocardial infarction, acute heart failure, Cardiac arrhythmias, orthostatic collapse, hypotension
Respiratory tract, thoracic cavity, and mediastinum	
Constant	Respiratory depression, dyspnea, hyperventilation, chest pain

The treatment of severe clinical symptoms in the context of a disulfiram-alcohol intolerance reaction is symptomatic (see also section 4.9).

4.6 Fertility, pregnancy, and lactation

Pregnancy
There is currently very limited experience with the use of disulfiram in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). Therefore, the use of Antabus – soluble tablets during pregnancy is not recommended.

Lactation
Disulfiram passes into breast milk. Breastfeeding should be discontinued during treatment with Antabus – soluble tablets.

4.7 Effects on the ability to drive and use machines

Antabus – soluble tablets can cause fatigue and drowsiness (see also section 4.8)
These side effects have a significant impact on the ability to drive and use machines. Patients experiencing these side effects should not participate in road traffic or operate machines.

4.8 Side effects

Estimation of frequency:

Very common:	≥ 1/10
Common:	≥ 1/100 to < 1/10
Occasional:	≥ 1/1,000 to < 1/100
Rare:	≥ 1/10,000 to < 1/1,000
Very rare:	< 1/10,000
Not known:	Frequency cannot be estimated from the available data

Within each frequency group, adverse reactions are presented in order of decreasing severity.

Immune system
Occasional: Hypersensitivity

Endocrine system
Very rare: Impotence, decreased libido

Psychiatric disorders
Very common: Confusion, memory and concentration disturbances, restlessness Very common to common Mania, depression
Rare Psychotic reactions (schizophrenia-like or in the form of acute confusional states), paranoia (delusions)
Nervous system Psychiatric symptoms are partly dose-dependent and occur especially in patients with a history of depression or schizophrenia. They are presumably triggered by increased dopamine activity due to the inhibition of dopamine-beta-hydroxylase.
Very common: Drowsiness, headaches, lassitude, fatigue
Rare: Sensory-motor polyneuropathies, tremor
Very rare: Optic neuritis, seizures, ataxia, intention tremor, disturbance of fine motor skills, slowed and slurred speech

Eye disorders
Rare: Disturbances in color vision

Cardiovascular system
Very rare: Hypertension

Gastrointestinal tract
Common: Vomiting, diarrhea, nausea, acetone-like body or mouth odor with metallic altered taste sensation Not known: Epigastric pain

Liver and biliary tract
Common: Jaundice
Very rare: Hepatic coma, acute liver failure, fulminant hepatitis, liver necrosis, liver cell damage*

Skin and subcutaneous tissue
Occasionally: Hypersensitivity reactions of the skin, allergic dermatitis, urticaria or acne-like skin rashes
Very rare: Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis
Not known Exanthema

Musculoskeletal system, connective tissue and bones
Rare: Muscle and joint pain

Investigations
Common: Increase in liver enzymes
Very rare: Increase in ketone bodies (acetonemia) and cholesterol * fatal outcomes have also been observed

Reporting of suspected adverse reactions
The reporting of suspected adverse reactions after approval is of great importance. It enables continuous monitoring of the benefit-risk ratio of the medicinal product. Healthcare professionals are encouraged to report any suspected adverse reactions via the national reporting system:

Federal Office for Safety in Health Care
Traisengasse 5
1200 VIENNA
Austria
Fax: + 43 (0) 50 555 36207
Website: http://www.basg.gv.at/

4.9 Overdose

Symptoms:
In the event of an overdose, a gradually increasing feeling of illness with fatigue, nausea and vomiting, facial erythema, dizziness, slurred speech, and intellectual impairment occurs, usually within 10–20 hours. In more severe cases, apathy, ataxia, coordination disorders,

psychotic behavioral disorders with motor restlessness, increased irritability, hallucinations, unconsciousness, and seizures occur. Doses of > 300 mg/kg body weight are potentially life-threatening.

Treatment:
The treatment of overdoses is symptomatic.

Treatment of an Antabuse-alcohol intolerance reaction:
The treatment of severe clinical symptoms in the context of a disulfiram-alcohol reaction is symptomatic with intravenous antihistamines, blood pressure stabilization, maintenance of respiratory function, □-blockers, if necessary, oxygen supply, infusions, adrenaline, and general shock treatment. In vagus-induced bradycardia, anticholinergics are recommended. In case of seizures: Diazepam.
Monitoring of serum potassium levels in digitized patients is indicated, as there is an increased risk of hypokalemia.
The intravenous administration of 4-methylpyrazole (fomepizole) stops the further formation of acetaldehyde by inhibiting alcohol dehydrogenase.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents for the treatment of alcohol dependence, disulfiram;
ATC code: N07BB01

Disulfiram irreversibly blocks the enzyme aldehyde dehydrogenase and also shows a weak inhibitory effect on dopamine-□-hydroxylase. Since alcohol is metabolized to acetic acid via acetaldehyde, after alcohol consumption under Antabuse treatment, there is a increase in acetaldehyde with immediate unpleasant somatic symptoms. Through this disulfiram-alcohol intolerance reaction, the patient experiences the negative somatic consequences of even small amounts of alcohol intensely and very directly. This supports abstinence from alcohol and stabilizes abstinence behavior. After administration of a single dose, aldehyde dehydrogenase is blocked for four days.

5.2 Pharmacokinetic properties

Absorption
After oral administration, disulfiram is absorbed approximately 90% from the gastrointestinal tract, as disulfiram is present in microcrystalline form in the soluble tablets. The strong increase in surface area achieves a high absorption rate.

Distribution
Disulfiram is lipophilic and distributes well into adipose tissue; the disulfiram concentration in plasma cannot be measured due to extremely rapid metabolism.

Metabolism
Disulfiram is very rapidly reduced to diethyldithiocarbamate, which is further metabolized to carbon disulfide, diethylamine, and the methyl ester of diethyldithiocarbamate.

Elimination
Within 72 hours, disulfiram and its metabolites are eliminated by more than 90% primarily renally; a portion is excreted as carbon disulfide via the lungs.

5.3 Preclinical safety data

Published data on the mutagenicity and carcinogenicity of disulfiram showed no corresponding risks.

In rats, disulfiram affected fertility and showed high embryotoxicity when administered from the beginning of pregnancy; in the surviving offspring, there were no signs of teratogenic effects. There is insufficient experience with use during pregnancy in humans. A number of case reports describe malformations in prenatally exposed children. Whether there is a causal relationship with the intake of disulfiram is not clarified.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20
Talc
Microcrystalline cellulose
Maize starch
Sodium bicarbonate
Tartaric acid
Povidone
Magnesium stearate
Colloidal silicon dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25 °C.

Store in the original package and keep the container tightly closed to protect from light and moisture.

6.5 Nature and contents of container

White HDPE tablet container with 50 soluble tablets and a desiccant capsule (cylindrical, white, marked "DO NOT EAT"; component of the desiccant capsule: silica gel).

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.
Reykjavikurvegur 76 - 78
220 Hafnarfjördur
Iceland

8. MARKETING AUTHORISATION NUMBER

Z. Nr.: 11605

9. DATE OF ISSUE OF AUTHORIZATION/RENEWAL OF AUTHORIZATION

Date of issue of authorization: 18.09.1961
Date of last renewal of authorization: 18.09.2006

10. DATE OF INFORMATION

08.2021

PRESCRIPTION/PHARMACY REQUIREMENT

Prescription and pharmacy only, repeated dispensing prohibited.