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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ANTABUSE dispergettes 400 mg effervescent tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg of disulfiram.

For the full list of excipients, see paragraph 6.1

3. PHARMACEUTICAL FORM

Effervescent tablets.

4. CLINICAL INFORMATION

4.1. Therapeutic indications

De-addiction therapy from alcoholism.

4.2. Posology and method of administration

The use of ANTABUSE dispergettes is restricted to adults.
The use of ANTABUSE dispergettes must be accompanied by an appropriate supportive psycho-therapeutic treatment.

Dosage

Starting dose

Eligible patients must not have consumed alcohol for at least 24 hours and must be fully conscious. After a thorough clinical examination, administer 2-3 tablets of ANTABUSE dispergettes orally at once for 3-4 days.

Maintenance dose

Half a tablet to one and a half tablets per day.
In order to avoid any relapse, maintenance treatment should be continued according to the doctor's judgement for a few months, but no longer than 5 months and reassessed regularly by the doctor.
The tablets can be swallowed normally or dissolved in water or another beverage; in the latter case, to ensure that the tablet dissolves easily, shake the liquid and drink the resulting suspension immediately in order to avoid settling.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in paragraph 6.1.
- Children and adolescents.
- Heart failure, coronary artery disease, serious cerebrovascular events.
- Untreated hypertension, serious personality disorder, psychosis, suicide risk, alcohol consumption.
- Patients treated with ANTABUSE dispergettes must not be given Ethylene dibromide and its vapours.
- If breastfeeding (see paragraph 4.6).

4.4. Special warnings and precautions for use

ANTABUSE dispergettes should be used under the direct supervision of doctors experienced in the treatment of chronic alcohol dependency and in selected, cooperative patients.
Disulfiram should never be administered without the knowledge of the patient.
ANTABUSE dispergettes should be used with caution in patients with renal or hepatic insufficiency, chronic respiratory disease, diabetes mellitus, hypothyroidism, hyperthyroidism, epilepsy and contact dermatitis caused by gum.
Patients beginning treatment should be informed and aware that they should not consume alcohol during treatment and for 14 days after discontinuation of ANTABUSE dispergettes, as disulfiram prevents the metabolism of ethanol and causes the accumulation of acetaldehyde in the body. This accumulation may cause the alcohol-disulfiram reaction with serious adverse effects (see paragraph 4.8).
Patients should be aware that the alcohol-disulfiram reaction is unpleasant, and is sometimes unpredictable and intense.
Appropriate tests are recommended before beginning treatment to determine the patient's suitability for treatment. Coagulation factors, amino transferase and alkaline phosphatase must be tested before beginning treatment. Amino transferases should be monitored during and after treatment; if values are very high (3 times the reference level), discontinue disulfiram.
Patients should be warned of the unpredictable and potentially serious nature of a disulfiram-alcohol reaction; in rare cases, there have been reports of death following high alcohol consumption by patients treated with disulfiram (see paragraph 4.8). Patients should be warned of the possible presence of alcohol in the liquid form of syrups, drops, foods, toiletries and mouthwashes that may contain alcohol in quantities sufficient to cause a reaction.
Caution should be exercised when consuming "non-alcoholic" or "alcohol-free" beverages, such as beers and low-alcohol wines, which, if consumed in large quantities, may provoke an alcohol-disulfiram reaction (see paragraph 4.8).

In rare cases, disulfiram can cause a serious liver injury, especially after 1-3 months of treatment.

Fatal cases have been reported (see paragraph 4.8).

The patient should have adequate family support and psychotherapeutic treatment to avoid alcohol use.

ANTABUSE dispergettes contain sodium
This medicine contains less than 1 mmol (23 mg) of sodium per tablet, i.e. it is essentially "sodium-free".

4.5. Interactions with other medicinal products and other forms of interaction

The intensity of the alcohol-disulfiram reaction may be increased by amitriptyline and chloropromazine.
Disulfiram inhibits the metabolism of certain benzodiazepines such as chlordiazepoxide and diazepam by increasing their sedative effect. Benzodiazepines may reduce the alcohol-disulfiram reaction.
Disulfiram inhibits the metabolism of various drugs that are metabolised in the liver such as coumarin-type oral anticoagulants (warfarin), oral hypoglycaemics, hypnotics and sedatives (e.g. theophylline), leading to an increase in their concentration and subsequent toxicity. Dose adjustment may therefore be necessary.
Animal studies have indicated a similar inhibition on the metabolism of pethidine, morphine and amphetamines.
Simultaneous intake of ANTABUSE dispergettes with metronidazole, isoniazid and paraldehyde may result in increased confusion, behavioural changes, psychosis and hallucinations.

An enhanced organic brain syndrome has been observed very rarely after pimozide administration.
Disulfiram reduces the biotransformation of phenytoin by increasing its concentrations and toxicity, as well as inhibiting the metabolisation of antipyrine, rifampicin, diazepam.
Pharmacodynamic interactions with serious clinical consequences are to be expected in patients taking blocking drugs (α, β), vasodilators or drugs whose actions on the CNS may be mediated by norepinephrine, dopamine or MAO inhibitor drugs (phenelzine, tranylcypromine).
Disulfiram should not be administered with drugs with a comparable activity on aldehyde dehydrogenase such as sulphanilureas, phenylbutazone, aminophenazone and certain cephalosporins (moxolactam, cefamandole and cefoperazone).

Absorption of ANTABUSE dispergettes may be reduced by concomitant consumption of antacids containing bi-valent cations or high doses of iron salts.

4.6. Fertility, pregnancy and breastfeeding

Pregnancy
ANTABUSE dispergettes should not be used during pregnancy. Using disulfiram in the first trimester of pregnancy is not recommended. Using disulfiram in pregnancy should only be considered after examining its risk/benefit in relation to the adverse effects of alcoholism in pregnant women.
There have been rare reports of congenital abnormalities in infants whose mothers took disulfiram in combination with other drugs during pregnancy.

Breastfeeding
ANTABUSE dispergettes should not be used during breastfeeding (see paragraph 4.3). It is unknown whether disulfiram is excreted in human milk.

4.7. Effects on the ability to drive vehicles and operate machinery

No studies on the ability to drive vehicles have been carried out. Disulfiram may cause drowsiness and fatigue, meaning that it may affect the ability to drive vehicles and operate machinery.

4.8. Undesirable effects

ANTABUSE dispergettes may cause undesirable effects that tend to subside during the course of treatment or after appropriate dosage adjustment.
Frequency classes are defined as follows: very common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100); Rare (≥1/10,000, <1/1,000); Very rare (<1/10,000); Not known (frequency cannot be defined on the basis of available data).

Psychiatric disorders
Rare: psychotic reactions, depression, paranoia, schizophrenia, mania.

Nervous system disorders
Common: somnolence (at the beginning of treatment),
headache. Rare: Peripheral neuropathy, optic neuritis.
Frequency not known: encephalopathy.

Gastrointestinal disorders
Common: nausea, vomiting, halitosis, stomach pain, diarrhoea.

Immune system disorders
Uncommon: hypersensitivity.

Hepatobiliary disorders
Rare: Jaundice, elevated ASAT, ALAT and bilirubin.
Very rare: liver damage, fulminant hepatitis, liver necrosis. Frequency not known: drug-induced liver damage*.
* Fatal cases have been reported.

Skin and subcutaneous tissue disorders
Uncommon: allergic dermatitis with rash, itching, acne-like rash. Frequency not known: rash.

Systemic disorders and conditions related to site of administration
Common: asthenia (at the start of treatment).

Reproductive system and breast disorders Uncommon:
decreased libido, sexual dysfunction.

Alcohol-disulfiram reactions
Disulfiram causes an irreversible blockade of aldehyde dehydrogenase, the enzyme that metabolises alcohol. In the event of alcohol intake, the accumulation of acetaldehyde is considered the main factor in the alcohol-disulfiram reaction.
The reaction often develops within 15 minutes of exposure to alcohol; symptoms generally peak within 30 minutes to 1 hour and gradually subside within a few hours. Symptoms can be severe and life-threatening.
The reaction includes the following symptoms:

- Intense vasodilation of the face and neck with flushing, redness, increased body temperature, sweating, nausea, vomiting, itching, hives, anxiety, dizziness, headache, blurred vision, palpitations and hyperventilation.
- In severe cases, tachycardia, hypotension, respiratory depression, chest pain, QT prolongation, ST depression, arrhythmias, coma and convulsions are possible.
- Rare complications include hypertension, bronchospasm, methaemoglobinaemia.
- In the event of particularly violent reactions following alcohol intake, intensive supportive therapy should be administered in addition to oxygen administration and reconstitution of body fluids.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important, as it allows for the continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are required to report any suspected adverse reactions via the national reporting system at https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

4.9. Overdose

Symptoms of overdose include:

- Nausea, vomiting, abdominal pain, diarrhoea, drowsiness, delirium, hallucinations, lethargy, tachycardia, tachypnoea, hyperthermia and hypotension. Hypotonia may be pronounced, especially in children, and tendon reflexes reduced. Hyperglycaemia, leucocytosis, ketosis (often disproportionate to the degree of dehydration) and methaemoglobinaemia have also been reported.
- In severe cases, cardiovascular collapse, coma and seizures.
- Rare complications include sensory-motor neuropathy, EEG changes, encephalopathy, psychosis and catatonia that may appear several days after overdose. Dysarthria, myoclonus, ataxia, dystonia and akinesia are all possible. Motor disorders may be related to direct toxic effects on the basal ganglia.

Treatment

Treatment must be symptomatic and the patient must be closely monitored. In the event of an acute overdose without concomitant alcohol intake, the usual supportive measures as well as those to counteract hypotension should be taken.
Gastric lavage and activated charcoal may be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ANTABUSE dispergettes (Disulfiram or tetraethylthiourane disulphide) interfere with normal alcohol metabolism in the body, causing an increase in the blood concentration of acetaldehyde. When a patient ingests alcohol during treatment, pronounced objective and subjective symptoms occur within about 10 minutes. The patient will experience dyspnoea, palpitations, headache, nausea, vomiting; these symptoms persist until the alcohol is eliminated.
The marked malaise caused by the ANTABUSE dispergettes/alcohol reaction produces a sense of disgust to alcoholic beverages. Consequently, the regular administration of ANTABUSE dispergettes in combination with sociotherapy and psychotherapy enables effective de-addiction even in chronic non-hospitalised alcoholics.

5.2. Pharmacokinetic properties

Disulfiram is rapidly absorbed from the gastrointestinal tract.
The therapeutic effect is not immediate due to the high fat-solubility of the drug, but takes effect within 12 hours of administration.
Elimination is very slow and one fifth of the administered dose still remains in the body after one week.

5.3. Pre-clinical safety data

DL50 in g/kg p.o.: rat = 8.6 - rabbit = 1.9 - dog > 3.5

6. PHARMACEUTICAL INFORMATION

6.1. List of excipients

Maize starch, polyvinylpyrrolidone, tartaric acid, sodium bicarbonate, precipitated silica, microgranular cellulose, magnesium stearate, polysorbate 20, talc.

6.2. Incompatibilities

None.

6.3. Shelf life

5 years

6.4. Special precautions for storage

Keep in original packaging to protect the medicine from moisture.

6.5. Nature and content of the container

High-density polyethylene bottle with a volume of 50 ml, containing a silica gel capsule in a polypropylene envelope. Polypropylene screw cap with tamper-evident ring nut and childproof closure. Pack containing 1 bottle of 24 tablets

6.6. **Special precautions for disposal and handling**

No specific instructions.

7. MARKETING AUTHORISATION HOLDER

Aurobindo Pharma (Italia) S.r.l. via
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8. MARKETING AUTHORISATION NUMBER

Marketing Authorisation no. 004308019

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10. DATE OF REVISION OF THE TEXT