SUMMARY OF PRODUCT CHARACTERISTICS.

1. NAME OF THE MEDICINAL PRODUCT

Refusal, tablets 250 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains:
250 mg disulfiram.

For excipients see 6.1.

3. PHARMACEUTICAL FORM

Tablets
White round tablets with a score line on one side and the inscription “RF 250” on the other side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Refusal can be used to support drinking cessation in the treatment of alcoholism.

4.2 Posology and method of administration

Posology
Initially 750 mg (= 3 tablets) per day for 2 to 3 days, which may be followed by an individually determined maintenance dose of 125 to 250 mg per day, or 500-750 mg twice a week.

Paediatric population
Refusal is not recommended for use in children.

Method of administration
Take the tablets with a glass of water.
To determine the effect on the patient, it may be useful to have the patient consume a “test drink” after taking disulfiram.

4.3 Contraindications

Refusal is contraindicated in the presence of:
- Hypersensitivity to disulfiram or to any of the excipients in Refusal
- Heart failure
- Manifest psychoses
- Severe brain injury
- Cirrhosis of the liver with ascites
- Acute alcohol intoxication

4.4 Special warnings and precautions for use

Foods, beverages or medicines that contain alcohol may also cause a disulfiram-alcohol reaction after intake of disulfiram.

Disulfiram should not be used as monotherapy but only as an adjunct to intensive psychological or psychiatric treatment. Although peak plasma levels are reached after only 1-2 hours, it takes 3 to 12 hours, and in some cases even up to 48 hours, to take effect. Disulfiram-alcohol reactions may still occur 1 to 2 weeks after the last dose.

4.5 Interaction with other medicinal products and other forms of interaction

Disulfiram is a CYP2E1 and CYP2C9 inhibitor, so it may inhibit the metabolism of medicinal products that are metabolised by these enzymes. Elevated plasma concentrations have been observed for the CYP2C9 substrates phenytoin and warfarin during concomitant use with disulfiram.
Aversion therapy is based on the interaction between disulfiram and alcohol. This combination causes a number of unpleasant sensations in the patient (see section 5.1 “Pharmacodynamic properties”).

Disulfiram is believed to inhibit the demethylation of chlordiazepoxide and diazepam, resulting in elevated serum levels and slower elimination. Disulfiram potentiates the effects of phenytoin and oral anticoagulants. Disulfiram increases the plasma concentration of tricyclic antidepressants. The reverse is true as well: tricyclic antidepressants potentiate the effect of disulfiram.
Concomitant administration of metronidazole, isoniazid and paraldehyde should be avoided, because this may cause confusion and/or psychotic reactions.

4.6 Pregnancy and lactation

There are insufficient data on the use of disulfiram during pregnancy in humans to assess its potential harmfulness. Combination with alcohol is believed to be teratogenic: abnormalities have been reported in a number of children after use of disulfiram in combination with alcohol during pregnancy. There are insufficient data from animal studies.
Refusal should only be used during pregnancy if strictly indicated.
It is not known whether disulfiram passes into breast milk, but based on the low molecular weight of disulfiram it is likely that it does. Refusal should not be used during breastfeeding.

4.7 Effects on ability to drive and use machines

In light of its undesirable effects profile, it is likely that it will have an effect on ability to drive and use machines. This should be kept in mind with regard to driving and using machines.

4.8 Undesirable effects

<u>Nervous system disorders</u>
Polyneuropathy, optic neuropathy, peripheral neuritis (usually as a result of high doses or an overdose).

<u>Gastrointestinal disorders</u>
Gastrointestinal disorders, bad taste initially (garlic and metallic taste) as a result of exhaling carbon disulfide.

<u>Hepatobiliary disorders</u>
Hepatotoxicity (usually as a result of high doses or an overdose).

<u>Skin and subcutaneous tissue disorders</u>
Allergic skin rash.

General disorders and administration site conditions
Transient fatigue, drowsiness.

4.9 Overdose

If a large amount of alcohol is consumed while taking therapeutic doses of disulfiram, the typical unpleasant symptoms may be followed by severe respiratory depression, cardiovascular collapse, cardiac arrhythmia, myocardial infarction, acute heart failure, unconsciousness or sudden death. Initiating treatment with gastric lavage, laxatives and activated charcoal is useful only if the alcohol was consumed not too long ago.
Otherwise the treatment is symptomatic. If it is an overdose of disulfiram only, the symptoms will usually be less pronounced than described above. In these cases, gastric lavage, laxatives and administration of activated charcoal is the indicated therapy. Further treatment is symptomatic as well.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Disulfiram is an alcohol antagonist (ATC code: V03AA01).
Disulfiram affects the normal metabolism process of alcohol in the body by inhibiting the enzyme alcohol dehydrogenase, which increases the acetaldehyde concentration in the blood. With concomitant intake of disulfiram and alcohol, this elevated acetaldehyde concentration causes a number of unpleasant sensations in the patient, consisting of: redness of the face, dyspnoea, pounding headache, nausea, vomiting and tachycardia. These sensations are expected to motivate the patient to avoid the use of alcohol. Consuming large amounts of alcohol together with disulfiram may result in hypotension and cardiovascular collapse. These typical disulfiram-alcohol reactions usually occur within 5 to 10 minutes but may still occur up to 14 days after the last dose of disulfiram. The abovementioned unpleasant symptoms will cause the patient to develop a strong aversion to alcohol.

5.2 Pharmacokinetic properties

Absorption
Disulfiram is absorbed well (80-90%) from the gastrointestinal tract after oral administration. Peak disulfiram plasma levels are observed after approx. 8 hours.

Distribution
Disulfiram is rapidly distributed to the tissues and is stored in the tissues.
Plasma protein binding is about 50%.

Metabolism
Disulfiram is metabolised extensively and primarily in the liver, where it is converted into diethyldithiocarbamate (DDC). Most of the DDC is glucuronidated.
Part of it is methylated into DDC methyl ester, which is then converted into thioalcohol glucuronide, formaldehyde and sulfate. In addition, part of the DDC is nonenzymatically converted into diethylamine, which is converted into carbon disulfide and finally into sulfate and carbon dioxide.

Elimination
The metabolites are primarily eliminated via the urine. About 50% of the disulfiram dose is eliminated as DDC glucuronide. A small part of the dose is eliminated via the lungs as carbon dioxide and carbon disulfide.

The plasma elimination half-life of disulfiram is approx. 7.5 hours, of DDC approx. 16 hours, of DDC methyl ester approx. 22 hours and of diethylamine approx. 14 hours.

5.3 Preclinical safety data

No particulars.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Corn starch, lactose, magnesium stearate, sodium lauryl sulfate, pregelatinised starch, talc, croscarmellose sodium, purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister pack: 3 years
Bottle: 12 months

6.4 Special precautions for storage

Refusal must be stored below 25 ºC in its original packaging.

6.5 Nature and contents of container

Package with 10 blister packs (Aluminium/PVC green) of 10 tablets each.
White HDPE bottle with white PP cap containing 30 tablets.

6.6 Instructions for use and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Ace Pharmaceuticals
Schepenveld 41
3891ZK Zeewolde

8. MARKETING AUTHORISATION NUMBER

RVG 03182

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 March 1986

10. DATE OF REVISION OF THE TEXT

Last partial change concerns sections 1, 3, 6.3, 6.5: 6 September 2021