Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Disulfiram 200mg Tablets

disulfiram

PL 00142/0944

Accord-UK Limited

LAY SUMMARY

Disulfiram 200mg Tablets
disulfiram

This is a summary of the Public Assessment Report (PAR) for Disulfiram 200mg Tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Disulfiram in this lay summary for ease of reading.

For practical information about using Disulfiram, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Disulfiram and what is it used for?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Antabuse 200 mg tablets (PL 30306/0036).

Disulfiram is used in the treatment of people with drinking problems. If a patient is treated with Disulfiram and drink alcohol they will experience unpleasant physical reactions, which may stop them from drinking further alcohol.

How does Disulfiram work?
Disulfiram (Disulfiram's active ingredient) is used as a supportive agent in the treatment of alcoholism. When a patient drinks alcohol it is changed in the body into acetaldehyde, disulfiram blocks the enzyme which breaks down acetaldehyde. This leads to an increased level of acetaldehyde in the blood causing unpleasant physical reactions.

How is Disulfiram used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth).

A check up is advised before starting treatment to check if the patient is suitable for treatment.

Treatment with Disulfiram is usually started in a hospital or specialised clinic. It is important that the patient has not drunk alcohol for at least 24 hours before taking the first dose. The patient should swallow the tablets with water.

The recommended dose is:
Adults and the elderly:
Initially 4 tablets (800mg) on day 1, then 3 tablets (600mg) on day 2, then 2 tablets (400mg) on day 3 and then 1 tablet (200mg) on days 4 and 5.

Then ½ to 1 tablet (100mg – 200mg) a day for as long as the patient is told by their doctor, but for no longer than six months without review.

For further information on how Disulfiram is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Disulfiram have been shown in studies?
Because Disulfiram is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Disulfiram?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Disulfiram is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

Why was Disulfiram approved?
It was concluded that, Disulfiram has been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Disulfiram?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Disulfiram. The RMP details the important risks of Disulfiram, how these risks can be minimised, any uncertainties about Disulfiram (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Disulfiram:

Important identified risks	• Disulfiram - alcohol interaction • Drug induced liver injury
Important potential risks	• Use in pregnancy
Missing Information	• Use in lactating mother

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Disulfiram are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Disulfiram

A marketing authorisation for Disulfiram was granted in the United Kingdom (UK) on 12 January 2024.

The full PAR for Disulfiram follows this summary.

This summary was last updated in February 2025.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Disulfiram 200mg Tablets (PL 00142/0944) could be approved.

The product is approved for the following indications:
Alcohol deterrent compound. Disulfiram may be indicated as an adjuvant in the treatment of carefully selected and co-operative patients with drinking problems. Its use must be accompanied by appropriate supportive treatment.

The effect of Disulfiram is primarily due to irreversible inactivation of liver 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 (DAR) are due partly 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 cause 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 oxidases (which are responsible for the metabolism of many drugs). Disulfiram may thus potentiate the action of drugs which are metabolised by these enzymes.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Antabuse 200 mg tablets that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation for Disulfiram was granted in the United Kingdom (UK) on 12 January 2024.

II QUALITY ASPECTS

II.1 Introduction

Each tablet contains 200 mg disulfiram.

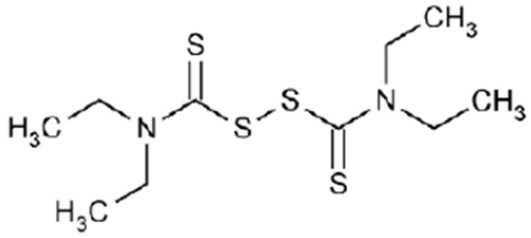
The other ingredients are microcrystalline cellulose, lactose monohydrate, maize starch, potato starch, sodium hydrogen carbonate, tartaric acid, povidone K30, polysorbate 20, colloidal anhydrous silica and magnesium stearate.

The finished product is packaged in a HDPE container with a polypropylene child resistant closure and is available in a pack size of 50 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: disulfiram
Chemical Name: Bis(diethylthiocarbamoyl) disulfide
Molecular Formula: $C_{10}H_{20}N_2S_4$



Chemical Structure:
Molecular Weight: 296.5
Appearance: White or almost white crystalline powder.
Solubility: Soluble in methylene chloride, sparingly soluble in alcohol. Sparingly soluble in water at 25°C and pH value from 1 to 10.

Disulfiram is the subject of a European Pharmacopoeia monograph.

The information related to the active substance was provided in an ASMF. The Active substance is the subject of a Ph.Eur. monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with no special storage conditions, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of disulfiram are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology

No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology

No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment

A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of disulfiram is well-known. With the exception of data from a single bioequivalence study undertaken, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following:

Study 1

This study was an open label, balanced, randomised, two-sequence, two-treatment, two-period, single oral dose, crossover bioequivalence study comparing two formulations of Disulfiram 200mg Tablets in normal, healthy, adult, human subjects under fasting conditions.

A single dose of either the test or reference product was administered after an overnight fast of at least 10 hours, in each study period. Blood samples were taken pre-dose and up to 48 hours post dose, with a washout period of 7 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Pharmacokinetic Parameter	Geometric Mean Ratio Test/Reference	90% Confidence Intervals	CV%[1]
$AUC_{(0-t)}$	106.7	102.55 - 111.09	15.2
C_{max}	114.8	107.87 - 122.12	23.7

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted for this application and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with disulfiram is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK version of the SmPC and PIL for this product are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**