Redacted under sections 40, 41 and 43 of the Freedom of information Act.

2.5 CLINICAL OVERVIEW

[redacted]

COMMON TECHNICAL DOCUMENT, MODULE 2, OVERALL SUMMARIES
CLINICAL OVERVIEW, MODULE 2.5
DISULFIRAM TABLETS 200mg

Module 2 Overall Summaries

2.5 Clinical Overview

Pharmacodynamic, pharmacokinetic, efficacy and safety properties of Disulfiram tablets are well known. As Disulfiram is a widely used, well-known active substance, [redacted] has not provided additional studies and further studies are not required. The following clinical-overview is based on literature review and is considered as appropriate.

The presented clinical-overview has been written by [redacted] Medical Doctor [redacted]

Clinical (pharmacology, pharmacokinetic, efficacy and safety):

Name of the expert: [redacted]

Signature: [redacted]

Date: 10-May-2016

[redacted]

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2.5 CLINICAL OVERVIEW

This clinical overview supports the marketing authorization application for Disulfiram tablets 200 mg with an updated research literature and relevant publications on pharmacodynamics, pharmacokinetics, efficacy and safety.

2.5.1 PRODUCT DEVELOPMENT RATIONALE

Alcohol dependency is a heterogeneous condition. As per the global safety reports on alcohol and health by the WHO (2008), world's highest alcohol consumption levels were found in Western and Eastern Europe. In the United Kingdom, alcohol dependence has been reported to be 7.5% in men and 2.1% in women, with peak prevalence in the age group of 16-29 years.

Drugs like Naltrexone, Topiramate and Acamprosate are also used for prevention and minimization of the relapse of alcohol dependency, however, Disulfiram proves to be effective in compliant patients. **(Grover et al., 2007)**

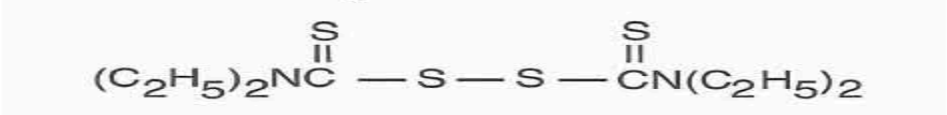
Nearly 27 clinical trials have been conducted to establish the safety and efficacy of Disulfiram in the treatment of alcohol dependency, cocaine abuse, and related anxiety disorders. The effectiveness of disulfiram in treating alcohol dependence was studied in comparison with other drugs. Nearly 12 clinical trials are ongoing to establish the effectiveness of disulfiram in treating various forms of cancer like breast cancer, glioblastoma multiforme **(Clinical Trials.gov).**

2.5.2 OVERVIEW OF BIOPHARMACEUTICS

Disulfiram has very poor water solubility (4.096 mg/L), which limits absorption rate and causes rapid metabolism, maybe due to increased residence time in stomach. **(Ramadhani. N et al., 2014).**

Disulfiram exists as white to off-white, odorless, almost tasteless powder.
Solubility: Disulfiram exhibits a solubility of 20 mg in 100 ml of water and about 3800 mg in 100 ml of alcohol.
Molecular formula: $C_{10}H_{20}N_2S_4$
Molecular weight: 296.54 g/mol
Chemical name: bis (diethylthiocarbamoyl) disulfide

The structural formula is represented below:



Under the Anatomical Therapeutic Chemical (ATC) classification system, Disulfiram are classified under the following headings:

N – Nervous System
N07 - Other Nervous System drugs
N07B- Drugs used in Addictive Disorder
N07BB- Drugs used in alcohol dependence.
N07BB01- Disulfiram **(WHO ATC DD Index).**

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

2.5.3.1 Pharmacodynamics

Disulfiram has been extensively used in the treatment of alcoholism. On oral administration, it undergoes reduction to diethyldithiocarbamate (DDC) which acts as an antioxidant. This DDC collects the reactive oxygen species such as peroxides, peroxynitrite and hydroxyl radicals and binds with the metal ions. **(Nabekura et al, 2000)**

Disulfiram undergoes a reduction in the disulfide bond and concurrent liberation diethyldithiocarbamate (DDTC) which induces the irreversible inactivation of the liver enzymes (acetaldehyde dehydrogenases) and accumulation of acetaldehyde in serum. **(Koppaka et al, 2012)**

Disulfiram tablets are used in the treatment of alcoholism, where it acts by inhibiting the liver enzymes involved in ethanol absorption. **(Mohan. L et al., 2010).**

2.5.3.2 Pharmacokinetics

2.5.3.2.1 Absorption

After oral administration, in the acidic environment of the stomach, disulfiram is reduced to unstable diethyldithiocarbamic acid (DDC) which rapidly decomposes to carbon disulphide and diethylamine. Some amount of the liberated DDC forms an acid stable copper complex, bis (diethyldithiocarbamate) (Cu $(DDC)_2$) having extremely hydrophobic nature, which allows the systemic absorption along the entire length of the upper gastrointestinal (GI) tract. **(Johansson. B et al., 1992)**

After administration, Disulfiram is rapidly but incompletely absorbed from the gastrointestinal tract. **(Eneanya et al, 1981)**

2.5.3.2.2 Distribution

After oral absorption, disulfiram is found mostly in the fat depots because of its high lipid solubility. Concentrations of Disulfiram and its metabolites are found in the plasma, liver, spleen, thyroid, muscles, intestines, heart and in very low concentrations in the brain. **(Eneanya et al, 1981)**

Following the variable absorption, disulfiram is distributed primarily to the kidneys, pancreas, liver, intestines and fat. **(Antabuse tablets SPC, 2011)**

2.5.3.2.3 Protein Binding

Disulfiram and its metabolite, diethylthiocarbamic acid has an affinity to bind with albumin. The affinity of albumin was lesser to the metabolite (Me-DTC) than disulfiram, due to its hydrophilic structure. **(Johansson. B et al., 1992)**

2.5.3.2.4 Metabolism

Disulfiram undergoes rapid metabolism in the tissues and plasma. Degradation of disulfiram is a two-step process, in the first step it undergoes reduction to diethyldithiocarbamate (DDC) followed by further degradation to carbon disulfide and other glucuronic acid conjugates. The rate of reduction of Disulfiram was first-order. **(Agarwal. R.P et al., 1986).**

Disulfiram undergoes rapid reduction to diethyldithiocarbamate (DDC). This reduction follows first order kinetics and is rapid in nature which results in the disappearance of the parent compound into the blood stream. Diethyldithiocarbamate (DDC) is further metabolized by four different pathways like glucuronidation, non enzymatic degradation, methylation and oxidation. **(Eneanya et al, 1981)**

2.5.3.2.5 Elimination

Elimination kinetics studies of disulfiram were conducted in 15 alcoholics. After a single oral dose administration, it was observed that 22.4% of disulfiram was eliminated in breath; 1.7% in urine and 8.3% of the dose was eliminated as DDTC-glucuronide. Disulfiram and its metabolites exhibit linear kinetics. **(Faiman et al., 1984)**

Excretion of Disulfiram and its metabolites is primarily through kidneys. **(Antabuse tablets SPC, 2011)**

2.5.3.2.6 Special Population

The prevalence of alcohol use and abuse in older population is under-diagnosed due to that fact that the effects of alcohol, use are less clearly visible. Medicinal adjuncts with strict compliance and monitoring of adverse effects are required for elderly population.

Disulfiram administration followed by alcohol consumption can cause inhibition of acetaldehyde dehydrogenase, causing increased levels of blood acetaldehyde and leading to disulfiram-ethanol reaction. The hypotension associated with the disulfiram ethanol reaction is greater in older patients. Caution must be exercised while administering disulfiram to older patients as they have less cardiovascular tolerance to the toxic reaction. **(Chick. J et al., 1999)**

2.5.3.2.7 Drug Interactions

Ingestion of alcohol after disulfiram treatment induces irreversible inhibition of liver enzymes, acetaldehyde dehydrogenase which is involved in the conversion of acetaldehyde to acetic acid. This result in accumulation of toxic levels of acetaldehyde in the blood which leads to the disulfiram-ethanol reaction, symptoms include nausea, vomiting, facial flushing, palpitations, tachycardia, and hypotension. **(Kitson et al., 1977).**

Concomitant administration of Disulfiram with Chlordiazepoxide or Diazepam leads to prolongation of elimination half-life and decrease in the clearance of both Chlordiazepoxide and Diazepam, leading to extensive accumulation during the long-term therapy of these drugs. **(MacLeod et al., 1978).**

2.5.3.2.8 Bioequivalence

Study Title:
An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover oral bioequivalence study of Disulfiram Tablets 200 mg of [redacted] and Disulfiram Tablets 200 mg of Actavis Group PTC ehf. Reykjavikurvegi 76-78, 220 Hafnarfjordur, Iceland in normal healthy, adult human subjects under fasting conditions.

Study Objectives:

Primary Objective:
To compare the rate and extent of absorption of Disulfiram Tablets 200 mg of [redacted] and Disulfiram Tablets 200 mg of Actavis Group PTC ehf, Iceland in healthy subjects, under fasting conditions.

Secondary objective:
To monitor clinical status, adverse events, laboratory investigations and assess relative safety and tolerability of the Disulfiram formulations.

Methodology:
An open label, balanced, randomized single-dose, two-treatment, two-sequence, two-period, crossover oral bioequivalence study in normal healthy, adult human subjects under fasting conditions.

Diagnosis and main criteria for inclusion:

- Human subjects aged from 18 to 45 years inclusive.
- BMI range from 18.5 to 24.9 kg/m^2 inclusive with the body weight $\geq$ 45 kgs.
- Normal systemic (laboratory tests) and physical evaluations.
- Normal clinical examination like vital signs (blood pressure, pulse rate, respiratory rate and body temperature).
- Medical and surgical history as approved by the physician or principal investigator prior to start of the study.

Test Product (T): Disulfiram Tablets 200 mg

Reference Product (R): Disulfiram Tablets 200mg.

Criteria for Evaluation:
Pharmacokinetic Parameters:

Analyte	Disulfiram
Primary pharmacokinetic variables	C_{max} (ng/ml) AUC_{0-t} (ng.h/mL)
Secondary pharmacokinetic variables	$AUC_{0-\infty}$ (ng.h/ml) T_{max} (h) AUC_{0-t}/ $AUC_{0-\infty}$ (ng.h/ml) $t_{1/2}$ (h) λz

Phoenix WinNonlin® Software Version 7.0 or higher version (Pharsight Corporation, USA).

Safety Assessment:
All volunteers underwent a screening procedure comprising medical history, clinical examination (vital signs (sitting blood pressure, oral temperature, radial pulse rate and respiratory rate), physical examination and systemic examination), urine pregnancy test (only for female subjects), recording of electrocardiogram, Chest X-Ray (PA view for subjects with any history of respiratory illness) and laboratory investigations of blood as well as urine, prior to first dosing.

On the day of admission at each period, urine screen for drugs of abuse and alcohol breath test, along with serum pregnancy test (for female subjects only) was performed. During the course of the study, subjects were monitored for adverse events, with clinical and physical examinations at regular intervals.

Bioanalytical Analysis: Validated LC-MS/MS method was employed for the determination of plasma concentrations of the active metabolite, methyl diethyldithiocarbamate, under sodium vapor lamp.

Statistical methods:

- Software: SAS®, version 9.4 or higher by using PROC GLM method.
- The statistical analysis of ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} was performed for the active metabolite, S-methyl N,N-diethyldithiocarbamate (Me-DDC).
- ANOVA, two one-sided t tests, ratio analysis, power test and 90% confidence intervals for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} of active metabolite, S-methyl N,N-diethyldithiocarbamate (Me-DDC).
- Based on the statistical results of the 90% confidence intervals for the difference of least square means of ln-transformed pharmacokinetic parameters C_{max} and $AUC_{0-t,}$ conclusions were drawn whether the test product is bioequivalent to the reference product under fasting conditions.

Statistical Results:
The acceptance range for bioequivalence is ≥ 80.00% and ≤ 125.00% for the 90% confidence intervals for the difference of means of ln-transformed pharmacokinetic parameters C_{max} and $AUC_{0-t,}$ of active metabolite, S-methyl N,N-diethyldithiocarbamate (Me-DDC).

90% confidence intervals for C_{max} and $AUC_{0-t,}$ for Disulfiram and its active metabolite are within the bioequivalence criteria.

Safety Results:
A single oral dose of either the Test or Reference product of Disulfiram tablets 200 mg was administered to healthy subjects, under fasting conditions. Only one subject experienced emesis, within 1 hr of dosing and was withdrawn from the study, as per investigator's discretion. All the other subjects tolerated the treatment well. There were no serious or unexpected adverse events observed during the course of the study.

Conclusion:
After an overnight fast of at least 10 hrs, the subjects were administered the Test or Reference product of Disulfiram tablets 200 mg, as per randomization schedule.

Based on the variability observed in earlier studies, 50 subjects (including drop-outs) were planned to be enrolled in the study to establish bioequivalence with sufficient power.
50 subjects were enrolled on the day of admission of Period I. Out of the 50 enrolled subjects, only 46 subjects received both the treatment arms as per randomization schedule and completed the study. The subjects who completed the study were considered for pK and statistical analysis.

2.5.4 OVERVIEW OF EFFICACY

2.5.4.1 Indications

Disulfiram is used as an adjuvant in treating patients with drinking problems. The use of this medication is always accompanied by appropriate supportive treatment. Disulfiram is known as an alcohol deterrent compound. **(Antabuse tablets SPC, 2011)**

Disulfiram is employed for the treatment of alcoholism. Also, study conducted with disulfiram, concluded that the drug and its metabolite are used either alone or in combination with copper have significant effect on multiple myeloma, acute myeloid and lymphoblastic leukemia in newly diagnosed and relapsed/ resistant patients. **(Conticello et al., 2012)**

2.5.4.2 Dosage and Administration

Dosage regimen is similar to adult and elderly patients. Treatment with Disulfiram is initiated in the presence of physicians, at dose of 4 tablets (up to 800mg) on day 1, followed by 3 tablets on day 2, 2 tablets on day 3 and 1 tablet on days 4 and 5. Subsequently the daily dosing should continue at either 1 or 1.5 tablets per day, as per physician's advice. Disulfiram therapy is provided to patients who haven't consumed alcohol for at least 24 hours. **(Antabuse Tablets SPC, 2011).**

Drug therapy isn't recommended for paediatric population, mainly due to the absence of any clinically relevant studies. Case study reported accidental administration in a 6 year old boy, led to flushing, headache, tachycardia, hallucinations, requiring hospitalization. The patient was treated with maintenance fluids intravenously and was discharged after 3 days. **(Benitz et al., 1984)**

2.5.4.3 Clinical Studies

A partial replicated study was conducted to determine the effect of disulfiram and placebo implants in alcoholic patients, with similar demographic characteristics. The relative effectiveness was assessed on the duration between the treatment assignments to first drink. Patients on disulfiram were abstinent for a mean of 361 days and those on placebo, for 307 days. Of the enrolled patients, 17 patients on disulfiram therapy didn't remain abstinent and resumption of drinking, 7 of them didn't experience any disulfiram-ethanol reactions and the remaining had mild to severe reactions. **(Wilson. A et al., 1980)**

Double blinded, clinical study was conducted to determine the efficacy of disulfiram in treating alcoholic patients. The assessment was based on the index of blindness of the clinic personnel to treatments administered; and primary end point was related to complete abstinence during the study period. Patients were randomly assigned either 250mg of disulfiram, 1mg of disulfiram or riboflavin. **(James. K et al., 1996)**

An open, randomized study was conducted to compare the efficacy of Disulfiram and Acamprosate in alcohol-dependent men undergoing detoxification. Following randomization, these patients received either 250mg Disulfiram as a single daily dose at the time of breakfast; or 1998mg of Acamprosate thrice daily after meals. Follow-up by the end of 8 months, showed that 88% of Disulfiram group had not relapsed, as compared to 46% in Acamprosate group (P=0.0001). Patients on disulfiram were abstinent for a mean of 123 days and those on Acamprosate for 71 days. **(De Sousa. A and De Sousa. A, 2005).**

2.5.5 OVERVIEW OF SAFETY

2.5.5.1 Contraindications

Disulfiram is remarkably safe and well tolerated in 250mg per day recommended dosage. Disulfiram therapy is contraindicated in patients with-

- History of severe allergic reaction to disulfiram
- History or existing conditions of liver and renal diseases.
- History of bronchospasm, cardiomyopathy or congestive heart failure, myocardial infraction. **(Peachy. J.E et al., 1984).**
- Alcoholic patients with psychotic conditions like depression, suicidal risks, severe personality disorders. **(Banys. P et al., 1988).**
- Coronary artery disease; previous history of cardiovascular disease, hypertension.
- Consumption of alcohol. **(Antabuse tablets SPC, 2011).**

2.5.5.2 Precautions and Warnings

Caution should be exercised while using disulfiram in patients with a history or existing conditions of-

- Renal failure
- Hepatic disease
- Respiratory disorder
- Diabetes mellitus
- Hypothyroidism
- Cerebral damage
- Epilepsy **(Antabuse® Tablets SPC, 2011).**

2.5.5.3 Pregnancy and Lactation

The use of Disulfiram during the first trimester of pregnancy isn't advised. Administration of disulfiram during of pregnancy can lead to teratogenic effects. **(Rosett et al., 1988).**

Case studies conducted on a 23 year old pregnant woman with long history of drug and alcohol dependency was treated with disulfiram (250mg/day) during the first 10 weeks of pregnancy. After 41 weeks of gestational period, the infant had benign course and demonstrated normal development. **(Helmbrecht et al., 1991).**

Disulfiram is contraindicated in lactating women. No studies have been conducted to establish the excretion of disulfiram in breast milk. **(Antabuse® Tablets SPC, 2011).**

2.5.5.4 Adverse Reactions

Mild reactions like sedation, drowsiness, garlic-like or metallic taste, skin rashes, gastrointestinal disturbances, elevated serum cholesterol, hypertension, orthostatic hypotension are observed in patients who ingest alcohol after the treatment with disulfiram. Concomitant use of disulfiram and alcohol can cause various degrees of hepatotoxicity, incoordination and psychosis which are dose dependent. **(Banys. P et al., 1988).**

Severe but rare central nervous system effects appeared on a dose-related continuum of disorientation, delirium and psychotic features. **(Kirubakaran. V et al., 1983).**

More serious behavioural toxicity includes psychosis and acute encephalopathy, especially in individuals with a history or evidence of depression or schizophrenia. Peripheral neuropathy with muscle weakness and motor incoordination, increases in cholesterol and serum triglycerides, increase in plasma noradrenaline, blood pressure and altered neuroendocrine function have also been reported. **(Peachy. J.E et al., 1984).**

Impaired consciousness and hypotension are featured in most cases of Disulfiram-ethanol reaction. **(Woolley. B et al., 1980)**

2.5.5.5 Over dosage and Treatment

Case report of an alcoholic patient who ingested excess disulfiram dose (7g) was studied. Disulfiram-ethanol reaction was precipitated and the following symptoms were observed-

- Drowsiness
- Flushing
- Vomiting
- On hospitalization, the patient was in coma, with hypotension and related transient oliguria.

Treatment:

- Oxygen administration
- Normal saline infusion followed by KCl
- Intravenous administration of Furosemide. **(Woolley. B et al., 1980)**

2.5.5.6 Worldwide Marketing Experience

As per the global safety reports of WHO, worldwide per capita consumption of alcoholic beverages in 2005 equaled 6.13 liters of pure alcohol consumed by every person aged 15 years or older. There are only few pharmacological treatments in the field of alcohol dependence, and many are alternative treatments. Disulfiram was oldest medical treatment for alcohol dependency. Disulfiram is the treatment of choice in a number of countries including Europe, United Kingdom, Australia, Canada and United States.

Disulfiram is one of the oldest and effective drugs in the treatment of alcohol dependence. It primarily acts by inhibiting alcohol metabolism and increasing the concentrations of acetaldehyde. **(Fox. C et al., 2008)**

2.5.6 BENEFITS AND RISKS CONCLUSIONS

2.5.6.1 Therapeutic Context

Disulfiram is an antioxidant that was medically used for treating scabies. The chance observation of unpleasant effects following alcohol consumption in workers handling thiol derivatives, like disulfiram, proposed the application of disulfiram for treating alcoholic dependence.

Disulfiram is the selected standard in alcohol treatment programs by the clinicians. It acts as a deterrent (alcohol sensitizing) drug. The antioxidant properties of disulfiram induce the inhibition of liver enzymes like acetaldehyde dehydrogenase, aniline hydroxylase and other oxidases. **(Banys. P et al., 1988).**

Disulfiram was proposed as the non-profit drug against refractory solid tumors, with negligible adverse effects in comparison with classical chemotherapy.

A study in patients with multiple melanoma concluded that the combination of Disulfiram and copper forms a complex with potent proteasome inhibiting and apoptosis-inducing

activity on several tumors. The cytotoxic effects of Disulfiram and copper combination were similar to that of the chemotherapeutic drug, at a dosage consistent to achieve serum concentration. **(Conticello et al., 2012)**

Disulfiram combined with psychotherapy proved to be a promising treatment strategy for individuals with cocaine-dependency with alcohol abuse.

Studies conducted to evaluate the effectiveness of disulfiram with manual guided psychotherapy for individuals with cocaine dependence and concurrent alcohol abuse, proved that disulfiram treatment was associated with significantly better retention in therapy and longer duration of abstinence from alcohol and cocaine use. **(Carroll et al., 1997)**

2.5.6.1.1 Disease or condition

As per the WHO, alcohol consumption is the world's largest risk factor for disease and disability. Almost 4% of the deaths worldwide have been attributed to alcohol. Alcohol consumption has socioeconomic impacts.

Alcohol (ethanol) is a psychoactive agent that acts on the central nervous system to alter the mood, thought processes or behaviour. It is estimated that within the United States, about 17 million people of age 18 years and older suffer from both alcoholism or alcohol abuse, as per the National institute on Alcoholism and Alcohol Abuse.

Disulfiram is used in treating alcohol addiction, during the maintenance phase of the treatment and act by irreversible inhibition of the liver enzymes that detoxify alcohol. **(Robinson. S et al., 2015)**

2.5.6.1.2 Current Therapies

A large variety of drugs which have acetaldehyde dehydrogenase (ALDH) inhibiting activity may sensitize patients to alcohol. Calcium carbimide (Temposil®) is the shorter acting alternative to disulfiram in treating alcoholic dependence. **(Banys. P et al., 1988).**

Drugs like g-hydroxybutyrate and naltrexone are also employed in treating alcoholism. The assessment was based on alcohol intake and cravings while on treatment and laboratory parameters of alcohol abuse. All the treatments proved to be equally effective. G-hydroxybutyrate produced a higher reduction of biological markers, indicating cellular protector effects. **(Nava. F et al., 2006)**

Various therapies with Naltrexone and Acamprosate also proved to be effective in treating alcohol dependence. These drugs are effective adjuncts to alcohol treatment and prevent alcohol relapse.

Based on the various studies conducted, Disulfiram proves to be an effective treatment in alcohol dependence under supervision.

2.5.6.2 Benefits

Use of Disulfiram, under supervision has been proven to be effective adjunct to alcoholism therapy.

A study conducted on the inpatient group at an alcoholism therapy centre, stated that the reasons for stopping the medication intake was the desire to drink alcohol, or the feeling that they didn't need disulfiram anymore. A very low rate of participants mentioned side effects as a reason. **(Liskow et al., 1987)**

The adverse effects and compliance to treatment with Disulfiram was studied in a group of alcoholics. The adverse events that occurred early in the treatment with disulfiram were gastrointestinal disturbances like nausea, vomiting, anxiety, depression and drowsiness. During the initial analysis, the frequency of adverse effects was more, however, on further examination, it was revealed that majority of these symptoms were present before the commencement of drug therapy and were not considered as an adverse effect of Disulfiram. The study indicated that adverse effects of Disulfiram were infrequent and mild. **(Srinivasan. T.N et al.)**

Disulfiram is associated with large and significantly greater reduction in relapse and more abstinent days, in alcoholic patients. Studies conducted concluded that supervised disulfiram is a very effective component for alcoholism treatment and is more effective than either naltrexone or Acamprosate. **(De Sousa. A.A et al., 2005).**

2.5.6.3 Risks

Disulfiram is extensively used in the treatment of alcoholism from many years. Numerous side effects including tiredness, sleepiness, dizziness, sexual problems, poor memory, headache, unpleasant taste, gastrointestinal disturbances have been reported by both patients and physicians, which often is a reason for withdrawing the treatment.

A double-blinded, randomized study of disulfiram versus placebo was conducted. The adverse symptoms like dizziness, gastrointestinal disturbances, palpitations, rashes, and shortness of breath were observed in participants from both the groups. The participants on the disulfiram therapy had additional complaints of stiffness in the neck, headache and unpleasant taste. **(Christensen et al, 1984)**

The alanine transaminase levels in certain individuals increased with disulfiram treatment. However, the effect was resolved either by a dose reduction or discontinuation of therapy in these individuals. **(Laaksonen. E et al., 2007)**

Disulfiram interferes with the activity of certain liver enzymes, but isn't considered a hepatotoxin. In patients with high incidence of alcohol induced hepatic toxicity, disulfiram is known to induce liver injury. Treatment with disulfiram has to be stopped in such cases and the symptoms of liver injury are resolved without any medication. **(Morris. J et al., 1978)**

2.5.6.4 Benefit-Risk Assessment

A randomized study was conducted to determine the effectiveness of the Naltrexone, Acamprosate and Disulfiram, in combination with psychological intervention, in the treatment of alcohol dependence. The study was conducted for duration of 52 weeks and the subjects were monitored for medication intake, alcohol use and any adverse effects. The subjects were also encouraged to attend support groups and receive detoxification, if required during the course of the study.

After the completion of 52 weeks of treatment, there was no significant difference observed across the groups, in terms of study completion. Early termination of study was either due to poor patient compliance or protocol violations. The study concluded that Disulfiram was effective with more abstinent days, lower alcohol consumption and prevention of relapse, in comparison to the other treatments. **(Laaksonen. E et al., 2007)**

The known likelihood of increased neuropathy or brain damage with exposure to alcohol must be weighed against the very low risk of nervous system damage from exposure to this medication.

Disulfiram therapy has shown high clinical safety and stable psychological effects in various treatment studies. This medication can be safely offered to a wide range of patients with alcohol problems.

The knowledge that has been gathered on Disulfiram in the addiction field continues to be contemporary and clinically relevant.

2.5.6.5 Appendix

A double blinded, randomized study to assess the side effects of Disulfiram therapy in alcoholic patients.

241 patients, including men and women between the age group of 18 years to 70 years, with previous treatment history of disulfiram were enrolled in the study. Patients who had history of liver or cardiovascular diseases and females who were pregnant weren't included in the study. These patients were initially given placebo for the first two weeks (wash-out period). Following the wash-out, the patients were administered either Disulfiram 400 mg effervescent tablets or placebo effervescent tablets, as a single daily dose of half tablet (200 mg), dispersed in plain soda water, under supervision. Symptomatic treatment with sedatives and hypnotics was provided to the patients.

Patients were followed up for side effects and after the first two weeks of treatment and at the end of six weeks; and for alcohol intake on weekly basis.

Of the 241 enrolled subjects, only 158 subjects completed the study. The symptoms after the wash-out period were comparable across the two groups. At the end of study, the adverse effects like gastrointestinal disturbances, dizziness, palpitations, and hypotension were observed in patients across both the groups; except for patients on disulfiram therapy had additional complaints of stiffness in the neck, headache and unpleasant taste.

The differences observed were not significant. It was concluded that the disulfiram treatment given didn't cause more subjective side effects than the treatment with placebo. **(Srinivasan. T.N et al.)**

An open label, non blinded, randomized study to compare Disulfiram and Topiramate in the treatment of alcoholic dependence.

Alcohol dependent men, between the age group of 18 to 65 years, with no history or presence of other substance use or any comorbid psychiatric conditions, undergoing inpatient detoxification were enrolled in the study. Based on the randomization schedule, the 100 enrolled subjects were divided into two groups of 50 subjects each, wherein one group received 250mg of Disulfiram as a single daily dose after breakfast and the other group was administered 50mg of Topiramate 3 times a day after meals. Subjects were also prescribed symptomatic treatment for depression or insomnia.

Patients were followed up on a weekly basis for the first 3 months and at each follow-up, they were assessed for cravings and compliance for alcohol consumption, and any side effects observed.

Abstinence was enforced and subjects who had relapses were considered as drop-outs, during the study conduct. After the treatment duration of 9 months, it was observed that although Topiramate reduced the cravings to a greater extent, 44% of the subjects on Topiramate had a relapse or alcohol intake during therapy.

Subjects on disulfiram showed a significant reduction in relapse and more abstinent days (206 days). The study concluded that Disulfiram therapy under supervision was effective in the treatment of alcoholism and was significantly more effective than Topiramate. **(De Sousa. A.A et al., 2007)**

2.5.7 LITERATURE REFERENCES

1. Grover et al., Pharmacoprophylaxis of alcohol dependence: Review and Update Part I: Pharmacology. Indian J Psychiatry 2007; 49: 19-25.
2. Clinical Trials clinicaltrials.gov
3. Ramadhani N et al., Preparation and Characterisation of Kolliphor® P 188 and P 237 solid dispersion oral tablets containing the poorly water soluble drug Disulfiram; International Journal of Pharmaceutics 475 (2014) 514-522.
4. WHO Collaborating Center, ATC/DDD Index.
5. Nabekura et al., Preparation and in vivo Ocular Absorption studies of Disulfiram Solid Dispersion; Biol. Pharm. Bull. 23(5) 616-620 (2000)
6. Koppaka et al., Aldehyde Dehydrogenase Inhibitors: a comprehensive review of the pharmacology, mechanism of action, substrate specificity and clinical application; Pharmacol Rev 64:520-539, 2012.
7. Mohan L et al., Pharmacotherapy of Alcohol dependence. Journal of Clinical and Diagnostic Research, 2010 August; 4:2947-2955.
8. Johansson. B et al., A review of the pharmacokinetics and pharmacodynamics of disulfiram and its metabolites; Acta Psychiatr Scan 1992: 86: 15-26.

9. Eneanya et al., The Actions and Metabolic fate of Disulfiram; Ann. Rev. Pharmacol, Toxicol 1981. 21:575-96.
10. Antabuse® Tablets Summary of Product Characteristics (SPC); 2011.
11. Johansson. B et al., Plasma Protein binding of Disulfiram and its metabolite diethylthiocarbamic acid methyl ester; J. Pharmacol. 1990, 42:806-807.
12. Agarwal et al., Serum Albumin and the metabolism of Disulfiram; Biochemical Pharmacology, Vol.35, No.19, pg.3341-3347, 1986.
13. Faiman et al., Elimination Kinetics of Disulfiram in alcoholics after single and repeated doses; 1984.
14. Chick. J et al., Safety Issues concerning the use of Disulfiram in treating Alcohol Dependence; Drug Safety 1999 May; 20(5):427-435.
15. Kitson et al., The Disulfiram-Ethanol Reaction, A Review; Journal of Studies on Alcohol, Vol. 38, No. 1, 1977.
16. MacLeod et al., Interaction of Disulfiram with benzodiazepines; Clinical Pharmacology and Therapeutics, 1977.
17. Conticello et al., Disulfiram, an old drug with new potential therapeutic uses for human hematological malignancies; International Journal of cancer; 2012.
18. Benitz et al., Disulfiram intoxication in a child; Clinical and Laboratory Observations; 1984.
19. Wilson. A et al., Disulfiram implantation, A trial using Placebo Implants and Two types of Controls; Journal of Studies on Alcohol; Vol.41, No.5, 1980.
20. James. K et al., An index for assessing blindness in a multi-centre clinical trial: Disulfiram for alcohol cessation-a VA cooperative study; Statistics in Medicine, Vol.15, 1421-1434 (1996).
21. De Sousa. A and De Sousa. A et al., An Open Randomized Study Comparing Disulfiram and Acamprosate in the treatment of Alcohol dependence; Alcohol and Alcoholism, Vol.40, No.6, pp.545-548, 2005.
22. Peachy. J.E et al., The Role of drugs in the Treatment of Alcoholism; Practical therapeutics, Drugs 27:171-182 (1984).
23. Banys. P et al., The Clinical Use of Disulfiram (Antabuse®): A Review; Journal of Psychoactive Drugs, 20:3, 243-261 (1988).
24. Rosett et al., Alcoholism-Clinical and Experimental Research; Vol. IV, No.2, April 1980.
25. Helmbrecht et al., First Trimester Disulfiram Exposure: Report of Two cases; American Journal; of Perinatology, Vol.10, No.1, January 1993.
26. Kirubakaran et al., case report of Acute Disulfiram Overdose; Am J Psychiatry 140:11, November 1983.
27. Woolley et al., Acute Disulfiram Overdose; Journal of studies on Alcohol, Vol 41, No 7, 1980.
28. Fox. C et al., Disulfiram for Alcohol Dependence; Cochrane Database of Systemic reviews 2003, Issue 3.
29. Carroll et al., Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram; Addiction (1998) 93(5), 713-728.
30. Robinson. S et al., The Role of Disulfiram in Alcohol Metabolism and the Treatment of Alcoholism; American Chemical Society; 2015.
31. Nava. F et al., Comparing Treatments of Alcoholism on cravings and Biochemical Measures of alcohol consumptions; Journal of Psychoactive Drugs, Volume 38(3), September 2006.

32. Liskow et al., Pharmacological treatment of Alcohol Intoxication, Withdrawal and Dependence: A Critical Review; Journal of Studies on Alcohol, Vol.48, No.4, 1987.
33. Srinivasan. T.N et al., Adverse Effects of Disulfiram and patient Compliance.
34. Christensen et al., Side Effects after Disulfiram; Acta psychiatr scand. 1984:69:265-273.
35. Laaksonen. E et al., A randomized, Multicenter, Open-label, Comparative Trial of Disulfiram, Naltrexone and Acamprosate in the Treatment of Alcohol Dependence: Alcohol & Alcoholism Vol.34, No.1, pp. 53-61, 2008.
36. Morris et al., Disulfiram Hepatitis; Gastroenterology 75:100-102, 1978.
37. De Sousa. A et al., An open randomized trial comparing Disulfiram and Topiramate in the treatment of alcohol dependence; Journal of Substance Abuse Treatment 34 (2008) 460-463.