1. NAME OF THE MEDICINAL PRODUCT

Cufence 200 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 300 mg trientine dihydrochloride equivalent to 200 mg trientine.

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

White, oval-shaped size 0 capsule printed with 'Cufence 200' in grey ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cufence is indicated for the treatment of Wilson's disease in patients intolerant to D-Penicillamine therapy, in adults, adolescents and children aged 5 years or older.

4.2 Posology and method of administration

Treatment should only be initiated by specialist physicians with experience in the management of Wilson's disease.

Posology

The starting dose would usually correspond to the lowest recommended dose and the dose should subsequently be adapted according to the patient's clinical response (see section 4.4).

The recommended dose is 800-1,600 mg (4-8 capsules) daily in 2 to 4 divided doses.

The recommended doses of Cufence are expressed as mg of trientine base (i.e. not in mg of the trientine dihydrochloride salt) (see section 4.4).

Special populations
Elderly
There is insufficient clinical information available for Cufence to determine whether there exist differences in responses between the elderly and younger patients. In general, dose selection should be cautious, usually starting at the low end of the dosing range as recommended for adults, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal impairment
There is limited information in patients with renal impairment. Therefore, the recommended dose in patients with renal impairment is the same as for adults. For specific precautions see section 4.4.

Hepatic impairment

There is limited information in patients with hepatic impairment. Therefore the recommended dose in patients with hepatic impairment is the same as for adults. For specific precautions see section 4.4.

Patients primarily presenting hepatic symptoms
The recommended dose in patients primarily presenting hepatic symptoms is the same as the recommended adult dose. It is advised, however, to monitor patients presenting with hepatic symptoms every two to three weeks after initiation of treatment with Cufence.

Patients primarily presenting neurological symptoms
Dose recommendations are the same as for adults. However, up titration should be done with moderation and consideration, and adapted according to the patient's clinical response such as worsening of tremor as patients could be at risk of neurological deterioration at initiation of treatment (see section 4.4). It is further advised to monitor patients presenting with neurological symptoms every one to two weeks after initiation of treatment with Cufence until target dose is reached.

Paediatric population
The dose is lower than for adults and depends on age and body weight. The dose should be adjusted according to clinical response; 400 – 1,000 mg (2-5 capsules) have been used at initiation of therapy. (see section 4.4).

Children < 5 years
The safety and efficacy of Cufence in children aged 0 to 5 years have not yet been established. No data are available.

Method of administration
For oral use.

Capsules should be swallowed whole with water.

It is important that Cufence is given on an empty stomach, at least one hour before meals or two hours after meals, and at least one hour apart from any other medicinal product, food or milk (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

When switching a patient from another trientine formulation, caution is advised because different trientine salts are available which may have a different trientine content (base) and a different bioavailability. Dose adjustment may be required (see section 4.2).

Trientine is a chelating agent which has been found to reduce serum iron levels. Iron supplementation may be necessary in some cases. Concomitant oral iron should be administred at a different time than trientine (see section 4.5).

The combination of trientine with zinc is not recommended. There are only limited data on concomitant use available and no specific dose recommendations can be made.

There is no evidence that calcium and magnesium antacids alter the efficacy of trientine but it is recommended to separate their administration (see section 4.5).

In patients who were previously treated with D-Penicillamine, lupus-like reactions have been reported during subsequent treatment with trientine, however it is not possible to determine if there is a causal relationship with trientine.

Monitoring
Patients receiving Cufence should remain under regular medical supervision and be monitored using all available clinical data for appropriate control of clinical symptoms and copper levels in order to

optimise treatment. Frequency of monitoring is recommended to be at least twice a year. More frequent monitoring is advised during the initial phase of treatment and during phases of disease progression or when dose adjustments are made as to be decided by the treating physician (see section 4.2).

The aim of maintenance treatment is to maintain free copper levels in plasma (also known as non-ceruloplasmin plasma copper) and the urinary copper excretion within the acceptable limits.

The determination of serum free copper, calculated using the difference between the total copper and the ceruloplasmin-bound copper (normal level of free copper in the serum is usually 100 to 150 microgram/L), can be a useful index for monitoring therapy.

The measurement of copper excretion in the urine may be performed during therapy. Since chelation therapy leads to an increase in urinary copper levels, this may/will not give an accurate reflection of the excess copper load in the body but may be a useful measure of treatment compliance.

The use of appropriate copper parameter target ranges is described in clinical practice guidelines related to Wilson's disease.

Like with all anti-copper agents, overtreatment carries the risk of copper deficiency, which is especially harmful for children and pregnant women (see section 4.6) since copper is required for proper growth and mental development. Therefore, monitoring for manifestations of overtreatment should be undertaken.

Patients with renal and/or hepatic impairment receiving trientine should remain under regular medical supervision for appropriate control of symptoms and copper levels. Close monitoring of renal and/or liver function is also recommended in these patients (see section 4.2).

Worsening of neurological symptoms may occur at the beginning of chelation therapy due to excess of free serum copper during the initial response to treatment. It is possible that this effect may be more evident in patients with pre-existing neurological symptoms. It is recommended to monitor patients closely for such signs and symptoms and to consider careful titration to reach the recommended therapeutic dose and to reduce dose when necessary.

Dose adjustments in the trientine dose should be considered in case of signs of reduced efficacy such as (persistent) increase in liver enzymes, and worsening of tremor. When trientine doses are adjusted this should be done in small steps. The trientine dose may also be reduced in case of side effects of trientine, such as gastrointestinal complaints and haematological changes. Trientine doses should be reduced to a more tolerable dose and may be increased again, once side effects have been resolved.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Zinc

There are insufficient data to support the concomitant use of zinc and trientine. The combination of trientine with zinc is not recommended as interaction of zinc with trientine is likely, thereby reducing the effect of both active substances.

Other anti-copper agents

No interaction studies have been performed on the concomitant administration of trientine with D-Penicillamine.

Food

Trientine is poorly absorbed following oral intake and food further inhibits trientine absorption. Specific food interaction studies have been performed with trientine in healthy subjects, showing a reduction of the extent of absorption of trientine up to 45%. Systemic exposure is critical for its principal mechanism of action, copper chelation (see section 5.1). Therefore, it is recommended that trientine is taken at least 1 hour before meals or 2 hours after meals and at least one hour apart from any other medicinal product, food, or milk to allow for maximum absorption and reduce the likelihood of the formation of complexes by metal binding in the gastrointestinal tract (see section 4.2).

Other products
Trientine has been found to reduce serum iron levels. Therefore, iron supplementation may be necessary in some cases. Concomitant oral iron or other heavy metals should be administred at a different time than trientine to prevent the formation of complexes (see section 4.4).

Although there is no evidence that calcium and magnesium antacids alter the efficacy of trientine, it is good practice to separate their administration (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There is a limited amount of data from the use of trientine in pregnant women.

Studies in animals have shown reproductive toxicity, which was probably a result of trientine-induced copper deficiency (see section 5.3).

Trientine should be used in pregnancy only after careful consideration of the benefits compared with the risks of discontinuing treatment in the individual patient. Factors to consider include the known risks associated with untreated or undertreated Wilson's disease, risks associated with the stage of disease, the risk of those alternative treatments which are available and the possible effects of trientine (see section 5.3).

If treatment with trientine is to be continued following a risk-benefit analysis, consideration should be given to reducing the dose of trientine to the lowest effective dose and monitoring compliance with the treatment regimen.

The pregnancy should be closely monitored in order to detect possible foetal abnormality and to assess maternal serum copper levels throughout the pregnancy. The dose of trientine used should be adjusted in order to maintain serum copper levels within the normal range. Since copper is required for proper growth and mental development, dose adjustments may be required to ensure that the foetus will not become copper deficient and close monitoring of the patient is essential (see section 4.4)

Babies born to mothers being treated with trientine should be monitored for serum copper and ceruloplasmin levels where appropriate.

Breastfeeding
There is limited clinical data suggesting that trientine is not excreted in breast milk. However, a risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from trientine therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
It is unknown whether trientine has an effect on human fertility.

4.7 Effects on ability to drive and use machines

Trientine has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Nausea can commonly occur on initial treatment and occasionally skin rash can occur. Duodenitis and severe colitis have been reported. Neurological deterioration can occur at the start of the treatment.

Tabulated list of adverse reactions
The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not

known (cannot be estimated from the available data).

MedDRA- system organ class database	***Adverse reaction***
Blood and lymphatic system disorders:	Uncommon: Anaemia
	Uncommon: Aplastic anaemia
	Uncommon: Sideroblastic anaemia
Nervous system disorders:	Uncommon: Dystonia
	Uncommon: Tremor
	Not known: Dysarthria
	Not known: Muscle rigidity
	Not known: Neurological deterioration
Immune system disorders:	Not known: Lupus-like syndrome
	Not known: Lupus nephritis
Gastrointestinal disorders:	Common: Nausea
	Not known: Colitis
	Not known: Duodenitis
Skin and subcutaneous tissue disorders:	Uncommon: Rash

Description of selected adverse reactions
There have been reports of neurological deterioration at the start of treatment in Wilson's disease patients treated with copper chelators including trientine, with symptoms of, for example, dystonia, rigidity, tremor and dysarthria (see section 4.2).

Paediatric population
Clinical trials with Cufence including a limited number of children in the age range of 5 to 17 years at the start of treatment indicate that frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Occasional cases of trientine overdose have been reported. In cases up to 20 g of trientine base there were no apparent adverse effects reported. A large overdose of 40 g of trientine base resulted in self-limiting dizziness and vomiting with no other clinical sequelae or significant biochemical abnormalities reported. In the event of overdose the patient should be observed, appropriate biochemical analysis performed and symptomatic treatment given. There is no antidote.
Chronic overtreatment can lead to copper deficiency and reversible sideroblastic anaemia. Overtreatment and excess copper removal can be monitored using values of urine copper excretion and of non-ceruloplasmin bound copper. Close monitoring is required to optimise the dose or adapt treatment if necessary (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism, various alimentary tract and metabolism products, ATC code: A16AX12

Mechanism of action
Trientine is a copper-selective chelator that enhances systemic elimination of divalent copper by forming a stable complex that is readily excreted by the kidneys. Trientine is a chelator with a polyamine-like structure and copper is chelated by forming a stable complex with the four constituent

nitrogens in a planar ring. Thus, the pharmacodynamic action of trientine is dependent on its chemical property of chelating copper and not on its interaction with receptors, enzyme systems or any other biological system that might differ between species. Trientine may also chelate copper in the intestinal tract and so inhibit copper absorption.

5.2 Pharmacokinetic properties

Absorption

The bioavailability of trientine capsules in human beings has not been established. Based on preclinical data, the mechanism of absorption and the high first pass effect, it is expected that trientine bioavailability is low and highly variable following oral administration. Clinical studies showed that trientine is absorbed with t_{max} occurring between 0.5 and 6 hours post-dose in healthy volunteers and patients. Exposure to trientine is highly variable between subjects, with a variation of up to 60%.
The intake of food within 30 minutes prior to trientine administration delays the time to peak concentrations by 2 hours and reduces the extent of absorption of trientine by approximately 45%.

Distribution

Trientine has low human plasma protein binding and is widely distributed in tissues with relatively high concentrations measured in liver, heart, and kidney in the rat.

Biotransformation

Trientine is acetylated in two major metabolites, N(1)-acetyltriethylenetetramine (MAT) and N(1),N(10)-diacetyltriethylenetetramine (DAT). Clinical data in healthy subjects indicate that the plasma exposure to the MAT metabolite is approximately 3 times that of unchanged trientine, while exposure to the DAT metabolite is slightly lower compared to trientine. The metabolites of trientine have Cu-chelating properties, however the stability of these Cu-complexes is low due to the introduction of the acetyl groups. Clinical data in healthy volunteers suggest limited contribution of chelating activity by the MAT and DAT metabolites.The extent of MAT and DAT's contribution to the overall effect of Cufence on copper levels in Wilson's Disease patients remains to be determined.

Trientine is metabolised by acetylation via spermidine/spermine N-acetyltransferase and not via N-acetyltransferase 2.

Elimination

After absorption trientine and its metabolites are rapidly excreted in the urine, either bound to copper or unbound. The unabsorbed fraction of orally administered trientine is bound to intestinal copper and eliminated through faecal excretion.
The elimination half-life of trientine is approximately 4 hours (mean $t_{1/2}$ of 3.8 ± 1.3 hours measured at steady state in WD patients and 4.4 ± 4.7 hours measured after a single dose in healthy volunteers). The elimination half-lives of the two metabolites were 14.1 ± 3.7 hours for MAT and 8.5 ± 3.0 hours for DAT after a single dose administration of trientine in healthy subjects.
Special populations
Age /Gender/ Body weight
Data from clinical studies conducted in adult healthy subjects indicate that age, gender and body weight do not seem to influence the pharmacokinetics of trientine.
Ethnicity
No pharmacokinetic analysis has been performed on interethnic differences.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on a series of studies investigating cardiovascular safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to embryofoetal development.

Effects in non-clinical studies were largely consistent with induced copper deficiency in the plasma and liver of previously copper normative animals and as such could be attributed to the pharmacological action of trientine. The main toxicological findings associated with trientine, which were generally seen across all species examined, included body weight loss or lower body weight gain, altered urinary electrolytes, low plasma copper levels and various histopathological changes in the lungs (mainly interstitial pneumonitis). All effects were reversible with the exception of the lung findings; however the dose levels where these effects were observed are far in excess of those used clinically. Moreover, there was some doubt about the relationship to trientine, as the lung findings were also observed in most of the control dogs in the 26 week study. In dogs, ataxia, tremors, abnormal gait and underactivity were observed following administration of very high levels of trientine. Some functional neurological abnormalities were also identified, particularly in severly affected animals, however no associated nerve damage was observed. Electrocardiography was also unaffected.

In pregnant animals, high dose trientine associated with significant reductions in serum copper, revealed an early effect on embryo survival and a marginally lower foetal weight. There was no evidence of embryo-foetal toxicity at lower dose levels despite dose-related reductions in serum copper. These effects were observed only at exposures sufficiently in excess of maximum human exposure to indicate little relevance to clinical use.

No fertility data are available but estrous cyclicity was unaffected and reproductive organs were not identified as target organs in general repeat dose toxicity studies.

The OECD SIDS triethylenetetramine 2002 classifies the genotoxic profile of trientine as low priority/concern. Some positive *in vitro* mutagenicity data were obtained but *in vivo* test systems showed no mutagenic activity. No long term animal carcinogenicity trials have to date been performed with trientine via the oral route, but via the dermal route, there was no increases in cancers above baseline. Moreover, there is evidence to suggest that trientine actually reduces endogenous DNA damage in a strain of rat (Long-Evans Cinnamon) considered to represent an appropriate model of Wilson's disease. This suggests a reduced carcinogenic risk for Wilson's disease patients as a result of trientine therapy.

Trientine dihydrochloride is a known irritant, especially to mucus membranes, upper respiratory tract and skin, and induces skin sensitisation in guinea pigs, mice and man (OECD SIDS triethylenetetramine 2002).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Magnesium stearate
Colloidal anhydrous silica

Capsule shell:
Gelatin
Titanium dioxide (E171)

Printing ink:
Shellac
Propylene glycol
Titanium dioxide (E171)
Iron oxide black (E172)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

After first opening the bottle: 3 months.

6.4 Special precautions for storage

Store in a refrigerator (2ºC-8ºC). Do not freeze.

Store in the original container in order to protect from moisture.

6.5 Nature and contents of container

Amber glass bottle with a polypropylene cap and induction heat seal liner with a sachet of dried silica gel as desiccant.

Pack size: 1 bottle of 100 hard capsules.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

MBI Pharma Ltd.
P.O.B 5061
Kadima

8. MANUFACTURER

Univar BV
Schouwburgplein 30-34, 3012 CL
Rotterdam
the Netherlands

9. MARKETING AUTHORISATION NUMBER

165-12-35600

Approved in July 2020