Marketing Authorisation Application

MODULE 2.5
CLINICAL OVERVIEW

Trientine 200 mg hard capsules

(Contains 300 mg trientine dihydrochloride)

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Table of Contents

GLOSSARY OF ABBREVIATIONS

Abbreviations	Definitions	Abbreviations	Definitions
^{64}Cu	Positron emitting isotope of copper	mg	Milligram
µg	Microgram	min	Minute
µmol	Micromole	ml/mL	Millilitre
AE	Adverse Event	ng	Nanogram
ATC	The Anatomical Therapeutic Chemical code	mol	Unit of measurement for amount of substance in the International System of Units (SI)
AUC	Area Under the Curve	n	Number
CAS	Chemical Abstracts Service registry number	NCC	Non-Ceruloplasmin-bound Copper
CI	Confidence Interval	OCED	Organisation for Economic Co-operation and Development
CLR	Renal Clearance	p	Probability
C_{max}	Observed maximum plasma concentration	PD	Pharmacodynamic
Cu	Copper	pH	A scale of acidity from 0 to 14
DAT	N1,N10-diacetyltriethylenetetramine	PK	Pharmacokinetics
DNA	Deoxyribonucleic acid	pKa	Negative log of the acid dissociation constant or Ka value
DPA	Penicillamine	QoL	Quality of Life
EMA	European Medicines Agency	SAE	Serious Adverse Event
EU	European Union	SD	Standard Deviation
F	Bioavailability	SmPC	Summary of Product Characteristics
GFR	Glomerular Filtration Rate	SOC	System Organ Class
g	Gram	$T_{1/2}$	Terminal elimination half-life
h	Hour	T_{max}	Time to maximum plasma concentration
INR	International Normalised Ratio	ULN	Upper Limit of Normal
kg	Kilogram	US	United States
L	Litre	USP	United States Pharmacopeia
MAT	N1-acetyltriethylenetetramine	UWDRS	Unified Wilson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Affairs	WD	Wilson’s disease

2.5.1Product Development Rationale

2.5.1.1 Introduction

Each 'Trientine 200 mg hard capsule' manufactured by Waymade plc, UK, contains 300 mg trientine dihydrochloride (TETA 2HCl) as the active ingredient, which is equivalent to 200 mg trientine base.

The proposed dosing regimen is 4 to 8 capsules (800 - 1600 mg), administered 2 to 4 times a day in adults and 2 to 5 capsules (400 -1000 mg), administered 2 to 4 times a day in children. The product is titrated to target according to clinical response and different copper parameters.

The indication applied for is the same as that for the reference product. 'Trientine 200 mg hard capsule' is indicated for the treatment of Wilson's disease (WD) in patients intolerant to D-penicillamine therapy, in adults, adolescents and children aged 5 years and older.'

The pharmacotherapeutic group is "various alimentary tract and metabolism products"; ATC code: A16AX12. Trientine is a chelating agent that acts due to a dual mechanism of action: primarily by promoting urinary copper excretion and to a lesser extent by reducing copper absorption from the gastrointestinal tract (and thus promoting faecal copper excretion).

Trientine was introduced in 1969 as an alternative copper chelating agent for the treatment of WD in patients who were intolerant to penicillamine. Trientine hydrochloride has been registered in the US and the United Kingdom (UK) since 1985 for the treatment of WD in patients who are intolerant of penicillamine. The sponsor's product, Trientine Hydrochloride Capsules USP 250 mg (Navinta LLC, ANDA #21125) was registered as a generic medicine to the innovator product SYPRINE (NDA #019194) in the US on 16 January 2019. Trientine was designated as an orphan drug for the treatment of WD (Submission No. PM-2019-03582-1-3) for the sponsor Waymade Australia Pty Limited on 7 August 2019.

The current marketing authorisation application is for 'Trientine 200 mg hard capsules', manufactured by Waymade Plc, UK, as a generic product, in accordance with the article 10(1) of the Directive 2001/83/EC of The European Parliament And of the Council. Each Trientine 200 mg hard capsule contains 300 mg trientine dihydrochloride, which is equivalent to 200 mg trientine base, and it is indicated for the treatment of WD in patients intolerant to D-Penicillamine therapy in adults, adolescents and children aged 5 years or older. The basis for this marketing authorisation application is the bioequivalence of this product with the reference medicinal product, 'Cufence 200 mg hard capsules' (each hard capsule of which also contains 300 mg trientine dihydrochloride, equivalent to 200 mg trientine base) manufactured by Univar BV, The Netherlands (EU/1/19/1365/001). No new toxicological, pharmacological or clinical data has therefore been presented in support of this application other than some discussions on the pharmacology, efficacy and safety of the product as derived from the public domain.

Apart from general regulatory guidance on the conduct of bioequivalence trials with pharmaceutical products, there are no specific guidelines for the development of trientine products. Regulatory advice was sought from MHRA on the legal basis of the application and scope of presented data to support the application [Scientific advice letter 2191, MHRA]. MHRA has agreed that submission under 10(1) article will be appropriate provided

bioequivalence results were convincingly demonstrated and recommended to supplement bioequivalence results with review of the published literature on use of trientine in WD. The Applicant has followed the advice and presented in current dossier results of bioequivalence study and comprehensive literature review on pharmacology, efficacy and safety of trientine.

2.5.1.2 Wilson's disease

Wilson's disease (WD), also known as hepatolenticular degeneration, is an autosomal recessive disorder that results in pathological copper accumulation. A mutation in the ATP7B gene, located on chromosome 13, is responsible for WD. The mutations lead to a defective ATP7B protein that normally mediates the binding of copper molecules to apoceruloplasmin in hepatocytes, forming ceruloplasmin, which can then safely transport the bound copper to its intended sites. In addition, the ATP7B protein serves to transport excess copper from hepatocytes into the bile for subsequent excretion, thus permitting safe elimination of excess copper. Such copper transport systems are required as copper is essential for cellular function; however, free copper is toxic and causes cell damage. In WD, copper homeostasis is impaired such that a large excess of copper accumulates initially in the liver. When the storage capacity of the liver is eventually exceeded, hepatocyte necrosis follows and the copper is released and subsequently stored in the brain and other organs and tissues [Cufence, EMA Public Assessment Report, 2019].

Normal dietary consumption and absorption of copper (1 to 5 mg per day) exceeds the metabolic need of approximately 0.75 to 0.9 mg per day. Homeostasis of copper is maintained exclusively by biliary excretion. Therefore, if the excretory capacity is exceeded, copper progressively accumulates in the liver and other tissues such as the brain, kidney, and cornea leading to the clinical manifestations of WD [Cufence, EMA Public Assessment Report, 2019].

Epidemiology and risk factors

WD is a rare disease but found worldwide with an estimated prevalence of approximately 1:30,000. This estimation may vary by population with Japan/Asia having a higher prevalence compared with an estimated prevalence in Europe of approximately 5.84 per 100,000 population [Cufence, EMA Public Assessment Report, 2019].

WD presents symptomatically at any age, with the majority between 5 and 35 years [EASL Guidelines, 2012]. Asymptomatic patients are most often detected by family screening. Symptoms at the time of the initial presentation, and those that subsequently develop are most commonly categorised as hepatic or neurologic/neuropsychiatric.

Untreated, WD is universally fatal. Copper accumulation in the liver eventually leads to the development of cirrhosis. Among patients with neurologic WD, neurologic disease may progress until the patient becomes severely dystonic, akinetic and mute. Progression is usually gradual, but sudden deterioration may also occur. The majority of patients will die from liver disease (cirrhosis or acute liver failure), while the remainder die due to complications due to progressive neurologic disease [Cufence, EMA Public Assessment Report, 2019].

Though data regarding life expectancy among untreated patients with WD are lacking, one study found that the median survival following the development of neurologic symptoms was

approximately five years [Dening 1988 - Cufence, EMA Public Assessment Report, 2019]. Patients who develop acute liver failure due to WD have an acute mortality rate of at least 95 percent in the absence of a liver transplantation, with death occurring in days to weeks [EASL Guidelines, 2012].

Clinical presentation, diagnosis and prognosis

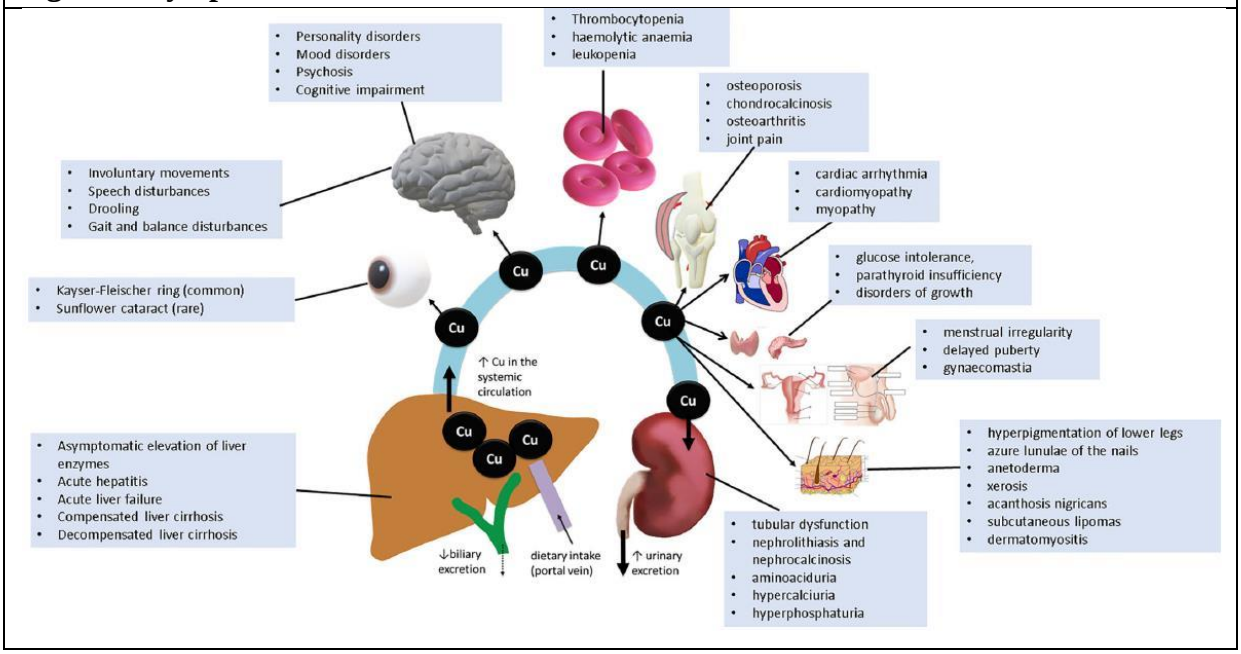
Clinical presentation

Clinical presentation can vary widely. Symptoms at the time of the initial presentation, and those that subsequently develop are most commonly categorized as hepatic/ neurologic or psychiatric. Hepatic symptoms are the initial clinical manifestation in about 40-50% of WD patients and may precede neurologic manifestations by as much as 10 years. Most patients with neurologic symptoms have some degree of liver disease at presentation. The hepatic dysfunction symptoms are highly variable, ranging from enlargement of the liver or asymptomatic biochemical abnormalities, to overt cirrhosis or acute hepatic failure [Pfeiffer 2007 - Cufence, EMA Public Assessment Report, 2019].

Neurologic or neuropsychiatric manifestations of WD typically present later than liver disease, most commonly in the third decade of life, but can also be present in childhood. There is a range of presenting neurologic abnormalities which are initially present in 40–50% of patients [Yarze, Martin et al, 1992 - Cufence, EMA Public Assessment Report, 2019]. They include Parkinson-like akinetic-rigid syndrome, pseudosclerosis with tremor, ataxia, and dystonic syndrome. Neuropsychiatric abnormalities can also develop. These most commonly include personality changes and mood disturbances, particularly depression, but may also manifest as impulsiveness, disinhibition, paranoia, or poor school performance [Cufence, EMA Public Assessment Report, 2019].

Other manifestations of WD include an ophthalmological marker, namely the presence of Kayser–Fleischer rings, which are caused by deposition of copper in Descemet’s membrane of the cornea. These are present in 95% of patients with neurologic symptoms and over 50% of those without neurologic symptoms. Figure 1 depicts various symptoms associated with WD [Czlonkowska A et al, 2018].

Figure 1. Symptoms associated with WD [Czlonkowska A et al, 2018]



Diagnosis

The diagnosis of WD is based on a combination of clinical, biochemical, and genetic tests. Genetic testing is feasible but currently of limited use since many mutations occur; the majority of cases are compound heterozygotes and a sizeable proportion of definite cases have no detectable mutation. Family screening of WD patients is an appropriate method for early diagnosis, the chance of a sibling being a homozygote and developing clinical disease is around 25% [Cufence, EMA Public Assessment Report, 2019].

For many patients, a combination of tests reflecting disturbed copper metabolism may be needed; any single test may result in a false ‘positive’ or false ‘negative’ [EASL Guidelines, 2012]. According to EASL clinical practice guidelines in the European Union (EU) [EASL Guidelines, 2012], “for routine monitoring, serum copper and ceruloplasmin, liver enzymes and international normalised ratio (INR), functional parameters, complete blood count and urine analysis as well as physical and neurological examinations should be performed regularly, at least twice annually (Grade II-2, B, 1, AASLD Class I, Level C)”.

The diagnosis of WD is therefore based on a combination of clinical, biochemical, and genetic tests. A scoring system, the ‘Ferenci score’ was developed at an international meeting in Leipzig for helping to determine the need to continue with diagnostic testing for WD and determine the certainty of diagnosis Score [Ferenci P et al, 2003]. This scoring system (Table 1) includes clinical and laboratory testing, and results yield in three categories of patients: those in whom other diagnoses should be considered (0-1 points), those in whom further diagnostic testing is needed (2-3 points), and those in whom there is certainty as to diagnosis (4 or more points) [Ferenci P et al, 2003].

Table 1. Criteria for the diagnosis of WD – Ferenci Score [Ferenci P et al, 2003]

Liver Copper (in absence of cholestatis)		Serum Ceruloplasmin	
Normal (<50 µ/g)	-1	Normal (> 0.2 g/L)	0
< 5 x ULN (50 – 250 µ/g)	1	0.1 – 0.2 g/L	1
> 5 x ULN (250 µ/g)	2	< 0.1 g/L	2
Rhodanine Stain (in absence of quantitative liver copper determination)		**Clinical Symptoms and Signs Kayser-Fleischer rings**	
Absent	0	Present	2
Present	1	Absent	0
Mutation Analysis		**Neurological Symptoms**	
2 chromosomes mutations	4	Severe	2
1 chromosome mutation	1	Mild	1
No mutation detected	0	Absent	0
Urinary Copper (in absence of acute hepatitis)		**Coomb's negative haemolytic anaemia**	
Normal (<0.9 µmol/d or < 100 mg/day)	0	Present	1
1-2 x ULN	1	Absent	0
> 2 x ULN	2		
Normal but > 5 x ULN after d-Penicillamine	2	Total Score*:	

Abbreviation: ULN = Upper limit of normal
*Patient was eligible for treatment for the study if the Ferenci (Leipzig) Score was >3

Assessment of the WD-diagnosis score:
4 or more: diagnosis of WD highly likely
2-3: diagnosis of WD probable, do more investigations
0-1: diagnosis of WD unlikely

Prognosis

WD is universally fatal if untreated. Prognosis for survival depends on the severity of liver and neurological disease, and, of upmost importance, compliance with drug treatment (Ala, Walker et al, 2007- Cufence, EMA Public Assessment Report, 2019]. The prognosis for patients who receive and are adherent to treatment for WD is excellent, even in some who already have advanced liver disease. In patients without advanced liver disease, life expectancy is normal, though treatment may lead to worsening of neurologic symptoms in a fraction of patients [Stremmel et al, 1991, Bruha et al, 2011 - Cufence, EMA Public Assessment Report, 2019].

2.5.1.3 Disease management and treatment options

WD is a rare condition for which there are limited treatment choices available. If left untreated, it is a fatal condition [Cufence, EMA Public Assessment Report, 2019].

Treatment of patients with WD may take many forms including drug therapy, diet management and liver transplantation. Dietary control of copper intake is not sufficient in most patients, and pharmacological treatments are therefore needed. The disease can be successfully managed with pharmacologic intervention [Cufence, EMA Public Assessment Report, 2019].

Chelating agents (D-penicillamine or trientine) are recommended to be used as the first line treatment of symptomatic patients by both the American Association for the Study of Liver Diseases (AASLD) and European Association for Study of Liver (EASL) [Roberts EA et al,

2008; EASL Guidelines, 2012]. WD patients receiving adequate and timely treatment with chelation therapy have a good prognosis for survival. With adherence to treatment, liver function can remain stable without progression of liver disease. Treatment is life-long and is aimed at removing excess accumulated copper and preventing its accumulation. It should not be discontinued, unless liver transplantation is performed [Cufence, EMA Public Assessment Report, 2019].

There are two currently approved types of copper chelating agents, D-penicillamine (DPA) and trientine. Due to its better efficacy, D-penicillamine is usually the first choice for patients with WD. However, about 20 to 30% of the WD patients using D-penicillamine will experience adverse reactions (Merle, Schaefer et al, 2007; EASL Guidelines, 2012 - Cufence, EMA Public Assessment Report, 2019] in the first 1–3 weeks of the treatment, which often result in discontinuation of treatment. Long-term use of D-penicillamine carries further risks of side effects. Penicillamine has also been shown to have cross-reactivity to those with a penicillin allergy and has been found to lead to worsening of neurologic symptoms in 13.8% of patients with neurologic WD [EASL Guidelines, 2012]. Around 30% of patients are resistant to penicillamine and can suffer severe adverse effects requiring the treatment to be discontinued. In all these patients, there is a need for an alternative chelating agent treatment and trientine hydrochloride was specifically developed to meet this unmet clinical need. According to EASL clinical practice guidelines and many other literature references, trientine may be better tolerated than D-penicillamine [Cufence, EMA Public Assessment Report, 2019].

The trientine salt TETA 2HCl was introduced in 1969 as a copper chelator alternative to D-penicillamine [Walshe, 1969 - Cufence, EMA Public Assessment Report, 2019]. TETA 2HCl is registered nationally in the UK and in the US and mostly used for treatment of WD in patients intolerant to D-penicillamine [Schilsky 2001; Ferenci 2004; Ala, Walker et al, 2007 - Cufence, EMA Public Assessment Report, 2019].

Zinc salts are also used for the treatment of WD. Zinc salts are usually not recommended for the initial therapy of symptomatic patients because of the slow onset of action, but may be used as monotherapy in asymptomatic patients or for maintenance therapy when copper levels are below toxic thresholds and patients are clinically stable. Zinc is centrally approved for the treatment of WD since 2004 [Wilzin, MAH: Orphan Europe S.A.R.L. - Cufence, EMA Public Assessment Report, 2019].

Pharmacological therapy remains the primary treatment in WD, although its efficaciousness may diminish in more advanced disease states. If patients are already presenting with decompensated cirrhosis, they may be treated intensively with chelators, however if patients are unresponsive to this approach a liver transplant would be required. Some other agents (e.g. tetrathiomolybdate and dimercaprol) are mentioned in clinical guidelines but these are (still) investigational products [Cufence, EMA Public Assessment Report, 2019].

For patients who develop acute liver failure, liver transplantation is the only option for survival, with survival rates reported up to 59-76% at 5-10 years [Medici, Mirante et al, 2005 - Cufence, EMA Public Assessment Report, 2019], with poorer outcomes observed in those patients with neurologic or neuropsychiatric symptoms. The use of liver transplantation has also been reported to be used in patients with severe neurological disease [Schumacher, Platz

et al, 1997 - Cufence, EMA Public Assessment Report, 2019]; however its use as a primary treatment is not recommended [Roberts EA et al, 2008].

2.5.1.4 Proposed product and similar products available worldwide

Trientine hydrochloride has been authorised in the US and the United Kingdom (UK) since 1985 for the treatment of WD in patients who are intolerant of penicillamine, and a number of generic products have been registered in the US and the UK since then. The sponsor's own product, Trientine Hydrochloride Capsules USP 250 mg (Navinta LLC, ANDA #21125) was registered as a generic medicine in the US on 16 January 2019. Trientine manufactured by the Sponsor's Waymade Australia Pty Limited was designated an orphan drug for the treatment of WD (Submission No. PM-2019-03582-1-3) on 7 August 2019. Table 2 summarises the current marketing authorization status of trientine dhydrochloride.

Table 2. Marketing authorisation status of Trientine hydrochloride

Market	Tradename (Sponsor)	Approval	Indication
US	SYPRINE trientine hydrochloride 250 mg capsules(Aton Pharma)*	8 November 1985 US / NDA019194	For the treatment of patients with WD who are intolerant of penicillamine.
US	Trientine hydrochloride 250 mg capsules*(Navinta LLC)	1 March 2019 US / ANDA211251	For the treatment of patients with WD who are intolerant of penicillamine.
UK	Trientine dihydrochloride 300 mg capsules(Univar Solutions BV)	8 August 1985 PL 41626/0001	For the treatment of WD in patients intolerant of D-Penicillamine therapy.
UK	Trientine dihydrochloride Tilomed 250 mg capsules, hard (Tilomed Laboratories Ltd)	17 January 2020 PL 11311/0661	For the treatment of WD in patients intolerant of D-Penicillamine therapy, in adults, adolescents and children aged 5 years or older.
Europe	CUPRIOR Trientine tetrahydrochloride150 mg film-coated tablets (GMP-Orphan SA, Paris)	05 September 2017 EU/1/17/1199/001	For the treatment of WD in adults, adolescents and children ≥5years intolerant to D-penicillamine therapy.
Europe	CUFENCE Trientine dihydrochloride 200 mg hard capsules (Univar Solutions BV, The Netherlands)	25 July 2019 EU/1/19/1365/001	For the treatment of WD in patients intolerant to D-Penicillamine therapy, in adults, adolescents and children aged 5 years or older.

2.5.2Overview of Biopharmaceutics

2.5.2.1 Composition, therapeutic indications, posology and method of administration

Composition of the drug product

Each 'Trientine 200 mg hard capsule' contains 300 mg trientine dihydrochloride as the active ingredient, which is equivalent to 200 mg trientine. The excipients include stearic acid, gelatin, titanium dioxide (E171), shellac (E904), propylene glycol (E1520), black iron oxide (E172) and potassium hydroxide (E525) – the first four excipients are the capsule content and the last four excipients are composition of the black ink used for imprinting on the hard gelatine capsule shell. All excipients and proposed capsule ingredients are EU Pharmacopeia compliant and were previously used in numerous orally administered products in the UK. *In-vitro* dissolution wasn't met, but based on the PK data, the bioequivalence of Waymade's 'Trientine 200 mg hard capsule' was within the bio-equivalence range of 80-125% compared to the reference product, and therefore the *in-vitro* dissolution profiles are not considered to be clinical relevant. As per the EU Guideline for the investigation of Bioequivalence, "In the event that the results of comparative *in-vitro* dissolution of the biobatches do not reflect bioequivalence as demonstrated *in-vivo* the latter prevails" [Guideline on BE, CHMP, EMA, Jan 2010]. The unusually low dissolution data for the RLD has already discussed in the corresponding regulatory documents [Cufience EPAR, Cuprior EPAR] as the previous formulation of the RLD exhibited much faster dissolution profile. Irrespectively, the faster dissolution of the test formulation does not pose any safety risk according to the safety evaluation of the bioequivalence study. Because the Waymade's formulation is rapidly dissolving, the differences in bio-dissolution profile were less impactful on the bioequivalence compared to previously approved trientine products which showed not only bio-dissolution differences, but also impact of these differences on PK exposure. In contrast to the other trientine analogies, Waymade was able to develop more rapidly dissolving formulation and did not observe any overt impact of bio-dissolution differences on demonstrating the bioequivalence. Therefore it is considered that the CHMP requirements laid in Guideline on the Investigation of Bioequivalence to evaluate the bio-dissolution and justify the differences were met through comprehensive range of bio-dissolution studies supported by analytical characterization and iterative formulation studies, and supported by findings from prior published and regulatory sources.

Therapeutic indications

Trientine 200 mg hard capsules are indicated for the treatment of WD in patients intolerant to D-Penicillamine therapy, in adults, adolescents and children aged 5 years or older.

Posology

The posology of the proposed Trientine 200 mg hard capsules (Waymade) is the same as that of the reference product Cufence 200 mg hard capsules (Univar Solutions BV) [SmPC, Cufence 200 mg hard capsules] and is in line with the posology of the nationally authorised UK trientine product, which is on the market for more than 30 years.

The starting dose of Trientine 200 mg hard capsules would usually correspond to the lowest recommended dose and the dose should subsequently be adapted according to the patient's clinical response (see section 2.5.5.3).

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

The recommended doses of Trientine 200 mg hard capsules are expressed as mg of trientine base and not as mg of the trientine dihydrochloride salt (see section 2.5.5.3).

Special populations

Elderly

There is insufficient clinical information available for Trientine 200 mg hard capsules 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 of Trientine 200 mg hard capsules in patients with renal impairment is the same as for adults (see section 2.5.5.3).

Hepatic impairment

There is limited information in patients with hepatic impairment. Therefore, the recommended dose of Trientine 200 mg hard capsules in patients with hepatic impairment is the same as for adults (see section 2.5.5.3).

Patients primarily presenting with hepatic symptoms

The recommended dose of Trientine 200 mg hard capsule in patients primarily presenting with 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 Trientine 200 mg hard capsules.

Patients primarily presenting with 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 beat risk of neurological deterioration at initiation of treatment (see section 2.5.5.3). It is further advised to monitor patients presenting with neurological symptoms every one to two weeks after initiation of treatment with Trientine 200 mg hard capsules until target dose is reached.

Paediatric population

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

Children < 5 years

The safety and efficacy of Trientine 200 mg hard capsules in children aged 0 to 5 years have not yet been established. No data are available.

Method of administration

The method of administration of the proposed Trientine 200 mg hard capsules (Waymade) is the same as that of the reference product Cufence 200 mg hard capsules (Univar Solutions BV) [SmPC, Cufence 200 mg hard capsules].

Trientine 200 mg hard capsules are meant for oral use, and the capsules should be swallowed whole with water. It is important that Trientine 200 mg hard capsules are 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 2.5.5.5).

2.5.2.2 Bioavailability and bioequivalence of the proposed formulation

An open label, balanced, randomised, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study [Study No. 62420] was conducted in 46 healthy, adult human subjects aged between 18 and 45 years under fasting conditions between the applicant's trientine dihydrochloride capsules 300 mg of Waymade Plc, UK, and the Cufence 200 mg hard capsules (equivalent to 300 mg of trientine hydrochloride) of Univar BV Schouwburgplein 30-34, 3012 CL Rotterdam, The Netherlands (EU/1/19/1365/001).

This study was conducted in accordance with the study protocol and all other pertinent requirements of the current version of the ICH 'Guidelines for Good Clinical Practices', "National Ethical Guidelines for Biomedical and Health Research involving Human Participants" published by Indian Council of Medical Research (ICMR), New Delhi, New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E) and 'GCP' guidelines issued by CDSCO and the Principles enunciated in the Declaration of Helsinki (WMA General Assembly, Fortaleza, Brazil, October 2013), Guideline on The Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/Corr, January 2010 and with procedures oriented to Good Laboratory Practice and applicable regulatory requirements and meet the ethical requirements of Directive 2001/20/EC.

The protocol of the study had been submitted to MHRA and was endorsed via National Scientific Advice on 9th January 2020 (Ref: 2191/Trientine dihydrochloride).

Study objectives

The primary objective of the study was to assess the bioequivalence of trientine dihydrochloride capsules 300 mg of Waymade Plc, UK, comparing with that of Cufence 200 mg hard capsules (equivalent to 300 mg of trientine hydrochloride) of Univar BV Schouwburgplein 30-34, 3012 CL Rotterdam, The Netherlands, in healthy, adult, human subjects under fasting conditions.

The secondary objectives of the study was to monitor the relevant factors associated with the pharmacodynamic action of trientine dihydrochloride to allow a more comprehensive

analysis of the test and reference products, and to monitor the adverse events and ensure the safety and tolerability of subjects.

Study population

Healthy, adult, human volunteers between 18 and 45 years of age (both inclusive) and weighing at least 50 kg and body mass index between 18.5 and 30.0 kg/height in m^2 (both inclusive) who were willing to participate in the study were included. Demographic data, medical history, physical examination, vital signs, ECG, chest x-ray, haematology, biochemistry, serology, urine analysis, urine pregnancy (for females), drug screening and alcohol test were performed. Clinical laboratory tests were conducted as per Appendix - I of the study protocol.

Study methodology

The study was an open label, balanced, randomised two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study in 46 healthy, adult human subjects aged between 18 and 45 years under fasting conditions.

All the 46 subjects enrolled were dosed in period-I & period-II, separated by a washout period of 10 days, and all the 46 subjects completed the clinical phase of the bioequivalence study and were included in the pharmacokinetic and statistical evaluation.

The test (T) and reference product (R) included trientine dihydrochloride capsules 300 mg, manufactured for Waymade Plc, UK, and Cufence 200 mg hard capsules (equivalent to 300 mg of trientine hydrochloride) manufactured by Univar BV Schouwburgplein 30-34, 3012 CL Rotterdam, The Netherlands, respectively. In each period, after an overnight fast of at least 10.00 hours, subjects received a single oral dose of 300 mg test (T) or reference (R) product while in sitting posture with about 240 ± 2 ml of drinking water according to the randomization schedule in the presence of investigator. A washout period of at least 10 days between each drug administration was considered to be sufficient based on about ten half-lives of the drugs. The total duration of the study from enrolment to the end of the study was approximately 15 days. In total, there will be 2 study periods, after the last period each subject will have received the study products, test (T) once and reference (R) once.

Blood samples were collected at pre-dose (0.00) and at 0.17, 0.33, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours post-dose in each period. Adverse events and vital signs were monitored at the specified time-points during the study.

Trientine (triethylenetetramine) and its metabolites N(1)-acetyltriethylenetetramine (MAT) and N(1), N(10)-diacetyltriethylenetetramine (DAT) in human plasma were determined using High Performance Liquid Chromatography with Tandem Mass Spectrometry Method over a concentration range of 10.075 ng/mL to 2000.6 ng/mL, 10.076 ng/ml to 2000.8 ng/mL, and 6.0686 ng/mL to 604.20 ng/mL, respectively.

The analytical method was developed and validated over a concentration range of 10.067 ng/ml to 2001.9 ng/ml, 10.066 ng/ml to 2001.8 ng/ml and 6.0625 ng/ml to 605.76 ng/ml for trientine (triethylenetetramine) and its metabolites N(1)-acetyltriethylenetetramine (MAT) and N(1), N(10)-diacetyltriethylenetetramine (DAT), respectively.

The criteria for evaluation of the bioequivalence include primary parameters such as the C_{max} and AUC_{0-t} and the secondary parameters such as the AUC_{0-inf}, AUC_{0-t}/AUC_{0-inf}, T_{max}, $t_{1/2}$, K_{el} and Residual Area as described below.

C_{max}	Maximum measured plasma concentration over the time span specified.
AUC_{0-t}	The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.
AUC_{0-inf}	The area under the plasma concentration versus time curve from time 0 to time infinity. AUC_{inf} is calculated as the sum of the AUC_t plus the ratio of the last measurable plasma concentration (Ct) to the elimination rate constant K_{el}. $AUC_{0-inf} = AUC_{0-t} + Ct/ K_{el}$.
t_{max}	Time of the maximum measured plasma concentration. If the maximum value occurs at more than one time point, t_{max} is defined as the first time point with this value.
AUC_{0-t} / AUC_{0-inf}	Ratio of AUC_{0-t} and AUC_{0-inf}
$t_{1/2}$	The elimination or terminal half-life will be calculated as $0.693 /k_{el}$.
K_{el}	Apparent first order elimination rate constant calculated from a semi-log plot of plasma concentration versus time point. The regression is calculated using the last three, then the last four, last five etc., non-zero concentration points prior to C_{max}. Adjusted R^2 for each regression is computed and the largest adjusted R^2 will be used for calculating terminal elimination rate constant.
Residual Area	$(AUC_{0-inf} – AUC_{0-t})/ AUC_{0-inf}$

Additional Pharmacodynamic Parameters

As proposed to UK MHRA and endorsed, the Applicant has collected additional plasma and urine parameters to support further the bioequivalence data and assess any potential impact of PK differences, if those to be observed, on the safety. These descriptive assessments were proposed to support PK bioequivalence data with recognition that some of the parameters are less likely to be influenced by a single dose of trientine and there might be relatively high inter-subject variability.

The following laboratory tests were also determined to monitor the relevant factors associated with the pharmacodynamic action of trientine dihydrochloride to allow a more comprehensive analysis of the test and reference products:

- eGFR (glomerular filtration rate) via Spot urine creatinine.
- eGFR (glomerular filtration rate) via Spot blood creatinine.
- Zinc using biological matrix blood
- Copper using biological matrix blood
- Iron, ferritin and soluble transferrin receptor parameters using biological matrix blood
- Ceruloplasmin using biological matrix blood
- Copper using biological matrix urine

These included evaluation of serum and urine copper, zinc, iron, serum ceruloplasmin, serum transferrin. These tests were carefully selected based on the prior knowledge that glomerular filtration rate can serve as a surrogate in evaluating the renal function. The copper is a target metal for trientine in terms of chelation and excretion when present in excess in patients with WD. The applicant has examined both serum and urine copper. The assessments of serum zinc, serum iron, serum ceruloplasmin and transferring were carried out because of well published inter-section of copper, zinc and iron absorption, metabolisms and excretion pathways , as well as the potential for trientine to chelate / reduce systemic levels of zinc and iron (Cuprior SmPC; Doguer et al., 2019)

The results for these parameters were analyzed using descriptive statistics and because these assessments were carried out following a single dose of the product and in a relatively small study and thus the results can be interpreted with caution and in context of met predefined criteria for bioequivalence and physiological variability.

Some samples were not analysed; details are given in the following table. However the overall proportion of non-evaluable samples was **Zinc, Copper, Ceruloplastin & eGFR (Blood)** 1.32% , **Iron & Ferritin** (0.82%), **Soluble Transferrin Receptor Parameters** (2.72%)and thus is not expected to impact the results.

S. No	Period	Sample (hr.)	Reason	Perametrs Not Evaluated
QPS Bioseve India Pvt Ltd				
S13	I	2.00	Serum sample could not harvest	Zinc, Copper, eGFR (Blood), Iron, ferritin and soluble transferrin receptor
Vijaya Diagnostic Centre (LAB-I)				
S1	I	2.00	Heamolysed	Zinc, Copper & eGFR (Blood)
S2	I	0.00	Heamolysed	Zinc, Copper, Ceruloplastin & eGFR (Blood)
S4	I	0.00	Heamolysed	Zinc, Copper, Ceruloplastin & eGFR (Blood)
S5	I	0.00	Heamolysed	Zinc, Copper, Ceruloplastin & eGFR (Blood)
LAL Path labs Hyderabad (LAB-II)				
S1	I	2.00	Heamolysed	Iron & Ferritin
S3	II	12.00	In Sufficent sample	Iron & Ferritin
LAL Path labs Delhi (LAB_III)				
S1	I	2.00	Heamolysed	Soluble Transferrin Receptor Parameters
S3	II	12.00	In Sufficent sample	Soluble Transferrin Receptor Parameters
S4	I	0.00	Heamolysed	Soluble Transferrin Receptor Parameters
S26	I	0.00	In Sufficent sample	Soluble Transferrin Receptor Parameters

Zinc concentrations in the blood were analysed as absolute concentrations determined at baseline, 2 h, 12 h and 72 h following trientine administration. The mean/median values and ranges between test and a reference product for zinc concentrations presented in both absolute concentration and with adjustment to baseline were comparable. There were no discernible trends observed in these comparisons.

Zinc concentrations (µg/dl) in blood:

Parameter	Time (hours)							
	0.00		2.00		12.00		72.00	
	R	T	R	T	R	T	R	T
N	43	46	46	44	46	46	46	46
Mean	162.21	162.86	154.72	159.19	155.81	155.03	168.52	171.57
Median	161.90	156.70	151.50	153.25	151.60	156.65	167.50	161.85
Geometric Mean	158.02	158.46	152.62	156.73	153.25	153.77	159.45	166.42
SD	37.78	39.90	26.00	28.91	29.20	19.76	47.12	43.40
CV%	23.29	24.50	16.81	18.16	18.74	12.75	27.96	25.29
Minimum	93.20	109.30	111.50	113.30	94.00	113.00	20.00	109.60
Maximum	262.80	279.00	216.00	224.80	240.00	200.00	272.10	296.10

Baseline adjusted zinc concentrations (µg/dl) in blood:

Subject	Time (hours)					
	RBL2_0	TBL2_0	RBL12_0	TBL12_0	RBL72_0	TBL72_0
N	43	44	43	46	46	46
Mean	-7.13	-1.61	-4.00	-7.83	35.92	8.71
Median	-1.40	-0.35	0.10	-0.70	34.90	4.85
Geometric Mean	--	--	--	--	--	--
SD	32.48	28.13	42.12	45.13	47.12	58.16
CV%	-455.27	-1746.25	-1052.30	-576.05	131.18	668.05
Minimum	-87.50	-68.80	-103.90	-122.40	-112.60	-125.50
Maximum	41.60	70.83	122.10	83.20	139.50	148.10

Copper concentrations in the blood were analysed as absolute concentrations determined at baseline, 2 h, 12 h and 72 h following trientine administration. The mean/median values and ranges between test and a reference product for copper concentrations presented in both absolute concentration and with adjustment to baseline were comparable. There were no discernible reduction in copper levels probably because of the single-dose administration and presence of sufficient systemic pools of copper.

Copper concentrations (µg/dl) in blood:

Parameter	Time (hours)							
	0.00		2.00		12.00		72.00	
	R	T	R	T	R	T	R	T
N	43	46	46	44	46	46	46	46
Mean	91.34	89.92	91.06	90.72	89.35	87.44	88.28	92.52
Median	89.40	91.55	91.25	89.05	87.30	85.85	90.00	93.15
Geometric Mean	89.68	88.51	89.60	89.50	87.83	86.19	82.89	89.67
SD	17.98	16.15	16.47	15.02	17.02	14.63	24.41	19.54
CV%	19.68	17.96	18.09	16.55	19.05	16.74	27.65	21.12
Minimum	53.30	56.60	52.80	59.60	50.70	49.90	19.30	19.40
Maximum	150.40	135.20	136.30	121.50	149.60	123.70	136.80	141.40

Baseline adjusted copper concentrations (µg/dl) in blood:

Parameter	Time (hours)					
	RBL2_0	TBL2_0	RBL12_0	TBL12_0	RBL72_0	TBL72_0
N	43	44	43	46	46	46
Mean	-0.53	0.11	-2.00	-2.48	-1.12	2.59
Median	-0.20	-0.55	-1.10	-3.30	0.60	3.25
Geometric Mean	--	--	--	--	--	--
SD	13.76	9.95	13.41	9.31	24.41	14.29
CV%	-2617.42	9122.88	-669.15	-375.31	-2171.86	550.87
Minimum	-30.80	-27.00	-33.00	-30.70	-70.10	-66.20
Maximum	54.70	26.50	47.50	21.80	47.40	30.10

Copper concentrations in the urine were analysed as absolute concentrations determined at baseline, and 2 hourly intervals until 12 hours following trientine administration. The mean/median values and ranges between test and a reference product for copper concentrations presented in both absolute concentration and with adjustment to baseline were comparable. Notably, there was a trend for increased copper levels in urine, which peaked

around 4-6 hours with gradual decline towards 12 hour sampling. This increase is likely to be due to some trientine-induced excretion of copper in the urine. However there were no discernible differences in the pattern of copper excretion between the test and reference products.

Copper concentrations (µg/l) in urine:

Parameter	Time (hours)													
	-2.00 to 0.00		0.00 to 2.00		2.00 to 4.00		4.00 to 6.00		6.00 to 8.00		8.00 to 10.00		10.00 to 12.00	
	R	T	R	T	R	T	R	T	R	T	R	T	R	T
N	46	46	46	46	46	46	46	46	46	46	46	46	46	46
Mean	10.15	20.35	25.99	62.21	117.80	111.98	89.19	98.39	76.34	78.93	68.86	69.23	24.88	24.89
Median	8.19	10.50	17.72	25.88	85.53	79.27	74.56	58.58	51.14	51.22	48.36	49.87	21.76	22.72
Geometric Mean	7.99	11.64	17.41	28.35	95.85	88.42	69.10	70.41	55.43	56.12	44.79	48.93	20.37	21.23
SD	7.75	34.50	29.16	170.91	77.55	80.86	58.55	92.82	78.39	89.42	90.69	69.39	19.25	14.37
CV%	76.36	169.56	112.23	274.74	65.83	72.22	65.64	94.34	102.68	113.28	131.71	100.22	77.39	57.76
Minimum	1.65	2.84	3.19	2.52	21.91	24.40	1.51	12.92	7.98	15.02	1.09	9.38	5.63	5.84
Maximum	43.53	214.67	144.30	1158.04	335.17	366.33	318.36	480.03	414.39	461.50	616.89	340.03	116.48	70.91

Baseline adjusted copper concentrations (µg/l) in urine:

Subject	RBL2_0	TBL2_0	RBL4_0	TBL4_0	RBL6_0	TBL6_0	RBL8_0	TBL8_0	RBL10_0	TBL10_0	RBL12_0	TBL12_0
N	46	46	46	46	46	46	46	46	46	46	46	46
Mean	15.84	41.86	107.65	91.63	79.05	78.04	66.20	58.58	58.71	48.89	14.73	4.54
Median	8.19	13.85	79.16	67.43	69.79	48.85	43.88	34.73	35.52	39.04	12.83	9.50
Geometric Mean	--	--	82.20	--	--	--	--	--	--	--	--	--
SD	28.64	160.73	77.80	88.22	60.07	97.20	79.69	96.42	89.49	82.46	19.98	38.17
CV%	180.83	383.98	72.27	96.28	75.99	124.55	120.39	164.58	152.42	168.68	135.60	840.84
Minimum	-15.04	-207.40	14.08	-140.54	-5.91	-63.03	-17.42	-138.62	-12.63	-205.29	-27.61	-202.25
Maximum	139.13	1045.47	329.40	354.00	312.30	475.21	407.67	443.78	597.54	335.21	104.99	57.27

Ceruloplasmin is a known copper transporter and implicated in copper transfer from enterocytes into systemic plasma pools and into the liver. Ceruloplasmin concentrations in the blood were analysed as absolute concentrations determined at baseline, 2 h, 12 h and 72 h following trientine administration. The mean/median values and ranges between test and a reference product for ceruloplasmin concentrations presented in both absolute concentration and with adjustment to baseline were comparable. There were no discernible trends observed in these comparisons.

Ceruloplasmin concentrations (mg/dl) in blood:

Parameter	Time (hours)			
	0.00		72.00	
	R	T	R	T
N	43	46	46	46
Mean	21	20	22	22
Median	21	20	22	22
Geometric Mean	20	20	22	22
SD	3	3	4	3
CV%	16	15	16	14
Minimum	13	13	15	15
Maximum	32	28	29	31

Baseline adjusted ceruloplasmin concentrations (mg/dl) in blood:

Parameter	Time (hours)	
	RBL72_0	TBL72_0
N	43	46
Mean	1.60	2.13
Median	2.00	2.00
Geometric Mean	--	--
SD	3.06	1.89
CV%	190.94	88.84
Minimum	-7.00	-2.00
Maximum	8.00	7.00

The evaluations of serum iron, soluble transferrin receptor and ferritin levels were carried out to examine iron metabolism changes. The concentrations for these markers in the blood were analysed as absolute concentrations determined at baseline, 2 h, 12 h and 72 h following trientine administration. The mean/median values and ranges between test and a reference product presented in both absolute concentration and with adjustment to baseline were comparable. Taking into account iron levels and iron transporting protein levels (transferrin and ferritin) and inter-individual variability for these tests, there were no discernible trends observed in these comparisons.

Iron concentrations (µg/dl) in blood:

Parameter	Time (hours)							
	0.00		2.00		12.00		72.00	
	R	T	R	T	R	T	R	T
N	46	46	46	44	45	46	45	46
Mean	57.72	80.51	62.85	74.76	56.90	56.30	60.81	61.98
Median	53.92	61.88	54.47	54.83	46.50	45.82	50.46	54.76
Geometric Mean	51.82	63.59	55.58	59.07	49.71	49.08	52.84	53.44
SD	26.13	64.13	30.96	63.35	40.13	30.65	33.95	33.25
CV%	45.26	79.65	49.25	84.74	70.53	54.45	55.84	53.65
Minimum	19.17	16.81	19.58	16.13	21.25	12.42	20.11	19.44
Maximum	118.94	392.38	132.28	382.43	284.92	167.12	156.39	134.83

Baseline adjusted iron concentrations (µg/dl) in blood:

Parameter	Time (hours)					
	RBL2_0	TBL2_0	RBL12_0	TBL12_0	RBL72_0	TBL72_0
N	46	44	45	46	45	46
Mean	5.13	-5.88	-1.63	-24.21	38.27	-18.53
Median	0.80	-1.10	-4.56	-9.91	27.92	-2.02
Geometric Mean	--	--	--	--	--	--
SD	18.02	26.30	43.26	49.35	33.95	55.61
CV%	351.06	-447.07	-2650.85	-203.82	88.73	-300.09
Minimum	-31.17	-74.63	-49.64	-275.22	-2.43	-270.66
Maximum	69.32	87.52	256.64	29.49	133.85	46.56

Soluble transferrin receptor concentrations (mg/l) in blood:

Parameter	Time (hours)							
	0.00		2.00		12.00		72.00	
	R	T	R	T	R	T	R	T
N	45	45	46	44	45	46	46	46
Mean	1.82	1.83	1.88	1.84	1.74	1.81	2.04	1.97
Median	1.66	1.66	1.72	1.63	1.68	1.59	1.87	1.89
Geometric Mean	1.65	1.67	1.75	1.71	1.52	1.60	1.83	1.74
SD	0.75	0.84	0.77	0.79	0.75	0.87	0.85	0.90
CV%	41.21	45.76	40.94	42.71	43.34	48.21	41.92	45.83
Minimum	0.14	0.75	0.80	0.80	0.14	0.14	0.14	0.14
Maximum	4.13	4.70	4.42	4.70	3.53	4.36	4.60	4.30

Baseline adjusted soluble transferrin receptor concentrations (mg/l) in blood:

Parameter	Time (hours)					
	RBL2_0	TBL2_0	RBL12_0	TBL12_0	RBL72_0	TBL72_0
N	45	43	44	45	46	45
Mean	0.06	0.02	-0.10	-0.01	-0.40	0.16
Median	0.03	0.00	-0.01	-0.05	-0.57	0.13
Geometric Mean	--	--	--	--	--	--
SD	0.71	0.57	0.88	0.75	0.85	0.71
CV%	1133.79	2624.73	-924.80	-11322.90	-211.85	450.68
Minimum	-1.94	-1.56	-2.94	-2.05	-2.30	-2.45
Maximum	2.24	1.92	2.23	2.81	2.16	1.90

Ferritin concentrations (ng/ml) in blood:

Parameter	Time (hours)							
	0.00		2.00		12.00		72.00	
	R	T	R	T	R	T	R	T
N	46	46	46	44	45	46	46	46
Mean	23.88	43.55	28.50	38.53	29.11	39.23	25.15	28.45
Median	14.20	15.58	14.25	13.17	17.00	12.77	13.11	12.26
Geometric Mean	16.21	19.84	17.52	17.34	19.11	16.14	15.44	15.44
SD	23.33	97.70	32.09	97.07	30.60	113.86	28.05	52.69
CV%	97.73	224.36	112.58	251.94	105.10	290.25	111.53	185.21
Minimum	2.83	3.24	2.63	3.33	3.60	2.94	3.30	2.98
Maximum	120.64	656.01	150.91	648.94	149.38	778.15	128.21	349.74

Baseline adjusted ferritin concentrations (ng/ml) in blood:

Subject	Time (hours)					
	RBL2_0	TBL2_0	RBL12_0	TBL12_0	RBL72_0	TBL72_0
N	46	44	45	46	46	46
Mean	4.62	-6.17	4.79	-4.32	19.46	-15.10
Median	-0.20	-0.69	-0.36	-0.70	7.42	-1.85
Geometric Mean	--	--	--	--	--	--
SD	28.63	24.86	29.06	31.59	28.05	50.75
CV%	618.95	-402.75	606.21	-731.86	144.14	-336.13
Minimum	-65.43	-138.08	-71.75	-138.42	-2.39	-306.27
Maximum	147.04	36.35	145.51	122.14	122.52	25.69

eGFR was measured at baseline and 12 hours for blood creatinine and at 2-hourly intervals from baseline till 12 hours for eGFR via urine spot creatinine as a surrogate attribute for the renal function. The mean/median values and ranges between test and a reference product presented in both absolute values and with adjustment to baseline were comparable. There were no discernible trends observed in these comparisons.

eGFR (glomerular filtration rate) via spot blood creatinine:

Parameter	Time (hours)			
	0.00		12.00	
	R	T	R	T
N	43	46	46	46
Mean	132.6	129.2	133.4	130.1
Median	130.8	130.0	133.0	129.0
Geometric Mean	130.8	127.0	132.1	128.2
SD	22.0	24.6	18.9	22.3
CV%	16.6	19.1	14.2	17.1
Minimum	88.7	88.0	87.4	89.0
Maximum	186.0	194.0	171.0	185.7

Baseline adjusted eGFR (glomerular filtration rate) via spot blood creatinine:

Parameter	Time (hours)	
	RBL72_0	TBL72_0
N	43	46
Mean	0.88	0.90
Median	3.00	2.50
Geometric Mean	--	--
SD	22.71	18.19
CV%	2570.31	2030.76
Minimum	-81.00	-67.00
Maximum	41.00	25.00

eGFR (glomerular filtration rate) (ml/min/1.73m^2) via spot urine creatinine:

Parameter	Time (hours)													
	-2.00 to 0.00		0.00 to 2.00		2.00 to 4.00		4.00 to 6.00		6.00 to 8.00		8.00 to 10.00		10.00 to 12.00	
	R	T	R	T	R	T	R	T	R	T	R	T	R	T
N	46	46	46	46	46	46	46	46	46	46	46	46	46	46
Mean	1.92	1.88	3.21	2.94	2.07	2.56	1.93	2.11	1.91	1.92	1.38	1.49	2.53	2.65
Median	1.34	1.10	2.75	2.55	1.63	1.89	1.32	1.51	1.30	1.32	0.97	0.82	2.04	2.19
Geometric Mean	1.29	1.11	2.57	2.22	1.56	1.97	1.39	1.42	1.30	1.39	1.01	1.00	1.92	2.11
SD	1.88	1.76	2.10	2.08	1.58	2.20	1.63	1.77	2.68	1.72	1.43	1.50	1.70	1.89
CV%	97.92	93.58	65.44	70.75	76.54	85.72	84.31	83.88	140.32	89.62	102.98	100.80	67.09	71.32
Minimum	0.27	0.15	0.42	0.21	0.34	0.44	0.37	0.24	0.29	0.25	0.20	0.27	0.14	0.55
Maximum	10.51	7.34	10.51	9.34	6.05	12.56	8.35	5.82	18.28	8.93	8.93	6.68	7.29	10.06

Baseline adjusted eGFR (glomerular filtration rate) (ml/min/1.73m^2) via spot urine creatinine:

Parameter	RBL2_0	TBL2_0	RBL4_0	TBL4_0	RBL6_0	TBL6_0	RBL8_0	TBL8_0	RBL10_0	TBL10_0	RBL12_0	TBL12_0
N	46	46	46	46	46	46	46	46	46	46	46	46
Mean	1.30	1.06	0.16	0.68	0.02	0.23	0.00	0.04	-0.53	-0.39	0.62	0.77
Median	1.38	1.02	0.19	0.67	-0.09	0.08	0.02	0.18	-0.25	-0.07	0.38	0.90
Geometric Mean	--	--	--	--	--	--	--	--	--	--	--	--
SD	1.44	2.07	1.73	2.41	2.15	2.50	3.38	2.44	2.30	2.31	1.92	2.25
CV%	111.13	195.28	1113.64	352.05	12555.74	1069.20	-86369.01	6235.57	-432.22	-598.45	311.81	291.87
Minimum	-3.74	-5.99	-4.46	-6.49	-9.70	-6.43	-10.11	-6.06	-9.75	-6.70	-5.41	-4.85
Maximum	4.43	5.05	5.07	9.24	4.60	5.44	17.33	8.22	7.98	5.19	4.71	5.20

Overall, these additional pharmacodynamic tests showed comparable longitudinal changes between the test and reference groups. The tests directly related to copper metabolism, such as copper excretion in the urine showed similar pattern between test and reference. Other tests (e.g. serum copper, zinc concentrations, iron concentrations, transferrin receptor, ferritin and ceruloplasmin) probably would require long-term dosing to observe any potential effect of trientine on systemic metabolic changes, including the effect of trientine treatment on displacement of copper, zinc and iron across different compartments. There were no notable differences observed for eGFR evaluations using blood creatinine and urine spot creatinine levels. Considering in totality and taking into account that PK bioequivalence has been convincingly established, these tests showed comparable mean/median values and ranges and further support the bioequivalence between the test and reference products. Further results are summarised in the study report contained in module 5.3.1.

Safety evaluation

The safety evaluation conducted during the study involved physical examination including vital sign measurements, 12 lead-ECG and chest X-ray (postero-anterior view), laboratory tests (haematology, clinical chemistry and serology), urine analysis, drugs of abuse in urine and, blood alcohol screen, all done prior to the study; checking on the adverse events and vital signs and collection of biological matrix (blood and urine) for safety monitoring during the study; and, haematology and clinical chemistry after the completion of the study.

Statistical considerations

46 healthy, adult, human subjects were enrolled in the study based on the following assumptions:

- T/R ratio = 92.0 to 108.7%
- Intra-Subject C.V (%) ~ 25%
- Significance Level = 5%
- Power =80 %
- Bioequivalence Limits = 80.00 – 125.00%
- Withdrawals – 15%

Descriptive statistics (N, mean, median, geometric mean, standard deviation, coefficient of variation, minimum and maximum) was performed for all safety and efficacy measure with baseline adjustment.

ANOVA was performed on the log-transformed pharmacokinetic parameters for C_{max} and AUC_{0-t} for trientine (triethylenetetramine) and its its metabolites N(1)-acetyltriethylenetetramine (MAT) and N(1), N(10)-diacetyltriethylenetetramine (DAT). The 90% confidence interval (T *vs.* R) for the difference of the least-square means of the logarithmic transformed values of C_{max} and AUC_{0-t} at 5 % level of significance should be

between 80.00% and 125.00% to meet bioequivalence criteria for trientine (triethylenetetramine). Data for metabolite N(1)-acetyltriethylenetetramine (MAT) and N(1), N(10)-diacetyltriethylenetetramine (DAT) was provided for supportive information.

Study results

The pharmacokinetic data obtained on trientine (triethylenetetramine) and its metabolite N(1)-acetyltriethylenetetramine (MAT) and N(1),N(10)-diacetyltriethylenetetramine (DAT) for the test and reference products are provided below in Tables 3, 4 and 5.

Table 3. Pharmacokinetic results for trientine (triethylenetetramine) in Study No. 62420

Parameter	Least square Geo Means				T/R Ratio (%)	90% Confidence Intervals		Power (%)	Intra subject CV (%)
	Test (T)	N	Reference (R)	N		Lower (%)	Upper (%)		
C_{max} (ng/mL)	703.0765	46	684.7324	46	102.68	92.29	114.24	96.3	31.2
AUC_{0-t} (hr*ng/mL)	3030.2903	46	2967.4327	46	102.12	92.31	112.97	97.6	29.4
AUC_{0-inf} (hr*ng/mL)	3161.1683	46	3099.1570	46	102.00	92.33	112.68	97.8	29.0

Table 4. Pharmacokinetic results for N(1)-acetyltriethylenetetramine in Study No. 62420

Parameter	Least square Geo Means				T/R Ratio (%)	90% Confidence Intervals		Power (%)	Intra subject CV (%)
	Test (T)	N	Reference (R)	N		Lower (%)	Upper (%)		
C_{max} (ng/mL)	634.1766	46	607.2029	46	104.44	97.02	112.44	99.9	21.3
AUC_{0-t} (hr*ng/mL)	6597.8877	46	6303.8912	46	104.66	97.40	112.47	100.0	20.7
AUC_{0-inf} (hr*ng/mL)	6915.5345	46	6611.7757	46	104.59	97.30	112.43	99.9	20.8

Table 5. Pharmacokinetic results for N(1),N(10)-diacetyltriethylenetetramine in Study No. 62420

Parameter	Least square Geo Means				T/R Ratio (%)	90% Confidence Intervals		Power (%)	Intra subject CV (%)
	Test (T)	N	Reference (R)	N		Lower (%)	Upper (%)		
C_{max} (ng/mL)	167.0553	46	157.1632	46	106.29	98.28	114.96	99.8	22.6
AUC_{0-t} (hr*ng/mL)	2431.5448	46	2327.2243	46	104.48	97.10	112.42	99.9	21.1
AUC_{0-inf} (hr*ng/mL)	2577.3828	46	2472.3121	46	104.25	97.08	111.94	100.0	20.5

Pharmacokinetic conclusions

In accordance with the study protocol, the study met the bioequivalence criteria, as 90% confidence intervals for the log-transformed parameters for the total systemic exposure (as inferred from the AUC_{0-t}) and the peak exposure (as inferred from the C_{max}) for the applicant's Trientine Dihydrochloride Capsules 300 mg of Waymade Plc, UK, and the reference product Cufence 200 mg hard capsules (equivalent to 300 mg of Trientine hydrochloride) of Univar BV Schouwburgplein 30-34, 3012 CL Rotterdam, The Netherlands, were within the acceptance range of 80.00% - 125.00% as stated in the study protocol based on the CHMP Guidance [CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, 2010]. The two products are therefore bioequivalent in healthy, adult, human subjects under fasting conditions.

Safety results

Both treatments were well tolerated, with no significant side effects and no relevant differences in safety profile observed between the preparations.

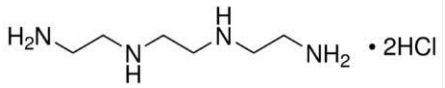
A total of three adverse events (two of itching all over the body and one of back pain) were reported by three subjects during the study. Out of these, one adverse event (of itching all over body) each was reported by subject S5 & subject S36 and one adverse event of back pain was reported by subject S18 during period-II. Out of these, two adverse events of itching all over body and one adverse event of back pain were unlikely to be related to the study drug and were moderate in nature. All these adverse events were resolved and did not result in subject discontinuation.

The study is further elaborated in Module 2.7.1 and the full study report is located in Module 5.3.1 (Clinical Study Reports).

2.5.3Overview of Clinical Pharmacology from Published Literature

Trientine hydrochloride is a chelating compound for removal of excess copper from the body. It is a white to pale yellow crystalline hygroscopic powder. The ATC code is: A16AX12. The chemical structure and physiochemical characteristics of trientine dihydrochloride are shown in Table 6.

Table 6. Structure and physiochemical characteristics of trientine dihydrochloride

Property	**Physicochemical characteristics**
Active	Trientine dihydrochloride
Synonyms	triethylenetetramine dihydrochloride, trientine hydrochloride (USP), trien, TETA
Chemical name	*N*,*N*'-Bis(2-aminoethyl)-1,2-ethanediamine dihydrochloride
CAS	38260-01-4
Formula	C6H18N4.2HCl
Structure	
Molecular weight	219.15 g/mol
Solubility	Freely soluble in water (>350mg/mL at pH 2-8). Soluble in methanol. Slightly soluble in alcohol. Insoluble in chloroform and in ether.
Log P	-1.8
pKa	9.33
pH	7.0-8.5 in solution
Source: https://pubchem.ncbi.nlm.nih.gov/compound/Trientine-hydrochloride	

2.5.3.1 Pharmacokinetics

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% [SmPC, Cufence 200 mg hard capsules].

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 [SmPC, Cufence 200 mg hard capsules].

Metabolism and 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 WD patients remains to be determined [SmPC, Cufence 200 mg hard capsules].

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 [SmPC, Cufence 200 mg hard capsules].

2.5.3.2 Pharmacodynamics

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 therefore inhibit copper absorption [SmPC, Cufence 200 mg hard capsules].

At least 16 published studies are available that discuss the pharmacokinetics and pharmacodynamics of trientine

- Two studies characterised the pharmacokinetics after a single oral dose of trientine in healthy volunteers (Kodama H et al, 1993) and patients with WD (Pfeiffenberger J et al, 2018).

- Four studies characterised the pharmacokinetics and pharmacodynamics of trientine in healthy volunteers (Kodama H et al, 1997; Lu J et al, 2007; Cho HY et al, 2009; Lu J et al, 2010).

- Two studies characterised the pharmacodynamics of trientine in healthy volunteers and Type 2 diabetic patients (Cooper GJS et al, 2004; Cooper JS et al, 2005).

- Eight studies characterised the pharmacodynamics of trientine in patients with WD (Walshe JM, 1973; Gibbs K et al, 1990; Siegemund R et al, 1991; Yamaguchi Y, 1992; Brewer GJ et al, 1993; Ishikawa S et al, 2001; Walshe JM, 2011; Pfeiffenberger J et al, 2019).

Kodama H et al (1993) and **Kodama H et al (1997)** examined the *in-vivo* metabolism of trientine in healthy human volunteers. The preliminary **Kodama H et al (1993)** study characterised plasma exposure and excretion in urine after a single oral 30 mg/kg dose. The parent trientine molecule was not detected in plasma and low levels were recovered in urine (1.6-1.7% of the dose over 8 h) which led to the discovery of an unknown metabolite in urine. The second **Kodama H et al (1997)** study subsequently identified the unknown metabolite in urine as the mono-acetylated metabolite, N_1-acetyltriethylenetetramine (MAT), and determined a cumulative recovery of 1% of the trientine dose in the urine as unchanged drug and 8% as the MAT metabolite.

Lu J et al (2007) performed an open-label, dose escalating study of trientine dihydrochloride (300, 600, 1200, and 2400 mg/day in healthy volunteers and patients with type 2 diabetes (n=13) in order to characterise the metabolism and excretion of trientine in plasma and urine, identify and quantify metabolites, and analyse trientine-induced changes in urinary copper and zinc excretion. The study characterised the MAT metabolite and a second major metabolite of trientine, N_1,N_{10}-diacetyltriethylenetetramine (DAT). The total drug (trientine plus metabolites) excreted in urine was 3.2 ± 1.1% of the oral dose for healthy volunteers and 9.2 ± 0.4% for diabetic patients. The urinary excretion of copper was dose-dependent and related to the urinary trientine concentration in healthy volunteers and urinary trientine +

MAT concentration in Type II diabetics. The urinary zinc response was related to trientine concentrations in both groups.

In a second study, **Lu J et al (2010)** assessed the PK of trientine after a single oral dose of 600 mg in healthy volunteers (n=24) with a fast acetylator or slow acetylator phenotype status in order to determine whether the NAT2 enzyme had any effect on trientine exposure. There was no significant difference between fast and slow acetylators for any of the trientine PK parameters confirming that the enzyme does play a substantial role in the disposition of trientine. Trientine was absorbed quickly with a T_{max} of 1.82 ± 0.813 h and C_{max} of 798 ± 330 ng/mL and a terminal $t_{½}$ of 2.48 ± 1.63 h. The T_{max} for the MAT and DAT metabolites were 5.38 ± 1.17 h and 4.71 ± 1.36 h, respectively. The metabolites had longer terminal $t_{½}$ than trientine (5.33 ± 4.27 h and 10.8 ± 6.17 h) although considerable variability was observed. The MAT and DAT metabolites peaked in plasma at similar times (MAT 60-120 min and DAT 120 min) leading the authors to conclude that trientine may be transformed directly to MAT or DAT rather than sequentially (MAT→DAT).

Pfeiffenberger J et al (2018) performed a phase I, open-label, and single-dose study to determine the steady-state PK of trientine in 20 patients with WD. The study included patients who were already stabilised on trientine dihydrochloride, and the PK of a single oral dose of trientine dihydrochloride (300-150 mg based on usual dose) was evaluated in children ≥12 years and adult patients. Trientine was absorbed quickly after oral administration with a median T_{max} of 1.49 h (0.48-4.08 h) and the terminal $t_{½}$ was 3.7 ± 1.28 h was similar to that in the **Lu J et al (2007)** study. No difference was observed in the PK parameters for adults (n=16) and children (n=4) although the paediatric sample size was small and the doses administered were variable.

Cho HY et al (2009) performed a randomised, double-blind, placebo-controlled, group-sequential, dose escalation trial to evaluate the PK profile, PD effects and PK/PD relationships using population approaches, as well as to determine the tolerability and safety of trientine after repeated oral daily doses of 200, 600, 1200 and 1800 mg twice daily for 14 days. Trientine exhibited linear PK with minimal accumulation across the dose range. The cumulative excretion of copper in urine over 24 h was dose-proportion. A two-compartment PK model with first-order absorption and lag time, together with a linear direct effect PD model, provided good fits for the plasma trientine concentrations and urinary copper excretion, respectively. A population PK/PD model described plasma clearance was dependent on glomerular filtration rate (GFR) and PD (dependence of slope on GFR and gender) of trientine. Daily doses up to 2400 mg/day were well tolerated and an increased frequency of adverse effects (AE) was observed at 3600 mg/day.

Cooper GJS et al (2004) conducted two studies to examine the PD effects of trientine. The first study was a double-blind, randomised, controlled study in patients with diabetes (n=20) and healthy volunteers (n=20) to examine the excretion of copper and iron in urine following 2400 mg trientine for six days. In this study, urinary copper excretion was elevated after a single dose of trientine in healthy volunteers and was significantly higher in diabetic patients. The urinary iron excretion was unchanged for both groups, which suggested that anaemia associated with trientine is not due to increased urinary iron excretion.

The second study was a randomised, placebo-controlled, parallel-group study to investigate the effect of oral trientine 1200 mg/day for six months on the left ventricular (LV) mass in

patients with type 2 diabetes. The mean LV mass decreased by 5% after 6 months of trientine treatment and increased by 3% in placebo-treated control subjects ($p<0.01$). The findings indicated that the sub-population of WD patients with Type 2 diabetes may derive enhanced effects from trientine treatment.

Cooper JS et al (2005) conducted two studies to examine the PD effects of trientine. The first study was a double-blind, randomised, controlled study in male patients with diabetes (n=20) and healthy male volunteers (n=20) in order to examine the excretion of copper, iron, zinc, calcium, magnesium, manganese, selenium and mercury in urine and faeces following an oral dose of 2400 mg trientine or placebo each day for six days. In this study urinary copper excretion was elevated after a single dose of trientine in healthy volunteers and was significantly higher in diabetic patients. The urinary iron excretion was unchanged for both groups which suggested that anaemia associated with trientine is not due to increased urinary iron excretion.

The second study was a dose-dependent study to determine the effects of increasing doses of oral trientine on urinary elements. Patients with diabetes (n=7) and healthy male volunteers (n=7) received 300 mg trientine/day for seven days, with increment to 600, 1200 and 2000 mg/day, with each increased dose taken for seven days (total duration of study 28 days). Urinary samples were taken before and after each treatment period and elemental analysis performed. Trientine increased urinary copper in both diabetic and non-diabetic subjects in a dose-dependent manner. Gradients for copper excretion did not differ between groups. Zinc showed similar results with increased urinary zinc in both diabetic and non-diabetic subjects in a dose-dependent manner; however, the gradients for zinc excretion was higher in the diabetic patients ($p<0.05$). The authors also noted the results for the other elemental elements and state trientine had no dosage-dependent effect on 24-hour urinary excretion, but did not include the data.

The findings by Cooper JS et al (2005) indicated that the subpopulation of WD patients with Type 2 diabetes may derive enhanced effects from trientine treatment.

Walshe JM (1973) performed an open-label study in adolescent and adult patients (n=18) with WD to support the therapeutic use of trientine (study described in the SYPRINE US Patient Information). The study compared the efficacy of trientine and penicillamine using urinary copper excretion rates and copper metabolism in little or untreated patient and penicillamine-treated patient groups. The differences in clearance of endogenous and radioactive copper following trientine and penicillamine treatment, and the ability of the chelators to free protein-bound copper in plasma was also compared. The results demonstrated that trientine was an effective capruretic in patients with WD although it was less potent than penicillamine on a molar basis. The radio-labelled copper study indicated that a different cupruretic effect between these two drugs could be due to a difference in selectivity of the drugs for different copper pools within the body. Both chelators were able to mobilise copper from plasma proteins.

Walshe JM (2011) performed a larger retrospective analysis of historical urinary copper excretion results for WD patients treated between 1955 and 2000 (n=192 patients) to determine the differences in the rate of urinary copper excretion at different stages of the disease and in response to treatment. Patients were studied for basal pre-treatment, 24-hour urinary copper excretion and for 6 h after a test dose of 500 mg penicillamine. The basal and

post-test dose were repeated after approximately 1 year and 2 years of chelation therapy with either penicillamine or, in some cases, with trientine (n=15). The ratio of increase in urinary copper clearances before treatment, at 1 year and at 2 years were 5.2, 4.0 and 3.0 for trientine-treated patients and 4.0, 7.6 and 6.0 for penicillamine-treated patients. Trientine appeared to become less able than penicillamine to mobilise copper over long periods of time although the basal levels approached the normal range of 30 μg/24 h after 2 years of trientine, which indicated a good continued response to trientine maintenance treatment.

Pfeiffenberger J et al (2019) performed a retrospective cohort of WD patients (n=321) treated at a tertiary care centre in Germany to evaluate 24 h urinary copper excretion rates and serum copper concentrations in patients under long-term treatment with different common medications (D-penicillamine, trientine, zinc) and to compare the results under therapy and after a 48-hour dose interruption before urinary copper clearance determination. The 24-hour urinary copper clearance rates were observed to be higher when measured during treatment than after a 48-hour dose interruption for trientine. The 24-hour urinary copper clearance rates increased gradually for trientine, peaking at 18 months after the start of therapy, and then decreased over time. In comparison, the 24-hour urinary copper clearance rates for D-penicillamine were highest 6 months after the start of therapy and then gradually decreased until month 24. The 24-hour urinary copper clearance rates for trientine were lower than D-penicillamineat all time points which was consistent with the observations by **Walshe JM (1973)** and **Walshe JM (2011)**. The urinary copper excretion rates in patients under D-penicillamine or trientine therapy were consistently much lower when measured after a 48-hour dose interruption than when determined under continued therapy, which demonstrated the short-term PD effect.

Gibbs K et al (1990) described a retrospective analysis of copper concentrations in single liver biopsy samples (n=69) from patients with WD over time. Some patients had serial liver biopsies (n=10) which allowed the effect of chelators in reducing liver copper load to be observed. From the serial concentrations, it was evident that trientine and the other chelators reduced the liver copper levels over time. In some patients, an increase could be explained by non-compliance with treatment. From the single determinations against time, it was apparent that the liver copper concentration falls rapidly after starting ‘anti-copper’ treatment and thereafter there is no relationship between copper levels and the duration of therapy, although poor compliers had substantially higher liver copper concentrations, which reinforced the need for life-long treatment to avoid copper re-accumulating in the liver.

Siegemund R et al (1991) described case series in nine WD patients intolerant of penicillamine who were treated with trientine. In these patients, urinary copper excretion and ^{64}Cu absorption studies were undertaken to evaluate the effectiveness of trientine treatment and to elucidate the mechanism of action of trientine through comparison with untreated healthy volunteers, untreated pre-symptomatic WD patients, and zinc-treated WD patients. Trientine was shown to have a dual mechanism of action in chelating copper and inhibiting the intestinal copper absorption. The authors suggested that decreasing the intestinal copper absorption might be due to the poor absorption of trientine. This mechanism is consistent with the results of a copper balance study in a single patient with WD reported by **Ishikawa S et al (2001)** which showed consistently higher faecal copper losses than urinary copper loss over seven days of initial treatment with trientine 1500 mg/day.

Yamaguchi Y (1992) performed a small open-label, crossover study of oral penicillamine (330-1200 mg/kg/day), trientine dihydrochloride (800-2500 mg/day) and trientine tetrahydrochloride (800-2500 mg/day) for 3-7 days in seven WD patients in order to evaluate the efficacy and safety of the two trientine salt forms. Penicillamine increased the urinary copper excretion 6.7-fold relative to the pre-dose basal levels. The capruretic effects of the trientine salts was approximately 1.5-2 times lower than penicillamine although were equivalent in their effect, increasing the urinary copper excretion rate by 4.5-fold and 3.7-fold relative to the baseline for trientine dihydrochloride and trientine tetrahydrochloride, respectively.

Brewer GJ et al (1993) performed a study in five WD patients to examine the possible antagonistic or additive effects of zinc taken orally in combination with trientine with doses separated by >1 h. The potential drug interaction was examined by determining by copper balance (dietary, urinary loss and faecal loss of copper) and ^{64}Cu uptake in the presence and absence of trientine. The trientine/zinc combination resulted in a small significant increase in urinary copper excretion compared with zinc alone ($p=0.03$). A non-significant decrease in faecal copper excretion was observed for the trientine/zinc combination compared with zinc alone. The separation of the zinc and trientine doses in the study precluded a full assessment of the potential for a pharmacokinetic interaction, which would seem probable given trientine also complexes with zinc (**Kodama H et al, 1997**).

The following key conclusions are based on the 16 published studies reviewed in this section:

- Trientine is absorbed quickly after oral administration with a T_{max} of approximately 1.5 h and has a moderate terminal $t_{½}$ of approximately 5.5 h according to the literature.

- The absorption of oral trientine is variable and comparisons of C_{max} between studies is challenging as the dose was not typically described as mg trientine base or mg trientine dihydrochloride salt.

- The oral bioavailability of trientine is unknown although it would appear to be low, based on a recovery of <2% of the unchanged drug in urine (Kodama H et al, 1997), and the highest urinary excretion occurs in the first 4 h post-dosing (Lu J et al, 2010).

- The two main metabolites are the mono- and di-acetylated metabolites, N_1-acetyltriethylene tetramine (MAT) and N_1,N_{10}-diacetyltriethylene tetramine (DAT), which are excreted in the urine (Kodama H et al, 1997; Lu J et al, 2007; Lu J et al, 2010). The NAT2 enzyme was not involved in the biotransformation of trientine (Lu J et al, 2010).

- Trientine has a linear PK and modest accumulation was observed following repeat oral dosing (Cho HY et al, 2009; Lu J et al, 2010). A higher accumulation index was observed for the MAT and DAT metabolites due to a longer terminal $t_{½}$ (Lu J et al, 2010).

- The MAT metabolite is less potent copper chelator than trientine (Kodama H et al, 1997).

- Urinary copper excretion was used as a surrogate clinical endpoint and trientine was shown to increase excretion of copper in urine in both healthy volunteers (Kodama H et

al, 1997; Cho HY et al, 2009; Lu J et al, 2007; Lu J et al, 2010; Cooper JS et al, 2005) and patients with WD (Walshe JM, 1973; Yamaguchi Y, 1992; Walshe JM, 2011).

- Urinary copper excretion after trientine treatment is higher in Type 2 diabetics than healthy volunteers and trientine also has favourable effects on left ventricular (LV) mass in Type 2 diabetics (Cooper GJS et al, 2004).

- The 24-hour urinary copper excretion rates in WD patients increased gradually following the start of trientine therapy, peaking 18 months after the start of therapy, and then decreases over time (Pfeiffenberger J et al, 2019).

- Urinary copper excretion rates are higher when measured during treatment than after a 48-hour dose interruption for trientine, which suggests that the PD effect of trientine is short (Pfeiffenberger J et al, 2019).

- The urinary copper excretion rate correlated with the recovery of trientine (Kodama H et al, 1997; Lu J et al, 2007; Cho HY et al, 2009) and trientine/MAT (Lu J et al, 2010).

- Trientine was shown to increase copper in faeces in a WD patient (Ishikawa 2001) and decrease the excretion of copper in the faeces in healthy volunteers (Cooper JS et al, 2005).

- A population PK/PD model revealed that GFR is the best predictor for the PK/PD of trientine (Cho HY et al, 2009).

- A population PK/PD model described complex PK (linear absorption and dependence of clearance on GFR) and PD (dependence of slope on GFR and gender) of trientine. GFR and gender may be useful clinical covariates for individualising trientine doses during chronic dosing (Cho HY et al, 2009).

- A two-compartment PK model with first-order absorption and lag time provided the best fit for serum trientine concentrations of trientine following 100, 300, 600 and 1800 mg twice-daily oral doses for 14 days in healthy volunteers. A linear direct effect PD model provided the best fit for urinary copper excretion (Cho HY et al, 2009).

- Trientine modifies zinc balance and increases the urinary excretion of zinc (Kodama H et al, 1997; Lu J et al, 2007; Cooper JS et al, 2005). Trientine also decreases faecal excretion of Zinc (Cooper JS et al, 2005), which is relevant to the safety profile of trientine.

- Trientine did not increase the urinary excretion of iron in the Cooper GJS et al, 2004 and Cooper JS et al, 2005 studies; however, it was shown to increase urinary excretion of iron in the Kodama H et al, 1997 study. Trientine has been shown to modify iron balance and decrease faecal excretion although the trientine-metabolic status interaction was insignificant (Cooper JS et al, 2005).

- Trientine has been shown to modify calcium and selenium balance mainly via decreased faecal excretion (Cooper JS et al, 2005).

- Trientine modifies magnesium balance mainly via decreased faecal excretion (Cooper JS et al, 2005).

- Trientine does not modify magnesium, molybdenum and chromium (Cooper JS et al, 2005).

- Trientine has a dual mechanism of action in chelating copper and inhibiting the intestinal copper absorption (Siegemund R et al, 1991).

- Serial liver biopsies confirmed that trientine reduces the copper concentration in liver tissue over time (Gibbs K et al, 1990).

The pattern and characteristics of PK of Waymade's 'Trientine 200 mg hard capsules' in the completed bioequivalence study were consistent with the findings in the published iterature and with the information for Cufence 200 mg hard capsules contained in the EMA assessment report [Cufence, EMA Public Assessment Report, 2019], thus supporting the notion that given the same pharmacology of the drugs, the anticipated efficacy and safety will be also the same with test product as with the reference.

2.5.4Overview of Efficacy from Published Literature

No randomised controlled trials have been identified that compares trientine as a monotherapy against an active comparator such as penicillamine (DPA). Thus, there is a lack of high-quality evidence to support the efficacy of available drugs in WD [SmPC, Cufence 200 mg hard capsules]. The European Medicine Agency (EMA) has also acknowledged that there is "*No prospectively planned and well-designed, controlled trials have been conducted with Cufence (or any other trientine product) that would meet scientific standards for high quality evidence*" [Cufence, EMA Public Assessment Report, 2019].

The findings from seven published studies which provided efficacy outcomes are summarised below. In addition, trientine is recommended for use by several clinical guidelines: European Association for the Study of the Liver (EASL) 2012 [EASL Guidelines, 2012], American Association for the Study of Liver Diseases (AASL) 2008 [Roberts EA et al, 2008], European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) 2018 [Socha P et al, 2018] and Australian Therapeutic Guidelines [Trientine-TGA Australia, 2019; eTG Complete-Wilson Disease-Therapeutic Guidelines, Australia, 2019].

1. A pivotal multicentre, retrospective observational study [**Weiss KH et al, 2013**] compared the efficacy and safety of trientine versus penicillamine (DPA) in patients with WD (n=380) treated at tertiary care centres in Germany and Austria, and additional patients (n=25) from the EUROWILSON registry. The cohort consisted of patients with WD treated with DPA (n=326) and trientine (n=141) for at least six months.

Only patients treated with monotherapy with DPA or trientine were included in the analysis. Treatment blocks with a follow-up period of less than 6 months were excluded, including patients who immediately underwent liver transplantation. Patients generally started chelation treatment when symptomatic, in accordance with the guidelines, and no systematic criteria were used regarding the choice of chelating agent (DPA or trientine).

Patients were categorised based on clinical presentation (asymptomatic, hepatic, neurological, or mixed hepatic and neurological symptoms). The primary efficacy outcome was the change in hepatic and neurologic outcomes (i.e. clinical symptoms and tests) at 6, 12, 24, 36, and 48 months after initiation of the treatment regimen. The outcome measures were stratified by first- versus second-line use of the drugs. Hepatic outcome measures were based on clinical symptoms, course of liver enzymes, and liver function tests. Patients with either of these clinical or biochemical signs of liver disease were considered symptomatic. The course of neurologic disease was evaluated by the physician. Both hepatic and neurologic outcomes were scored as follows: unchanged, improved to normal, improved but not normal, deteriorated, or asymptomatic over the duration. For hepatic symptoms, the classification of "improved to normal" implies normalised liver enzyme levels and liver function tests. The number of patients showing improvement or worsening of symptoms was calculated and stratified by the presence or absence of symptoms and by first- versus second-line therapies.

The secondary outcome was initial and subsequent therapies for treatment efficacy and events leading to a discontinuation of medication and categorised the reasons for discontinuation. Events leading to a change/discontinuation of treatment were analyses using Kaplan-Meier estimation. Adverse events related to discontinuation of therapy were recorded and classified. P values for comparison between treatments with DPA versus trientine monotherapy were

calculated by the Pearson chi-square and the Fisher exact tests.

In symptomatic hepatic patients, comparable rates of improvement were observed under first-line DPA therapy (185 of 204; 90.7%) and first-line trientine therapy (25 of 27; 92.6%). In the same group, stable hepatic disease in terms of unchanged hepatic symptoms was observed for first-line DPA treatment in 15 of 204 (7.4%) treatments versus 2 of 27 (7.4%) in the trientine group. When chelators were given as second-line therapy, rates of improvement were generally lower, but still not statistically different between the groups. Stable hepatic disease under second-line therapy was reported for 4 of 16 (25%) DPA treatments and for 10 of 45 (22.2%) trientine treatments. No hepatic worsening was seen in chelation monotherapy for patients who presented without hepatic symptoms. No statistically significant differences were found for the rate of improvement for first-line (DPA 77 of 114, 67.5% versus trientine 11 of 20, 55%) or second-line (DPA 3 of 13, 23.1% versus trientine 26 of 51, 51%) chelation therapy.

Stable neurologic disease was observed for first-line in the DPA group in 31 of 114 (27.2%) treatments versus 5 of 20 (25%) in the trientine group. Stable neurologic disease for second-line therapy was reported for 9 of 13 (69.2%) DPA treatments and for 17 of 51 (33.3%) trientine treatments. With second-line therapy, neurologic worsening was comparable between groups, with a trend favouring DPA (DPA: 1 of 13, 7.3%; trientine: 8 of 51, 15.7%). A significantly higher rate of neurologic worsening was reported for first-line therapies of symptomatic neurologic patients treated with trientine (4 of 20; 20%) versus DPA (6 of 114; 5.3%) (p=0.042).

There were no differences between the treatments based on the number of overall discontinuations (p=0.36) with 142/326 (43.6%) discontinuing from DPA and 36/141 (25.5%) from trientine therapy. Discontinuation as a result of adverse events was more frequent for DPA treatment than for trientine treatment with 94/326 (28.8%) of DPA treatments stopped because of adverse events versus 10/141 (7.1%) of trientine treatments (p=0.039).

2. A multicentre, retrospective cohort study of medical records that evaluated the efficacy, safety and tolerability of trientine for at least 6 months as a second-line treatment in 77 patients with WD is described in the CUFENCE European Public Assessment Report (EPAR) [**UNV-TRI-002 retrospective study, Weiss KH et al, 2018**]. The study also included a prospective part which was a continuation of the retrospective study (n=52) to assess efficacy and quality of life (QoL) outcomes [UNV-TRI-002 prospective study, Weiss KH et al, 2019], which is described further below.

The objectives of the study [UNV-TRI-002 retrospective study, Weiss KH et al, 2018] were to assess the clinical course of copper stores, neurological disease, and hepatic disease following initiation of treatment with trientine following withdrawal of penicillamine; to assess the safety of trientine treatment based on the reported adverse events (AEs), including AEs leading to discontinuation of trientine; and, to determine the duration of treatment with second line therapy trientine, defined as the time to discontinuation of treatment due to AEs and/or inadequate response.

The study did not define a primary endpoint. The main efficacy endpoint was the clinical

course of hepatic or neurological disease based on the investigator's scores at the time of initiating trientine (similar 5-point score as used in the Weiss 2013 study), and 6, 12, 24, 36, 48 months and at the last available time point while taking second line trientine and the time to discontinuation of trientine due to AE and/or inadequate response. No statistical comparisons were performed. Copper storage and metabolism were measured as surrogate endpoints at the time of initiation, and 6, 12, 24, 36, 48 months and at the last available time point after initiation of trientine. A total of 81 patients were enrolled in the retrospective part of the study; however, four patients were excluded from the intention to treat (ITT) population as they had received an alternative brand to the sponsor's Univar trientine at initiation of trientine.

A total of 38 (49.4%) patients showed improved hepatic symptoms with 17 (22.1%) patients classified as 'improved to normal' and 21 (27.3%) patients classified as 'improved but not normal', 27 (35.1%) patients were 'asymptomatic', 8 (10.4%) patients had 'unchanged' symptoms, and 4 (5.2%) patients had 'worsened symptoms'. Hepatic outcome was generally similar after 6, 12, 24, 36 and 48 months of treatment. A total of 11 (14.3%) patients showing improved neurological symptoms with 2 (2.6%) patients classified as 'improved to normal' and 9 (11.7%) patients classified with 'improved but not normal', 36 (46.8%) patients were 'asymptomatic', 28 (36.4%) patients had 'unchanged' symptoms, and 2 (2.6%) patients had 'worsened symptoms'.

A change in 24-hour urine copper excretion over the course of trientine treatment was determined for 10 patients, with seven showing a decrease, indicating efficacy, and three showing an increase, which could be linked to mobilisation of copper. Concentrations of serum ceruloplasmin and total serum copper are used to derive the concentration of non-ceruloplasmin bound copper (NCC) using the following equation: NCC (μmol/L) = Serum copper (μmol/L) – [47.2 x serum ceruloplasmin (g/L)]. Overall, the median NCC concentration showed a decrease from baseline to latest follow up (n = 35 [−0.613 ± 1.7318]).

Within the two years of observation, 12 (15.6%) of patients discontinued trientine and switched to another treatment option. At the individual last available observation, treatment with trientine was ongoing in 65 (84.4%) patients of the ITT population.

3. The **UNV-TRI-002 prospective study [Weiss KH et al, 2019]** was a continuation of 'UNV-TRI-002 retrospective study, Weiss KH et al, 2018 study' and the objectives and design were described as similar to the retrospective study, apart from an additional QoL objective included in the prospective study. Unified WD Rating Scale (UWDRS) neurologic subscale assessments were also performed. All patients had also been enrolled in the retrospective study and were continued to be observed in the prospective study. The mean age was 42.3 ± 14.52 years.

Fifty of the 51 patients (98.0%) treated with trientine were considered to have responded to treatment, while only one patient (2.0%) showed a mild worsening of disease at 12 months. A breakdown of the overall improvement versus deterioration was not available for independent review. A total of 29 (56.9%) patients were asymptomatic over the duration of therapy. In 12 patients (23.5%) symptoms remained unchanged and there was one patient (2.0%) with worsening of neurological symptoms.

For neurological presentations, the neurological symptoms improved but not to normal in

eight patients (15.7%), and improved to normal in one patient (2.0%). A total of 29 (56.9%) patients were asymptomatic over the duration of therapy. In 12 patients (23.5%) symptoms remained unchanged and there was one patient (2.0%) with worsening of neurological symptoms. The UWDRS neurologic subscale assessment was 11.3 ± 24.31 at baseline, 9.7 ± 23.85 at month 6 and 8.8 ± 22.86 at month 12 which indicated a neurological improvement.

The PD results reported the mean 24-hour basal urine copper excretion which were similar at month 6 and month 12 (4.011 µmol/24 h versus 4.452 µmol/24 h, respectively); the mean serum copper at baseline was 4.505 ± 3.4036 µmol/L, 4.648 ± 2.9990 µmol/L at month-6 and at 4.753 ± 3.6092 µmol/L at month-12; and the NCC concentration at month-6 was 1.1542 ± 0.92618 µmol/L and 0.9051 ± 0.88075 µmol/L at month-12.

The QoL data indicated that overall, the anxiety and depression improved during treatment with trientine. The other QoL indicators (mobility, self-care, usual activities and pain/discomfort) were stable and generally similar at month-6 and month-12.

4. Walshe reported a case series of 20 patients who were treated with trientine following severe penicillamine intolerance [**Walshe JM, 1973**]. The series reflected 13 years' of clinical experience of using trientine dihydrochloride in patients with WD for duration of 43-53 months. Changes in copper metabolism, clearance, PD parameters and clinical symptoms as well as safety outcomes were reported. No statistical analysis was undertaken. Patients were grouped according to length of previous penicillamine treatment.

• In the first group of patients who became intolerant soon after starting penicillamine (n=8), all responded well to trientine treatment. Blood and urine copper levels fell sharply with therapy coinciding with the clinical improvement (i.e. reduction in symptoms and density of Kayser-Fleischer rings).

• In the second group of patients who were intolerant of penicillamine and switched to trientine (n=3), all showed improvement in neurological status, although two patients had some residual deficit. Hepatic and renal function showed no deterioration. The copper status of these patients was satisfactory when penicillamine was discontinued and remained satisfactory during treatment with trientine.

• The final group who had been on long-term treatment and were considered 'adequately de-coppered' at the time of changeover (n=9) remained well-controlled on trientine for an average of 4 years. The penicillamine toxicities, immune-complex nephritis and white-cell dyscrasias responded specifically to withdrawal of penicillamine and did not recur on trientine. One patient within this group still had mild dysarthria and ataxia and these continued to improve on trientine. The copper status of all nine has been well controlled.

5. Dahlman et al (1995) reported a case series of trientine treatment outcomes in 19 patients with WD [**Dahlman T et al, 1995**]. Of the patients, 17 were initially on DPA at the time of diagnosis and subsequently switched to trientine, and 2 were treated with trientine from the outset. The aim of this study was to examine the long-term effects of trientine. The trientine dose was 1000-1800 mg daily for a mean duration of treatment of 8.5 years.

The presenting symptoms were signs of abnormal liver function in 60% and neurological symptoms in 50% of the patients. Treatment with trientine led to reversal or improved clinical symptoms in 16/19 patients. The authors reported that 13/19 patients were still on

trientine treatment at the time of publication which indicated the long-term safety and efficacy of trientine for up to 17.5 years.

6. Ala et al (2015) reported a prospective pilot study of once-daily trientine 15 mg/kg (rounded to the nearest 250 mg) for maintenance in 8 WD patients aged 22-71 years who had been clinically stable, treated for 4-50 years, and had stable liver disease [**Ala A et al, 2015**]. The aim of the study was to determine the safety and effectiveness of a 12 month course of a once-daily trientine for maintenance treatment of WD instead of multiple divided doses of zinc acetate (n=2), penicillamine (n=1) and trientine (n=5).

All patients remained clinically well with their physical examination remaining unchanged and no new neurological signs detected. ALT and AST levels were not statistically changed by treatment in 6/8 patients. Total bilirubin, albumin and INR were relatively unchanged for all patients. There were no interruptions in treatment or study discontinuations. No patients were removed from the study for abnormal laboratory values or clinical evidence of worsening disease. In the study group, there were two patients in whom past symptoms included neurological and psychiatric symptoms, but in one of these individuals the psychiatric symptoms were resolved, and in both neurological symptoms were stable. Urine copper excretion and serum copper remained stable for patients before and during the study which was consistent with no clinical evidence of disease deterioration. The study provided PD insights on the duration of effect.

7. Arnon et al (2007) reported a retrospective cohort study of medical records to evaluate the efficacy and adherence to treatment with trientine 250-500 mg twice daily (~20 mg/kg/day) and/or zinc 25-50 mg twice a day (~1 2 mg/kg/day of elemental zinc) for at least 12 months in paediatric patients with WD (n=10, 8-17 years) [**Arnon R et al, 2007**]. The primary endpoints used in the retrospective review included clinical status, normalisation of serum ALT and AST levels, and reduction of 24-hour urinary copper levels to a target of 50 200 µg/day.

None of the patients showed worsening of liver disease or developed other WD-related symptoms despite mildly increased ALT levels. The mean 24-hour urine copper level was 156 µg at presentation which increased to a peak of 494 µg/24 h at 1-2 months after the start of trientine therapy. Following the peak in urine copper levels, the levels gradually decreased during the first year of treatment with a mean level of 72 µg/24 h (range 62-92 µg/24 h) at 12 months which was twice the upper normal limit.

Efficacy conclusions

Together, these studies demonstrate a beneficial effect of trientine in the majority of patients for hepatic as well as neurologic forms of disease (symptoms improved or remained stable in most patients). The benefit appears larger in patients with hepatic than neurologic disease. Very few patients deteriorated under treatment. The results further indicate that patients usually stay on trientine treatment for quite a long time before switching to an alternative, which indicates good tolerability, and might support the assumption that trientine can be used over long periods of time without its efficacy being compromised. It also shows that trientine is effective and essential for WD patients intolerant to D-Penicillamine and it has been used since decades for the treatment of WD with increased life expectancy in these patients.

2.5.5Overview of Safety from Published Literature

2.5.5.1 Exposure and tolerability of trientine hydrochloride

Trientine is a well-known active substance used since decades for the treatment of WD. The data provided to support the safety part of this full mixed application include published references on trientine use in WD patients. WD is a very rare condition. Affected patients require life-long treatment and though, although not many patients exist, long-term exposure data are available from most of the identified/studied patients from the literature. What can be derived from the literature is that most of the patients received trientine for many years/decades. Based on estimates provided by Cufence MAH, the post-marketing cumulative exposure with trientine based on the product distribution and sales data was approximately 900 patients for period 2001-2014 (Cufence EPAR, 2019).

Longstanding experience with the active substance in the clinical practice as well as the evidence from the published literature support a favourable safety profile of trientine in the treatment of WD in patients intolerant to D-penicillamine therapy, in adults, adolescents and children aged 5 years or older [Cufence, EMA Public Assessment Report, 2019].

Overall, the amount of reported AEs, TEAEs and trientine-related AEs is very low. The safety profile of trientine is also considered favourable when compared to D-penicillamine. Non-clinical data also did not raise any particular concerns from a safety point of view [Cufence, EMA Public Assessment Report, 2019].

Trientine has often been found to be used as a first line option in paediatric patients (instead of D-penicillamine), probably due to the more favourable safety profile, and the overall safety results in children are in line with the results for adult patients. No relevant differences in the quality or quantity of reported AEs of paediatric patients compared to adults have been observed [Cufence, EMA Public Assessment Report, 2019]. However, some concern remains about a certain risk of copper deficiency with over-treatment with trientine (or in general, any chelator treatment) that could impair juvenile developmental processes [Cufence, EMA Public Assessment Report, 2019].

2.5.5.2 Adverse Events

Nausea can commonly occur on initial treatment and occasionally skin rash can occur [SmPC, Cufence 200 mg hard capsules]. Duodenitis and severe colitis have been reported [SmPC, Cufence 200 mg hard capsules]. It is known from the information on other trientine products licensed in the EU that possible AEs comprise gastrointestinal disorders, iron deficiency anaemia, and skin conditions such as rash, pruritus, erythema and urticaria [Cufence, EMA Public Assessment Report, 2019]. Neurological deterioration can occur at the start of the treatment [SmPC, Cufence 200 mg hard capsules]. The FDA approved ‘Syprine’ mentions systemic lupus erythematosus, muscular spasm and myasthenia gravis [Cufence, EMA Public Assessment Report, 2019].

There have been reports of neurological deterioration in WD patients treated with copper chelators including trientine, with symptoms of, for example, dystonia, rigidity, tremor and dysarthria. Restless leg syndrome (RLS) was identified in the literature as possible trientine AE and one case of RLS was also recorded in study UNV-TRI-002 [Weiss KH et al, 2018]. This event was attributed to causes other than the use of trientine.

The mechanism of action of trientine makes copper deficiency a possible adverse reaction. 'Sideroblastic anemia' was described as possible result of copper deficiency in WD patients under treatment [Perry et al, 1996; Roberts and Schilsky, 2008; EASL, 2012 - Cufence, EMA Public Assessment Report, 2019] and it is duly included as an adverse effect in the proposed SmPC.

Treatment guidelines recommend that treated WD patients should be monitored and closely followed for development of new neurologic or hepatic symptoms, and undergo regular assessments of liver function and urinary copper excretion to detect signs of inadequate response to treatment, possible overtreatment, or even potential long-term toxicity despite the appearance of clinical stability [Cufence, EMA Public Assessment Report, 2019]. The proposed PIL adequately covers these issues.

Adults

Trientine is a well-known active substance used since decades for the treatment of WD [Cufence, EMA Public Assessment Report, 2019]. Safety data from the largest retrospective cohort study to date, of patients with WD in European tertiary care centres and patients recorded in the EuroWilson registry [Weiss KH et al, 2013] indicate that trientine is well tolerable, also in comparison to the first line treatment D-penicillamine. Other, smaller studies support this conclusion and many authors report that in the majority of patients where serious adverse reactions occurred with D-penicillamine therapy symptoms had improved or disappeared under trientine [e.g. Scheinberg et al, 1987]. The majority of significant events were gastrointestinal complaints and skin and musculoskeletal issues. One patient in the Weiss KH et al, 2013 study withdrew from trientine due to nephropathy, a rather unexpected event.

In the UNV-TRI-002 study, the mean applied doses/day (1005.7 mg TETA) were on the lower end of the proposed dose range for adults (1140 mg TETA) as well as paediatric patients (629.7 mg TETA) [Weiss KH et al, 2018; Weiss KH et al, 2019]. The maximum doses as recommended in the product information (2400 mg TETA for adults and 1500 mg TETA for children) were hardly ever reached. One patient received 2100 mg TETA/day and 5 received 1800 mg TETA/day according to the information in the original dossier [Cufence, EMA Public Assessment Report, 2019]. All other patients were on lower doses throughout the study duration. Consequently, there are no safety data available from patients with high exposure and the safety profile at high doses cannot be assessed. Limited data from the literature indicate that some safety events could be dose-dependent [Cufence, EMA Public Assessment Report, 2019].

Children

The study on 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 [SmPC, Cufence 200 mg hard capsules].

Taylor et al (2009) retrospectively reviewed the medical records of children diagnosed with WD at a single European centre between 1981 and 2006 and who had converted from D-penicillamine to trientine [Taylor et al, 2009]. Trientine was discontinued in three of the 13 children due to allergic rash, low copper excretion (3.9 years after starting trientine), and one with possible compliance problems resulting in the requirement of a liver transplant.

Trientine was re-started (after 5.1 years of zinc monotherapy) in the patient who discontinued due to a rash when symptoms deteriorated during treatment with zinc, and was well tolerated.

Arnon et al (2007) retrospectively reviewed the medical records of children with WD evaluated and treated in a paediatric liver/liver transplant program [Arnon et al, 2007] The children did not show any significant adverse effects of treatment with trientine (n=10). One patient stopped trientine after 12 months due to elevated liver enzymes which was thought to be due to mild hepatic toxicity as a result of trientine therapy.

Sarles et al (2001) investigated the tolerance and efficacy in case-studies of 10 children with WD, nine of whom were prospectively treated with trientine [Sarles et al, 2001 - Cufence, EMA Public Assessment Report, 2019]. The authors report that four patients switched from trientine to D-penicillamine: two because of a high level of transaminases after 5.5 and six years of treatment; one for a secondary rise of transaminases after an uneventful pregnancy; and, one for personal reasons. One patient died following several months of an intentional break in treatment.

Manolaki et al (2009) reviewed medical records of patients who received a diagnosis of WD between 1983 and 2004 in a tertiary care unit in Greece [Manolaki et al, 2009 - Cufence, EMA Public Assessment Report, 2019]. The mean age (± standard deviation [SD]) at diagnosis was 9.27 ± 3.6 years (range, four months to 18 years), and the median age was nine years. In all, 54 patients initially received D-penicillamine; however, nine patients (16%) discontinued D-penicillamine because of adverse effects that occurred within the first 12 months of treatment (hepatotoxicity - five patients; neutropenia – two patients; and, nephrotoxicity – two patients). Of these, five patients continued treatment with trientine (250 to 750 mg/day), three with zinc, and one with a combination of trientine and zinc, with no significant adverse effects. Two patients discontinued treatment 15 and 12 years after diagnosis and had rapid deterioration of the disease.

Dhawan et al (2005) retrospectively reviewed the medical records of 74 children with WD treated at the Paediatric Liver Service, King's College Hospital between 1967 and 2000 [Dhawan et al, 2005]. In total, 57 patients were referred because of liver disease, and a further 17 were asymptomatic siblings diagnosed during family screening. Of the 49 symptomatic children treated with long-term chelation, 47 were alive up to 37 years after commencing treatment. Side effects attributable to D-penicillamine were observed in 18 patients, requiring dose reduction in six children, and conversion to trientine in 12 patients.

Adverse reactions to trientine, as presented in the SmPC for the reference product, Cufence 200 mg hard capsules, as well as in the SmPC for the proposed product, Trientine 200 mg hard capsules (Waymade Plc), are summarised in Table 7 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).

Table 7. Adverse effects observed during treatment with trientene hydrochloride [SmPC, Cufence 200 mg hard capsules]	
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: Neurologicaldeterioration	
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

2.5.5.3 Special Warnings and Precautions for use [SmPC, Cufence 200 mg hard capsules]

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

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 administered at a different time than trientine.

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.

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.

<u>Monitoring</u>

Patients receiving trientine 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.

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 100-150 µg/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 WD.

Like with all anti-copper agents, overtreatment carries the risk of copper deficiency, which is especially harmful for children and pregnant women 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.

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.

2.5.5.4 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients of the drug product [SmPC, Cufence 200 mg hard capsules].

2.5.5.5 Interactions

No interaction studies have been performed [SmPC, Cufence 200 mg hard capsules].

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. 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.

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 administered at a different time than trientine to prevent the formation of complexes.

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

2.5.5.6 Effect on fertility and use during pregnancy and lactation [SmPC, Cufence 200 mg hard capsules]

Fertility

It is not known whether trientine has an effect on human fertility.

Pregnancy

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

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 WD, risks associated with the stage of disease, the risk of those alternative treatments which are available and the possible effects of trientine.

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 2.5.5.3).

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.

2.5.5.7 Dependence and withdrawal

No such effects have been observed.

2.5.5.8 Effects on ability to drive and use machines

Trientine has no or negligible influence on the ability to drive and use machines [SmPC, Cufence 200 mg hard capsules].

2.5.5.9 Overdose

Experience with doses higher than the recommended therapeutic dose is limited. In the event of overdose the patient should be observed, appropriate biochemical analysis performed and symptomatic treatment given. There is no antidote [SmPC, Cufence 200 mg hard capsules].

Occasional cases of trientine overdose have been reported. In cases up to 20 g of trientine base there were no apparent adverse effects reported. In a second case, a large overdose of trientine base (40 g) resulted in self-limiting dizziness and vomiting with no further clinical sequelae or significant biochemical abnormalities [SmPC, Cufence 200 mg hard capsules].

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 2.5.5.4).

2.5.5.10 Post-marketing surveillance

Periodic benefit-risk evaluation report/PSUR is available for the safety data received for trientine dihydrochloride by Univar Solutions BV from 01 April 2012 to 31 March 2015 inclusive [Cufence, EMA Public Assessment Report, 2019].

During this 3-year reporting period, Univar Solutions BV distributed 53,848 bottles of trientine dihydrochloride (300 mg capsules), each containing 100 capsules. Based on the assumption that patients take on average six capsules per day (recommended dose four to eight capsules daily) and that trientine is taken continuously, each patient would take 2,190 capsules per year. The number of patients can therefore be calculated by multiplying the number of bottles by 100 to obtain the number of capsules, and dividing by 2,190 (the estimated number of capsules taken in a year by a patient). Thus, the 53,848 bottles of trientine dihydrochloride (300 mg capsules) distributed during the 3-year reporting period equates to 820 patients with WD being treated. Of the 53,848 bottles, 45,108 bottles (84%) were exported and 8,740 bottles (16%) were distributed in the UK, equating to 686 and 133 patients with WD, respectively. Cumulative exposure information using the current method is only available from 2001 onwards. Until 2014, 117,825 bottles of trientine dihydrochloride capsules were distributed in total. The figures for the total number of bottles sold each year during the period 2001 to 2014 and the estimated patient exposure are shown in Table 8 [Cufence, EMA Public Assessment Report, 2019].

Table 8. Cumulative Patient Exposure to (2001 to 2014) [Cufence, EMA Public Assessment Report, 2019]

	Total	
	Bottles	**Patients**
2001	4,500	205
2002	4,800	219
2003	5,200	237
2004	5,600	256
2005	6,500	297
2006	5,400	247
2007	5,550	253
2008	5,750	263
2009	6,250	285
2010	6,927	316
2011	7,500	342
2012	16,669	761
2013	17,381	794
2014	19,798	904

The data indicated an overall increase of patients treated with trientine over time. The significant increase in the years 2011/2012 was not comprehensively explained. It was assumed that the number of WD patients throughout the world remains relatively stable. The data captured also supported that WD is a rare disease as the total number of treated WD patients (potential study population) is small. No additional information on patient characteristics (such as age, gender, etc.) or on use in special populations or the patterns of use was available [Cufence, EMA Public Assessment Report, 2019].

Collection of trientine AEs from the post-marketing setting was carefully reviewed for cases of hepatic toxicity and possible relation to trientine treatment was discussed. While a connection could not be fully excluded based on the available data, it was very difficult to allocate recorded toxicity to (i) either the disease or the lacking treatment compliance or (ii) to the treatment itself. The data situation was ambiguous and there was no clear indication that trientine causes hepatic toxicity. Therefore, hepatic reactions were not included as adverse drug reaction in the patient information. Liver enzymes are monitored regularly in WD patients and changes in hepatic status are recorded by treating physicians [Cufence, EMA Public Assessment Report, 2019].

2.5.6Benefits and Risks Conclusions

WD, also known as hepatolenticular degeneration, is a rare autosomal recessive disorder of copper metabolism caused by an autosomal recessive inheritance of ATP7B gene mutations. WD is characterised by defective incorporation of copper into ceruloplasmin leading to copper accumulation in the liver, brain and kidneys as well as decreased biliary copper excretion. The clinical manifestations of WD are predominantly hepatic, neurologic and psychiatric, with many patients having a combination of symptoms. Patients may present with a wide variety of symptoms (especially those with neurologic symptoms). The aim of therapy is reduction of the total amount of copper and treatment of copper overload/ accumulation in body tissues. Treatment is considered in two phases: (i) removing the tissue copper that has accumulated ('de-coppering phase') and (ii) preventing re-accumulation (maintenance phase), which is the goal of long-term treatment.

It is a progressive disease that is universally fatal if left untreated. For WD patients who develop acute liver failure, liver transplantation is the only option for survival. Survival rates of 59 - 76% at 5-10 years have been reported [Medici, Mirante et al, 2005 - Cufence, EMA Public Assessment Report, 2019], with poorer outcomes in patients with neuropsychiatric symptoms. Early diagnosis and treatment may prevent serious long-term disability and life-threatening complications.

Treatment of patients with WD encompasses drug therapy, diet management (i.e. alimentary copper restriction) and ultimately liver transplantation in patients who progress to liver failure. If untreated, the disease is fatal. Chelating agents such as D-penicillamine or trientine are the cornerstone of drug therapy in WD, recommended by both the American Association for the Study of Liver Diseases (AASLD) and European Association for Study of Liver (EASL). There are currently two approved copper chelating agents for the treatment of this disorder: D-penicillamine (DPA) and trientine. D-penicillamine is usually the first choice for patients with WD. However, about 20 to 30% of the WD patients using D-penicillamine will experience adverse reactions in the first 1–3 weeks of the treatment, which often result in discontinuation of treatment. Long-term use of D-penicillamine carries further risks of side effects. Trientine, which was introduced in 1969 as an alternative treatment, has been found to be better tolerated than D-penicillamine in patients with WD.

'Trientine 200 mg hard capsules', manufactured by Waymade Plc, UK, have been observed to be bioequivalent to Cufence 200 mg hard capsules, manufactured by Univar BV, The Netherlands, within the conventional limits for AUC. Hence, the Trientine 200 mg hard capsules (Waymade plc) can be expected to provide the same amount of clinical efficacy and safety as that of Cufence 200 mg hard capsules (Univar BV) in the treatment of WD in adults, adolescents and children aged 5 years or older who are intolerant to D-Penicillamine therapy.

The Applicant has conducted a bioequivalence study under fasting conditions in 46 healthy subjects. The study has been conducted with full compliance to GCP and using state-of-art and well-validated bioanalytical methods. Bioequivalence for $AUC_{0\text{-}inf}$ and C_{max} has been established for parental trientine drug and both of its metabolites with 90% confidence intervals being within the EMA recommended 80-125% criteria (please see tables 3, 4 and 5 in section 2.5.2.2 for individual PK values). As agreed during the Scientific Advice with MHRA, if the bioequivalence of the proposed trientine against the reference Cufence is convincingly established in the bioequivalence study, there is no expected impact or

differences in terms of bioavailability, efficacy and safety of the proposed product and scientific bridge to the published clinical efficacy and safety data with Cufence can be readily established. It is therefore appropriate to apply the content of the SmPC of Cufence to that of Waymade's trientine capsules.

Trientine has a linear pharmacokinetics. It has a well-defined pharmacokinetic and pharmacodynamic profile and causes a dose-proportionate excretion of copper in urine. Waymade's bioequivalence study has demonstrated convincingly bioequivalence of the proposed capsules versus reference Cufence. Additional parameters evaluated in serum and urine (copper, zinc, iron, ceruloplasmin and transferrin) showed similar pattern of changes between study groups. In addition to the results from the bioequivalence study, the published information presented in this application further support the safety and efficacy of trientine for the treatment of WD, when administered at the recommended dose of 800-1600 mg/day (4-8 capsules) in adults and 400-1000 mg/day in children aged 5 years and above in 2 to 4 divided doses daily.

The efficacy of trientine is maintained during long-term treatment through the reduction of the accumulated copper stores in symptomatic patients and maintenance of copper levels in patients with stable disease. Treatment effect can be routinely monitored in the WD patient population using copper storage and metabolism tests which are surrogate clinical efficacy markers.

Trientine has been in clinical use for more than 30 years and that, according to the literature, trientine causes fewer side effects than the first line treatment D-penicillamine and that D-penicillamine´s side effects mostly resolve during trientine treatment. Trientine has a well-established safety profile and a long history of use globally. Trientine is also recommended for use in WD in patients intolerant to D-Penicillamine by various international guidelines.

The benefit-risk profile of trientine is thus considered positive for the treatment of WD when administered according to the recommendations and precautions provided in the Product Information.

2.5.7 Literature References

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