29 May 2019
EMA/330602/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cufence

International non-proprietary name: trientine dihydrochloride

Procedure No. EMEA/H/C/004111/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under curve
AUC_{0-t}	Area under the plasma concentration-time curve from 0 hours to the last quantifiable concentration in the profile
AUC_{0-t}/D	Area under the plasma concentration-time curve from 0 hours to the last ^ quantifiable concentration in the profile normalised for dose
BMI	Body mass index
BP	Blood pressure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COMP	Committee for Orphan Medicinal Products
C_{max}	Maximum plasma drug concentration
CPGs	Clinical practice guidelines
CPN	Ceruloplasmin
CPP	Critical process parameter
CQA	Critical Quality Attribute
CRF	Case report form
CSR	Clinical study report
CTA	Clinical Trial Authorisation
Cu	Copper
CV	Coefficient of variation
CY	Cytochrome
DETA	Diethylene triamine
EASL	European Association for Study of Liver
EU	European Union
GC	Gas Chromatography
GCP	Good Clinical Practice

GGT	γ-glutamyltranspeptidase
HCl	Hydrochloric acid
HDPE	High Density Polyethylene
Hgb	Haemoglobin
IC	Ion chromatography
ICH	International Council for Harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
IR	Infrared
ITT	Intent to treat
LC-MS	Liquid chromatography mass spectrometry
LDPE	Low density polyethylene
MA	Marketing authorisation
MAA	Marketing Authorisation Application
max	Maximum
MEDA	Monoethylene diamine
MedDRA	Medical dictionary for regulatory activities
min	Minimum
MS	Mass Spectrometry
N	Number of patients in the treatment group analysis set
n	Number of patients in the specified category with non-missing values
NA	Not applicable
NaOH	Sodium Hydroxide
NAT2	N-acetyltransferase 2
NCC	Non-ceruloplasmin bound copper
NDA	New Drug Application
NMR	Nuclear Magnetic Resonance
PD	Pharmacodynamic
Ph. Eur.	European Pharmacopoeia
PI	Package insert
PK	Pharmacokinetic
PL	Product licence
Q1	First quartile
Q3	Third quartile

SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
SmPC	Summary of product characteristics
SOC	System organ class
TEAE	Treatment-emergent adverse event
TETA	Triethylenetetramine
TETA 2HCl	Triethylenetetramine dihydrochloride
USP	United States Pharmacopoeia
UV/Vis	Ultraviolet/Visible
WD	Wilson´s disease

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Univar BV submitted on 8 February 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Cufence, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 November 2014.

Cufence was designated as an orphan medicinal product EU/3/03/172 on 24 October 2003 in the following condition: treatment of Wilson's disease. Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 6 June 2019 on request of the sponsor. The relevant orphan designation withdrawal assessment report can be found under the 'Assessment history' tab on the Agency's website ema.europa.eu/en/medicines/human/EPAR/cufence.

The applicant applied for the following indication:

Cufence is indicated for the treatment of Wilson's disease in patients intolerant to D-Penicillamine therapy, in adults and children aged 5 - ≤17 years.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant indicated the active substance trientine dihydrochloride contained in the above medicinal product to be considered as a known active substance.

Protocol Assistance

The applicant received Protocol Assistance on 22 March 2007 (EMEA/H/SA/840/1/2006/PA/II), and 19 April 2012 (EMEA/H/SA/840/1/FU/1/2012/PA/III) for the development programme supporting the

indication granted by the CHMP. The Protocol Assistance pertained to the following non-clinical and clinical aspects:

- Concurrence that no additional non-clinical studies are necessary to support a marketing authorisation application (MAA), given the available non-clinical literature data and established long-term clinical experience.
- Adequacy of literature data on the pharmacokinetics and pharmacodynamics of trientine in Wilson's disease patients, and acceptance of not performing additional PK/PD studies in support of a MAA.
- Acceptance of a retrospective investigation of the efficacy and safety of trientine to support a MAA for a second-line indication (patients intolerant to D-penicillamine)

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Milena Stain Co-Rapporteur: Constantinos Markopoulos

The application was received by the EMA on	8 February 2018
The procedure started on	1 March 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	22 May 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	22 May 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	4 June 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 June 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	30 November 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	8 January 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 January 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	31 January 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 February 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	13 March 2019
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	26 March 2019
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the	28 March 2019

applicant on	
The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on	29 April 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	15 May 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Cufence on	29 May 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The Applicant applied for the following indication:

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

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, although copper is essential for cellular function, 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.

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.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Wilson disease is 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.

Information entered into the EuroWilson database between 2005 and 2008 indicated that the average yearly incidence of new cases in Europe per million population ranged from 0.11 in Sweden to 4.23 in Croatia (median of 0.60 [EuroWilson, 2011]). The apparent incidence is higher in central Europe (e.g., Poland, Austria, Croatia) than in Western European countries. In an epidemiological study, prevalence in France was estimated to be 1.5/100,000 (Poujois, 2016).

WD presents symptomatically at any age, with the majority between 5 and 35 years (EASL 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, Wilson disease is universally fatal. Copper accumulation in the liver eventually leads to the development of cirrhosis. Among patients with neurologic Wilson disease, 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.

Though data regarding life expectancy among untreated patients with Wilson disease are lacking, one study found that the median survival following the development of neurologic symptoms was approximately five years (Dening 1988). 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 2012).

2.1.3. Biologic features, Aetiology and pathogenesis

Wilson disease is due to a genetic abnormality inherited in an autosomal recessive manner that leads to impairment of cellular copper transport. It 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.

See also section 2.1.1.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

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).

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). 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.

Other manifestations of WD include an ophthalmological marker, namely the presence of Kayser–Fleischer rings, which are caused by deposition of copper in Descemets membrane of the cornea. These are present in 95% of patients with neurologic symptoms and over 50% of those without neurologic symptoms.

Diagnosis

According to EASL clinical practice guidelines in the European Union (EU) (EASL 2012), “for routine monitoring, serum copper and ceruloplasmine, 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)".

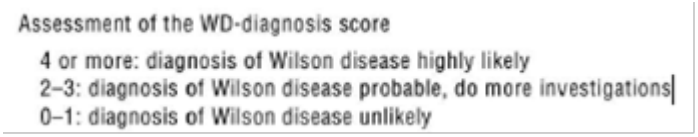
The diagnosis of Wilson's disease is based on a combination of clinical, biochemical, and genetic tests. Genetic testing is feasible but currently of limited use since many mutations occur; the majority of cases are compound heterozygotes and a sizeable proportion of definite cases have no detectable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

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, 2012). Therefore diagnosis of Wilson's disease is based on a combination of clinical, biochemical, and genetic tests. A scoring system, the 'Ferenci score' was developed at an international meeting in Leipzig (Ferenci 2003) for helping to determine the need to continue with diagnostic testing for Wilson disease and determine the certainty of diagnosis. This scoring system 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).

Table 9-2 Criteria for the Diagnosis of Wilson Disease – Ferenci Score

Liver Copper (in absence of cholestasis)		**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
Source: Ferenci, 2003



Untreated WD is universally fatal. 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). The prognosis for patients who receive and are adherent to treatment for Wilson disease 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).

2.1.5. Management

Wilson's disease is a rare condition for which there are limited treatment choices available. If left untreated, it is a fatal condition.

Treatment of patients with Wilson's disease 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.

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). Wilson's disease 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.

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 2012; D-penicillamine SmPC 2014) 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. According to EASL clinical practice guidelines and many other literature references, trientine may be better tolerated than D-penicillamine.

The trientine salt TETA 2HCl was introduced in 1969 as a copper chelator alternative to D-penicillamine (Walshe 1969). 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). In 2017, Cuprior (trientine as TETA 4HCl) was approved as second line treatment in WD for patients aged 5 years and older in the EU via the centralised procedure.

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 Wilson's disease since 2004 (Wilzin, MAH: Orphan Europe S.A.R.L.).

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.

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), 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); however its use as a primary treatment is not recommended (Roberts and Schilsky 2008).

About the product

Cufence contains the active substance trientine dihydrochloride (TETA 2HCl) and is presented as 300-mg hard capsules equivalent to 200 mg trientine base.

The proposed dosing regimen is 2-8 capsules of Cufence, administered 2 to 4 times a day in adults and 1-4 capsules administered 1 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 '*Cufence is indicated for the treatment of Wilson's disease in patients intolerant to D-penicillamine therapy, in adults, adolescents and children aged 5 years 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).

Type of Application and aspects on development

This marketing authorisation application (MAA) for Cufence 300 mg tablets is in accordance to Article 8(3) of the Directive 2001/83/EC as amended, a "Full-mixed Marketing Authorisation" application. Thus, this MAA relies on studies conducted by the Applicant with trientine dihydrochloride and on relevant bibliographic references to support non-clinical and clinical aspects.

There is no specific CHMP guidance for studies in Wilson's disease.

The Applicant obtained CHMP protocol assistance in 2007 and 2012, where CHMP stated that a retrospective study and review of clinical experience together with PK and PK/PD data may be sufficient for a second-line indication. In a clarification letter issued 2012, the CHMP recommended the following:

- *PK/PD data in special populations, especially in children, will be required. There are currently no PK or PD data in children to support the proposed dose. Thus, regarding the planned studies in children, PD data should be collected in addition to any PK data. Regarding the planned PK studies in adults, it is also strongly recommended to include PD assessments.*

A PK study was conducted in 16 adults and 4 children ⩾12 years, but no meaningful PD parameters were evaluated. Study TR-001 PK reveals shortcomings in trial design and conduct affecting the interpretation of the results.

- *The Applicant should develop lower capsule strengths for use in children and for purposes of dose titration when initiating treatment.*

This request was not followed by the Applicant.

- *In vitro studies to assess the potential of trientine to inhibit and induce CYP450 isoenzymes will be required. In addition, in vitro studies to exclude a significant involvement of CYP450 isoenzymes in the metabolism of trientine are strongly recommended.*

Respective non-clinical tests were conducted.

- *It is recommended that the Applicant evaluate the effect of food and zinc on trientine absorption.*

The effect of food and zinc on trientine/Cufence absorption was not fully investigated in this application.

- *Additional studies to investigate relationships between dose/titration schemes and serum copper/urinary copper excretion levels in patients may provide further useful information. This would be valuable to support appropriate dosing recommendations, such as for patients with neurological symptoms.*

The relationship between dose, plasma concentration and clinical effect of Cufence was not

comprehensively investigated.

Deficiencies observed in the non-clinical data as previously pointed out in the CHMP comments would be expected to be addressed at the time of MAA, for either first or second line indication.

The applicant conducted own studies and provided relevant bibliographic references to support both nonclinical aspects.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as white opaque size 0 gelatine capsules, containing 300 mg of trientine dihydrochloride equivalent to 200 mg of trientine base as active substance.

Other ingredients are capsule content: magnesium stearate, colloidal anhydrous silica; capsule shell: gelatine, titanium dioxide (E171); printing ink: shellac glaze, titanium dioxide (E171), iron oxide black (E172), propylene glycol, iron oxide yellow (E172).

The product is available in amber glass bottle with a polypropylene cap and induction heat seal liner with a sachet of dried silica gel as desiccant.

2.2.2. Active Substance

General information

The chemical name of trientine dihydrochloride is triethylenetetramine dihydrochloride (TETA 2HCl) corresponding to the molecular formula $C_6H_{18}N_4.2HCl$. It has a relative molecular mass of 219.20 g/mol and the following structure:

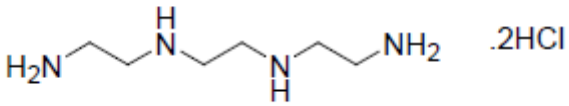


Figure 1: Active substance structure

The active substance is a white to pale yellow crystalline hygroscopic powder, freely soluble in water and dilute acid and alkali, soluble in methanol, slightly soluble in ethanol, insoluble in chloroform, ether.

The chemical structure of trientine dihydrochloride was elucidated by a combination of ^{13}C and ^{1}H-NMR spectroscopy, elemental analysis, IR spectroscopy and MS analysis together with characteristic chemical reactions and x-ray crystallography. There are no chiral centres in the molecule.

Trientine dihydrochloride is known to exhibit polymorphism. Three crystalline forms of trientine dihydrochloride have been identified in the literature, two anhydrous forms, Form I and Form II, which are both monoclinic, and a dihydrate. Form I and the hydrate form appear to exist in equilibria, with an increase in relative humidity increasing the dihydrate form, and an increase in temperature resulting in an equilibrium shift in favour of the anhydrate. The applicant showed that this polymorph form (Form I) is manufactured and stable over the proposed retest period.

Manufacture, characterisation and process controls

Trientine dihydrochloride is synthesized in in a three-stage process (purification, salt formation and recrystallization) using commercially available well defined starting materials with acceptable specifications. A detailed description of the manufacturing process and a flow scheme have been provided.

The starting material, triethylene tetramine (TETA), is acceptable in line with ICH Q11 and Q&A on Q11 as commercially available chemicals can be considered to be acceptable as starting materials without further justification. This is applicable for TETA, as it is well known that it is a commodity used also in non-pharmaceutical market. Schematic details, including catalysts or other materials used, of both suppliers have been provided.

The description of the simple manufacturing process of TETA 2HCl from the starting material TETA was considered acceptable. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The manufacturing process is well established and was developed over 30 years ago. More recently, an evaluation of critical quality attributes (CQAs) and critical process parameters (CPPs) were performed based on the definitions provided in ICH Q11. CPPs have been identified and controls are in place to ensure that CQAs meet the required standard.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in high-density polyethylene (HDPE) drums, collecting into double low-density polyethylene (LDPE) liners which comply with the Ph. Eur. chapter 3.1.4 and EC directive EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance (visual), clarity of solution in water (Ph. Eur.), solubility, identification (IR, chemical), melting point (Ph. Eur.), pH (Ph. Eur.), assay (titrimetry), hydrogen chloride content, loss on drying (USP), sulfated ash (Ph. Eur.), elemental impurities (ICP-MS), purity (GC), impurities (GC), related substances (IC), residual solvents (GC, GC-MS), a starting material process impurity(LC-MS), particle size distribution (Ph. Eur.) and microbiological purity (Ph. Eur.).

The maximum daily dose of trientine is 1600 mg. The corresponding reporting (RT), identification (IT) and qualification (QT) thresholds defined in ICH Q3A are RT: 0.05%, IT and QT: 0.06%. The impurities are specified according to ICH Q3A. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies. The limit for “other individual impurities” is also set to the identification limit (0.06%). Elemental impurities are controlled in line with ICH Q3D Guideline for Elemental Impurities.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from a significant number of historical batches (including 22 within the proposed commercial production scale range) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three production scale batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 18 months under long term (5°C ± 3°C) and intermediate (25°C ± 2°C 60% RH ± 5% RH) conditions and for up to 6 months under accelerated conditions (40°C± 2°C/75% RH ± 5% RH), according to the ICH guidelines, were provided. The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating. Additional supportive stability data was provided from five historic batches (3x2005, 2009, 2014) which were tested to previous, more limited, specifications and supplemented by testing of retained samples. All tested parameters were within the specifications.

Photostability testing following the ICH guideline Q1B was performed on one batch. No differences in the impurity profiles were observed between the samples that were exposed and the samples that were not exposed to light. Results showed that the active substance is not sensitive to light.

Results from forced degradation studies performed on samples under stress conditions (thermal, humid, acidic pH, alkaline pH, oxidising) and analysed using the GC, LC-MS and IC impurity analytical methods were provided. Some increases in impurities were observed. The results demonstrated the active substance susceptibility to heat degradation and the stability indicating nature of the analytical methods.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 24 months.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Cufence finished product is presented as white opaque size 0 gelatine capsules, containing 300 mg of trientine dihydrochloride equivalent to 200 mg of trientine base, for oral administration.

The capsules are imprinted with “Cufence 200” in grey ink and are packed in quantities of 100 in 175 ml amber wide-necked glass bottles (Type III), fitted with a white polypropylene cap with a heat induction foil inner-seal. A sachet of dried silica gel is included in the bottle.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, where applicable. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report. The influence of functionally related characteristics of excipients has been assessed in sufficient detail.

This product (with the same formulation and method of manufacture) was granted a marketing authorization in the UK in 1985. The formulation development has been adequately described. A risk assessment of the manufacturing process was performed and critical parameters were investigated. The discriminatory power of the dissolution method has been demonstrated.

Proposed bulk holding times have been investigated. The primary packing material for bulk capsules conform to Ph.Eur. standards. The Applicant is performing a hold time study on recent batches to confirm the holding times.

The primary packaging for the finished is amber wide-necked glass bottles (Type III), fitted with a white polypropylene cap with a heat induction foil inner-seal. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. Compliance of containers used for storage and transport of the bulk product to relevant guidance has been shown.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: blending, sieving, blending, encapsulation and packaging. The process is considered to be a standard manufacturing process.

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form; appearance (visual), loss on drying (gravimetric), identification (IR), assay (UV/Vis), dissolution (Ph. Eur.), pH of 1% solution (Ph. Eur.), uniformity of dosage units (Ph. Eur.), degradation products (LC-MS, IC) and microbiological purity (Ph. Eur.).

The finished product is released on the market based on the release specifications, through traditional final product release testing. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Impurity limits have been set in line with the ICH Q3B guideline.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Elemental impurities are controlled in the active substance specification. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results from four batches produced in 2012 and 2013 and four full scale batches produced in 2017 are presented. All parameters are in compliance to the specification current at the time of production. The results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three production scale batches of finished product (manufactured in 2017) stored for up to 18 months under long term (5°C ± 3°C) and intermediate (25 ºC / 60% RH± 5% RH) conditions and for up to 6 months under accelerated conditions (40°C± 2°C/75% RH ± 5%) according to the ICH guidelines were provided. The batches of Cufence are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested in line with the proposed shelf life specifications for appearance, loss on drying, assay, dissolution, pH of aqueous solution, related substances / degradation products, microbiological purity. The analytical procedures used are stability indicating. No significant changes have been observed.

Additional supportive stability data from studies of three production scale batches of finished product (manufactured in 2013) and stored up to 36 months at 2-8°C, were also provided. Samples were tested in line with the shelf life specifications in place at the time for appearance, disintegration, assay, HCl content, acidity/alkalinity of solution, loss on drying, related substances. The analytical procedures used were stability indicating. All tested parameters were mostly within set specifications, without any obvious

trends (loss on drying, content, HCl, disintegration and pH). Dissolution and related substances were either not tested or based on an old method. Additional testing of 39 months old samples revealed low levels of related substances, far below the specified levels.

Results from forced degradation studies are presented. The samples were exposed to the stress conditions (humidity, acid hydrolysis, base hydrolysis, oxidation and tested after one day (20-23 hours), three days and 14 days. A photostability study has not been conducted, because photostability testing on the active substance demonstrated that the active substance is not sensitive to light. Only one degradation product was identified using LC-MS. The degradant levels were increased under oxidising and thermal conditions. The IC method indicated an increase of a degradation product under thermal, acid and high humidity conditions.

Data from in-use stability studies confirmed the stability of the product up to 3 months at 2-8°C. An additional batch should be tested at the end of shelf-life, as committed by the Applicant, to confirm generated data.

Based on available stability data, the proposed shelf-life of 36 months when stored at 2-8°C in the proposed container closure system as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided. No other materials of animal and/or human origin are used either in the synthesis of the drug substance or in the manufacture of the drug product.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Trientine is a well-established active substance and was licensed in the United Kingdom (UK) in 1985. This full, mixed application is made to the European Medicines Agency in accordance with Article 8(3) of Directive 2001/83/EC, as amended. Thus, this MAA relies on studies conducted by the applicant and relevant bibliographic references to support both nonclinical and clinical aspects.

Protocol assistance was provided by EMA (EMEA/H/SA/840/1/2006/PA/II) in 2007 on the need to conduct new nonclinical studies for the purpose of MAA, and follow-up protocol assistance (EMEA/H/SA/840/1/FU/1/2012/PA/III) on the same aspect was sought in 2011.

In line with the EMA response the applicant conducted GLP compliant validation studies to assay PKs in rat and human sera, an in vitro CYP450 interaction study, a GLP-compliant AMES test in a single strain (w and w/o copper supplementation) with trientine dihydrochloride, a non-GLP compliant dose range finding study in pregnant rats, in silico evaluations of the genotoxic potential of the five main impurities using DEREK and Leadscope assays.

The majority of data provided for nonclinical assessment rely on literature. Search terms for literature search together with databases and publisher websites used as sources are provided with the dossier. Details on GLP concordance for published data cannot be provided, but the peer-reviewed nature provides at least a minimum level of scientific integrity.

The AMES test as well as validation of PK analysis were compliant with applicable GLP standards. The claim of GLP compliance is in accordance with the OECD Test Guidelines and Principles of GLP.

The absence of GLP compliance for the dose-range finding EFD study in rabbits is acceptable, facing that it was conducted according to the SOPs of the test facility (which are in accordance with OECD GLP regulations) and facing that this study is only one element for evaluating developmental risk.

It is recognized that *in silico* evaluations used for evaluation of genotoxic potential of impurities cannot be performed in GLP compliance, but it was confirmed that the report has been generated from output from the respective program versions.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The Applicant provides evidence from literature for non-clinical proof of concept in several animal models: LEC rat model mimics to some degree WD, with elevated hepatic copper levels, hepatitis and jaundice. Trientine is able to increase urinary excretion, reduce hepatic copper levels in LEC rats and showed a dose-related reduction in liver concentrations of copper in beagles. Results of trientine tested in other non-clinical models of WD (toxic-milk mouse, Atp7b knockout mouse, Labrador retriever) were not provided, but likely would not add value.

Secondary pharmacodynamic studies

Secondary pharmacodynamic effects published for trientine at the non-clinical level relate to anti-cancer activity, Alzheimer´s disease, diabetic kidney- and cardiovascular disease, together with a potential chelating effect of other divalent cations, i.e. zinc and iron, but also magnesium and calcium addressing aspects of potential pharmacodynamic drug interactions. Possible interaction with these ions and the separation of their administration is reflected in the SmPC. The Applicant clarified that the therapeutic potential of trientine in animal models of cancer, Alzheimer's disease, diabetes-induced kidney and cardiovascular disease, is – from a general perspective – most likely driven by its copper-chelating properties and not a consequence of off-target secondary effects.

Safety pharmacology programme

No formal safety pharmacology studies have been undertaken by the applicant. Neurological examinations, electrocardiography and blood pressure measurements were included in the repeated dose toxicity studies in dogs (Maemura et al, 1998). No treatment-related changes in blood pressure or

electrocardiogram measurements were observed. Neurological changes were observed at high dose levels, which recovered on cessation of treatment and were considered to be consistent with the effects of copper deficiency.

Regarding safety pharmacology, published evidence from repeated dose toxicity studies in dogs of 4- and 26-weeks duration indicates no safety concerns.

Pharmacodynamic drug interactions

Based on bibliographic data trientine has been shown to chelate iron and zinc in vitro. Iron deficiency is a recognised side effect of trientine treatment, and trientine has been shown to increase zinc excreted in the urine of patients. Therefore an interaction with iron and zinc, particularly if given at the same time, cannot be excluded. As patients treated with trientine may develop symptoms of iron deficiency, precautionary statements were included into the SmPC that iron supplementation may be needed and should be administered at a different time than trientine. The concomitant use with zinc is not recommended in the SmPC as interactions with trientine are likely. No pharmacodynamic drug interaction studies have been undertaken this was considered acceptable by the CHMP..

2.3.3. Pharmacokinetics

Oral bioavailability of trientine shows strong variability in the range of 5-25%, with relatively short half-life, as reported from literature. Autoradiographic data shows a maximum around 1 hour after administration, with high radioactivity mainly in the liver and kidney, with no evidence of retention in tissues after IV or oral administration. Plasma protein binding was confirmed to be low, with data generated by the Applicant (Study APT-REP-01).

Trientine is mainly absorbed by the plasma membrane of intestinal epithelial cells, with low contribution of tight junction permeation. Several non-clinical studies show that oral bioavailability is strongly impaired by food intake. In this regard, reference is made to the clinical assessment report.

The uptake characteristics by rat intestinal brush-border membrane vesicles indicate similarity to spermine and spermidine, as well as dose-dependent inhibition by these physiological polyamines; as such, their presence in the GI tract likely contributes to the high variability in oral bioavailability.

Toxicokinetic data derived from 4- and 26-week studies in dogs do not indicate accumulation or sex differences.

The Applicant´s own data are derived from TK analysis conducted in the frame of a dose-range finding embryo-foetal development study in pregnant female rats. Oral dosing results in plasma AUC0-t values increasing in a slightly greater than dose-proportional manner.

In vitro CYP450 interaction studies showed no inhibition of CYP450-mediated metabolism as tested in studies conducted by the Applicant with human liver microsomes and singly expressed human CYP450 isoforms. These results are consistent with literature-derived data showing metabolisation primarily via acetylation, a non-CYP450 mediated reaction.

The predominant metabolite in rat was N1-acetyltriethylenetetramine (MAT), which was also found in the urine of treated subjects, besides trientine, N1, N10-diacetyltriethylenetetramine (DAT) and three minor metabolites. SSAT2 (thialysine acetyltransferase) was shown to be the main metabolizing enzyme responsible for low oral bioavailability. The SmPC accordingly mentions under section 5.2 that "*Trientine is metabolised by acetylation via spermidine/spermine N-acetyltransferase and not via N acetyltransferase 2.*"

Urinary excretion presents the central route of excretion for trientine, mainly as acetylated metabolites (MAT and DAT). Comparison of urinary excretion in intact animals after intravenous and oral dosing and in bile duct-cannulated rats dosed orally suggests that at least 40% of the trientine dose is absorbed after oral administration.

There is no interaction between trientine and the substrate of the H^+/organic cation antiporter or aminoglycoside antibiotics. A specific transport system (Na^+/spermine antiporter on the renal brush-border membrane) is responsible for renal excretion of trientine (but does not recognize the trientine-copper complex). Drugs that change the concentration of sodium ions in renal proximal tubules, such as diuretics, can increase the trientine excretion since the increase in the luminal concentration of sodium ions accelerates the Na^+/spermine antiporter. The low protein binding properties of trientine make drug interactions as a consequence of displacement of trientine from plasma protein binding unlikely.

2.3.4. Toxicology

Single dose toxicity

Based on submitted literature trientine is considered to have moderate acute toxicity after oral administration (LD_{50} rat > 2000 mg/kg bw) and moderate toxicity after dermal application (LD_{50} rabbit 550-805 mg/kg bw). No formal single dose studies have been conducted by the applicant this was considered acceptable by the CHMP.

Repeat dose toxicity

The NOAEL of trientine following oral administration for 26 weeks in rats was considered to be 50 mg/kg/day for females and less than 50 mg/kg/day for males, without measuring systemic exposure. NOAEL in dogs was established to be 50 mg/kg/day in a 26 week (oral administration) study, associated with a mean Cmax and AUC of approximately 22 µg/mL and 73 µg.h/mL, respectively – presenting an adequate margin of exposure.

Main toxicological findings are consistent across different species and manifested in reduced body weight gain, altered urinary electrolytes, low plasma copper levels (except mice), liver findings and various histopathological changes in the lungs (mainly interstitial pneumonitis). Exclusively the latter observations were not reversible, and are of doubtful importance, as those were also seen in the control animals. In dogs, ataxia, tremors, abnormal gait and underactivity were observed following administration of very high levels of trientine.

Genotoxicity

The OECD SIDS triethylenetetramine 2002 classifies the genotoxic profile of trientine as low priority/concern. Trientine shows mutagenicity in bacterial cells with and without S9 fraction in a broad range of bacterial strains, which could indicate that this is not caused solely by oxidative stress (triggered as a consequence of copper depletion). Supplementation with $CuCl_2$ showed reduction or elimination of mutagenic effects, but is confounded by the bactericidal effects of copper. Oxidative stress also has an impact on tests in cultured mammalian cells, where contradictory results were observed with trientine. Published results of mouse micronucleus tests after oral or intra-peritoneal administration examining the bone marrow or peripheral blood were negative, but had some deficiencies in the protocol. According to Option 2 of ICH S2(R1) a second in vivo assay would be required, but any outcome would need to be discussed against the confounding issue of oxidative stress caused by copper depletion. However, as it is

evident that the copper chelating property of trientine reduces the oxidative stress associated with the disease such study can be waived.

Carcinogenicity

Only dermal, but no oral carcinogenicity studies with trientine in rodents are reported. Standard 2-year rodent bioassays in healthy rodents would anyhow have limited impact on the overall carcinogenicity risk assessment, based on confounding primary pharmacology of the compound. Importantly, LEC rats showed reduced levels of single strand breaks after treatment with trientine, indicating a reduction of endogenous DNA damage in a WD model. Thus it can be agreed, that separate carcinogenicity studies are not needed for trientine.

Reproduction Toxicity

No teratogenic effects were observed in rabbits, while rats showed foetal abnormalities in the high dose group, significantly reduced after copper supplementation. In a dose-range finding study in pregnant rats conducted by the Applicant at lower doses, despite a dose dependent reduction in serum copper levels, there was no evidence of teratogenicity and the NOAEL was considered to be 750 mg/kg/day. Nevertheless, there was evidence of an early effect of treatment on embryo survival, which is not surprising as the impact of copper deficiency on the developing foetus is well established: different newborn copper-deficient species show similar abnormalities as known with swayback (enzootic ataxia) in lambs. Positive teratogenicity signals observed after prenatal exposure of mice, for instance, still leave it open if this represents an intrinsic property of the compound or a consequence of copper deficiency. Published experience with the use of trientine in pregnant women does not indicate major birth defects - but is too limited to make final conclusions. But clear evidence is given for the increased clinical risk of spontaneous abortions in untreated WD.

Trientine is also intended for treatment of children, but no juvenile toxicity studies were performed or results of PPND studies are available – which is acceptable from a non-clinical perspective.

Impurities identified for trientine have been sufficiently qualified through DEREK and LEADSCOPE analysis.

No fertility data are available but oestrous cyclicity was unaffected and reproductive organs were not identified as target organs in general repeat dose toxicity studies; hence, the absence of data on fertility is acceptable.

Toxicokinetic data

Please refer to chapter 2.3.3.

Local Tolerance

No data were presented. However according to OECD SIDS triethylenetetramine 2002 exposition to saturated vapour was tolerated without impairment whereas the exposition to aerosol leads to reversible irritations of the mucous membranes in the respiratory tract. The aspect of irritation is appropriately mentioned in the SmPC under 5.3. The same document reports that triethylene tetramine induces skin sensitization in guinea pigs, mice and man. This information is adequately reflected in the SmPC.

Other toxicity studies

Immunotoxicity is not anticipated with trientine. The predominant metabolites of trientine are the acetylated metabolites MAT and DAT. They are discussed and assessed in the PK section of this report with data provided from literature. This is considered adequate for this application.

2.3.5. Ecotoxicity / environmental risk assessment

Persistence, bioaccumulation and toxicity assessment is based on data from OECD SIDS publication for triethylene tetramine on the octanol/water partition coefficient, concluding that no bioaccumulation is expected. This seems justified, also recognizing the chemistry of the compound.

Referring to the respective guideline (EMEA/CHMP/SWP/4447/00 corr 21*), the highest recommended dose (and not the mean daily dose of 670 mg trientine base) should be used to calculate the predicted environmental concentration PEC surfacewater, which then (applying 1600 mg according to SmPC based on trientine base) would equate to a refined value of 0.0144 µg/L. Additional data in order to refine the Fpen were provided by the Applicant. Due to a reprocessed correction factor for Fpen, based on a prevalence estimation by Orphanet published in June 2018, and considering more recent annual prevalence data from France (Poujois *et al.*, 2017 replacing older data referred by Rodriguez-Castro *et al.*, 2015), a new $PEC_{surfacewater}$ of 0.0037 µg/L was calculated, clearly below the action limit of 0.01 µg/L.

The requirements for not conducting a Phase II environmental fate study with the drug substance are thus met.

Summary of main study results

Substance (INN / Invented Name): Trientine dihydrochloride			
CAS-number (if available): 38260-01-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	calculated	Log Kow=-1.4	Potential PBT No
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined (e.g. prevalence, literature)	0.006	µg/L	< 0.01 threshold No

2.3.6. Discussion on non-clinical aspects

Trientine is able to increase urinary copper excretion and reduce hepatic copper levels in the LEC rat, a model mimicking to some degree WD in humans. The compound also showed a dose-related reduction in liver copper concentrations in Beagles.

Secondary pharmacodynamic effects are basically explained by the chelating effect of trientine for divalent cations. Thus, besides copper, zinc, iron, magnesium and calcium are considered, also concerning potential pharmacodynamic drug interactions.

Safety pharmacology is covered by published results from repeated dose toxicity studies in dogs of 4- and 26- weeks study duration, indicating no safety concerns.

Non-clinical PK after oral administration shows highly variable (5-25%) bioavailability, relatively short half-life (maximum at around 1 hour post administration), no indication for retention in tissues and low plasma protein binding. Several non-clinical studies consistently show that oral bioavailability is impaired by food intake.

The applicant conducted TK analysis in the frame of a dose-range finding embryo-foetal development study in pregnant female rats, largely supporting conclusions derived from published data.

The absence of CYP450-mediated metabolism was confirmed by studies conducted by the Applicant.

Literature data provides sufficient evidence that there is no interaction between trientine and the substrate of the H^+/organic cation antiporter or aminoglycoside antibiotics. The Na^+/spermine antiporter on the renal brush-border membrane is responsible for renal excretion of trientine, but does not recognize the trientine-copper complex. The low protein binding nature of trientine makes a drug interaction as a consequence of displacement of trientine from plasma protein binding unlikely.

The NOAEL of orally administered trientine (derived from 26-week studies from literature) was established at 50 mg/kg/day for dogs and female rats, and less than 50 mg/kg/day for male rats. The main toxicological findings were consistent across different species with reduced body weight gain, altered urinary electrolytes, low plasma copper levels (except in mice), liver findings and various histopathological changes in the lungs.

Mutagenicity for trientine was shown in bacterial cells with and without S9 fraction; it was reduced after supplementation with $CuCl_2$, but also confounded by the bactericidal effects of copper. A mouse micronucleus test showed negative results. The Applicant did not conduct a second in vivo assay (in line with Option 2 of ICH S2(R1) as any result would be confounded by increased oxidative stress as a consequence of copper depletion (as published, for instance, for cattle showing increased chromosomal aberrations and comet induction as a consequence of copper depletion). This primary PD effect of copper depletion would also have an impact on standard 2-year rodent carcinogenicity studies, as such agreed to be not relevant for this MAA. Importantly, in LEC rats as a model for WD, reduced levels of endogenous DNA damage (single strand breaks) were shown for trientine.

Copper deficiency presents also a well-known teratogenic mechanism in animals (i.e. enzootic ataxia in lambs), and is also suspected causative for the positive teratogenicity signals in mice – while other effects of trientine on organogenesis cannot be completely excluded.

Absence of genotoxic risk was shown for impurities identified for trientine and qualified through QSAR analysis.

In regard of the ERA, the requirements for not conducting a Phase II environmental fate study with the drug substance were met and further ERA-studies are not needed.

2.3.7. Conclusion on the non-clinical aspects

The review of non-clinical data available for trientine indicates no issues for concern.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

- Tabular overview of clinical studies

Type of Study	Study #	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treat-ment
Pharmaco-kinetics (PK) profiling study	TR-001 PK	To evaluate the PK of a single dose of trientine 2HCL in children ≥ 6 years and adult patients with Wilson's disease by PK analysis. To evaluate the tolerability and safety of a single dose of trientine 2HCL	Open, single-dose, single-centre study	Trientine 2HCL 300 mg capsules; Dosing as per patient's prescribed daily dose; Oral, preferably in the morning about 30 minutes before the first meal.	20 patients planned; 20 patients analysed & included in PK analysis.	Wilson's Disease patients	single dose study
Observational	UNV-TRI-00 2	To assess the clinical course of copper stores, neurological disease, and hepatic disease following initiation of treatment with trientine following withdrawal of D-penicillamine. To assess safety based on reported adverse events (AEs), including AEs leading to discontinuation of trientine. To determine duration of treatment with second line therapy trientine, defined as time to discontinuation of treatment due to AEs and/or inadequate response.	Retrospectiv e part – historical review of medical records	Trientine 2HCL 300 mg capsules; Dosing as per patient's prescribed daily dose; Oral	Approx. 90 planned; 77 included in ITT analysis	Wilson's Disease patients	≥ 6 months as 2nd line treatment after receiving D-penicill-amine

2.4.2. Pharmacokinetics

Little is known about the pharmacokinetics of trientine. While some PK data exist for trientine in healthy volunteers, mainly from two publications (Cho et al. 2009; Lu et al. 2010a), there are only limited data available on trientine PK in WD patients, obtained from two small studies (Miyazaki et al., 1990; Tanabe 1996a).

As the relevant literature data is scant, the CHMP (EMA protocol assistance obtained in 2007 and 2012) recommended that the Applicant conduct a pharmacokinetic (PK)/pharmacodynamic (PD) study to support the Cufence dossier. Collection of additional PK data in special populations and especially in children was highly recommended.

The Applicant conducted a Phase I PK profiling study (Study TR-001 PK) in adult and paediatric WD patients treated with trientine dihydrochloride. The study medication is commercially available in the UK for the treatment of Wilson's disease in patients intolerant of D-penicillamine therapy.

Study TR-001 PK

The objectives of this Phase I, open-label and single-centre study were to evaluate the PK of a single dose application of trientine in children ≥ 6 years and adult patients with WD whilst also evaluating the safety and tolerability of a single dose of trientine.

According to the clinical study report, the single dose of trientine administered in the study was the dose routinely taken by the individual patient. Since all patients had been on treatment with trientine dihydrochloride prior to the study, they were assumed to be in steady state. The study was initiated 04 June 2013 (first patient enrolled) and completed (last patient completed) 06 March 2014.

The batch of trientine dihydrochloride (batch number 005428) used in the PK study was manufactured by a previous manufacturer of Univar´s trientine capsules.

Blood samples were taken from all subjects pre-dose and at 10 time-points (at 30 min, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours) post-dose to investigate the PK profile of trientine up to 12 hours post-dose.

20 patients (9 males and 11 females) were planned and finally included in the study; 4 of them were children aged 12 - 16 years and 16 were adults aged 19 - 61 years. All 20 patients completed the study and included in the analyses of PK variables and safety.

Study conduct

No inclusion or exclusion criteria were violated and no patients were excluded from either the safety or the PK analyses.

Prior and concomitant medications were reported: 18 (90%) out of the 20 patients were treated with D-penicillamine or similar agents prior to treatment with trientine (thus compiling the target population). The time lag between D-penicillamine discontinuation and trientine initiation is not known for the individual patient; all enrolled patients have been treated with trientine for several months or several years. 14 patients (70%) patients reported intake of concomitant medication other than trientine.

Results

Trientine absorption was found to be low and variable in WD patients, with t_{max} occurring between approx. 0.5 and 4 hours post-dose. These values are similar to those published for healthy volunteers and WD patients. Trientine exposure was highly variable between subjects, as also reported in the literature. The plasma elimination $t_{1/2}$ of trientine was rather short (approx. 3.6 h in median) and comparable to that reported for healthy subjects.

Study TR-001 PK exhibits several major deficiencies and inconsistencies with regard to the planning, conduct and reporting of the study:

- Timing of last trientine dose:

Information on when patients received their last trientine dose before the start of the PK study is not available, as patients were not instructed to record their last trientine intake before study initiation. The possible influence of different administration time points on study outcomes was not discussed by the Applicant, but seems very likely. The high variability in pre-dose levels of trientine could have resulted from these variances.

- Dose regimen:

Originally, only sparse information was provided in the study report about the usual dose regimen for each patient. According to Pfeiffenberger et al. 2018, who published the results from PK study TR-001 PK: *'Twenty patients with Wilson disease were enrolled in the study. Patients had a confirmed diagnosis of Wilson disease and were receiving a stable regimen of twice daily trientine, as well as their other*

prescribed medication.' Based on the information in the study report and the publication, it was assumed that all 20 WD patients were on a twice-daily dosing regimen. It was later clarified by the Applicant that this was the case for only 11 out of the 20 patients; the other patients received trientine either three times daily (n=5), four times daily 3 (n=3) or once daily (n=1). Hence, the 20 patients were in fact on four different dosing regimens.

Calculation of the steady state:

The Applicant states that for the calculation of the steady state as described in study report TR-001PK a twice-daily dosing regimen and a 12-hour time interval from the last trientine dose before the PK study was assumed. However, as these assumptions do not obviously correspond to the facts and the respective conclusions are rejected.

- Origin/sourcing of trientine:

All 20 patients took Univar´s Trientine capsules prior to study initiation, however it remains unclear if they were manufactured by the previous manufacturer of Univar's trientine capsules or Aesica (both products significantly differ with regard to their dissolution characteristics). As there was no wash out period, differences between the products could have further influenced trientine concentrations measured in the studies and contributed to the variable pre-dose levels of trientine.

- Food administration:

The patients received no standardized meals nor were there any explicit restrictions with respect to food intake during the study. Hence, food as a root cause for the observed high variability of PK results cannot be excluded.

The Applicant has also not discussed possible influences of concomitant medications on the PK results.

- Additional data – *in vitro* Dissolution

The batch of trientine dihydrochloride used in the PK study (batch #005428) was manufactured by the previous manufacturer of Univar´s trientine capsules. Since September 2013, Cufence capsules have been manufactured by Aesica. Relevant differences in the manufacturing process (the qualitative and quantitative composition of the Univar capsules remained the same) and in the *in vitro* dissolution behavior between the batches of the previous manufacturer and the batches of Aesica were observed. The batches made by Aesica exhibit a much slower dissolution (mean ± SD 61.47±5.12 % after 45 minutes) than the batches of the previous manufacturer (mean ± SD: 97.25±7.91 % after 45 minutes).

In the Applicant´s point of view, *in vitro* dissolution is not considered a critical factor for the pharmacokinetics of trientine. The Applicant states that "*the physicochemical properties of trientine, whilst being responsible for the very tight binding of copper making this an effective treatment for Wilson's disease, are also responsible for the mechanism of absorption and extensive metabolism resulting in low and variable bioavailability. With this being inevitably linked to the chemical structure, the additional impact of slightly less than optimal dissolution for an immediate release product is unlikely to have any meaningful impact on bioavailability or on clinical safety and efficacy*".

Taking what is known about trientine pharmacology into account, there is reason to assume that the formulation of the product can have significant influence on the exposure. From the EPAR of the centrally approved trientine product, 'Cuprior' (published 03/10/2017), it is evident that markedly faster *in vitro* dissolution resulted in a much higher exposure.

The impact of the formulation changes on the reliability of the PK results is unknown and applicability of the results of the PK study for the Aesica product is thus questioned. No reliable bridging between the two formulations can be made. The Applicant subsequently identified the root cause for the slow dissolution of the Aesica product and developed a new rapidly dissolving formulation (intended for future submission).

Keeping this in mind, and also in light of the deficiencies of study TR-001 PK described above and its limited value, no further questions on the applicability of the TR-001 PK results for either the Aesica product were raised.

Absorption of trientine following oral administration is known to be low (8-30%, according to Lu et al. 2010a) and potentially influenced by intake of food or certain liquids containing binding partners/metal ions. There is a certain risk of inactivation of the drug by metal binding in the gastrointestinal tract. Prolonged dissolution times increase the potential for local interactions in the upper digestive tract and consequently could influence trientine absorption. However these potential interactions with zinc, other anti-copper agents or metal ions as well as food are adequately addressed in the product information.

Absorption

- **Bioavailability**
    - *Study TR-001 PK*

Trientine plasma concentrations by time point and patient are presented in Figure 2 (linear concentration scale).

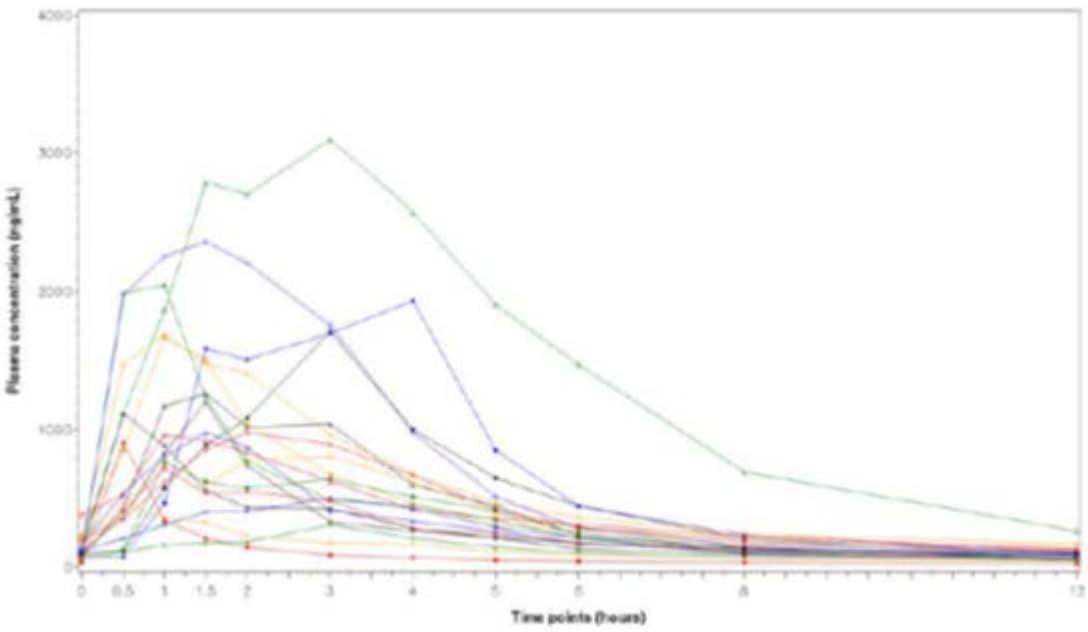


Figure 2 Plasma concentration per time point*.

The descriptive statistics for individual trientine PK parameters are summarised in Table 1 .

Table 1 Pharmacokinetic analysis: PK endpoints descriptive summary – PK population.

Trientine PK Parameter	Trientine Dihydrochloride [N=20]
C_{max} (ng/mL)	
Available Observations	20
Mean	1274.9
SD	707.27
CV (%)	55.5
Median	1050.5
Q1; Q3	781.5; 1700.0
Min; Max	309; 3100
T_{max} (h)	
Available Observations	20
Mean	1.738
SD	1.0600
CV (%)	61.0
Median	1.490
Q1; Q3	1.000; 2.985
Min; Max	0.48; 4.08
$T_{1/2}$ (h)	
Available Observations	14
Mean	3.772
SD	1.2775
CV (%)	33.9
Median	3.640
Q1; Q3	2.790; 4.570
Min; Max	2.33; 6.99
AUC_{0-t} (ng/mL.h)	
Available Observations	20
Mean	5075.5
SD	3533.56
CV (%)	69.6
Median	4650.0
Q1; Q3	3025.0; 5815.0
Min; Max	1240; 17100
AUC_{0-inf} (ng/mL.h)	
Available Observations	14
Mean	5942.1
SD	4054.45
CV (%)	68.2
Median	5560.0
Q1; Q3	3390.0; 6620.0
Min; Max	1480; 18000
C_{max} Dose-normalised ([ng/mL]/[mg])	
Available Observations	20
Mean	1.937
SD	1.0801
CV (%)	55.8
Median	1.635
Q1; Q3	1.370; 2.035
Min; Max	0.84; 5.63

AUC_{0-t} Dose-normalised ([ng/mL.h]/[mg])	
Available Observations	20
Mean	7.624
SD	4.7302
CV (%)	62.0
Median	5.955
Q1; Q3	5.205; 7.975
Min; Max	2.06; 23.90

Data source: Table 14.2.1, Section 14

AUC_{0-inf} = area under the plasma concentration-time curve from 0 hours to infinity; AUC_{0-t} = ; area under the plasma concentration-time curve from 0 hours to the last quantifiable concentration in the profile; C_{max} = maximum plasma drug concentration; CV = coefficient of variation; h = hours; max = maximum; min = minutes; N = number of observations; PK = pharmacokinetic(s); Q1 = lower quartile; Q3 = upper quartile; SD = standard deviation; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to maximum plasma concentration

Levels of trientine pre-dose and post-dose and several PK parameters were assessed over a period of 12 hours and 12 hours was the assumed dosing interval for all patients. In Table 1 PK endpoints are summarized. It is noted that some parameters were reported only for 14 patients instead of 20 for unknown reasons.

According to the Applicant, levels of trientine in pre-dose samples were generally similar to those measured at 12 hours post-dose, thus confirming that PK parameters are representative of steady state.

Differences between pre-dose and 12 hours post-dose levels for trientine were observed in a number of subjects. Plasma levels were lower at 12 hours post dose in the larger share of patients (which could be comprehensible if the patient´s usual time between doses was < 12 hours), but also some patients with higher post-dose values compared to baseline are included.

Applicability of single dose PK results to picture steady state condition in study TR-001 PK

A bid dosing regimen with a 12 hour time interval was assumed for all included patients. A 12-hour time interval was also assumed between last trientine dose before the PK study and intake of study medication. However, in the course of the assessment it has emerged, that the 20 patients were in fact on four different dosing regimens (bid (N=11/20), tid (N=5/20), qid (N=3/20) or qd (N=1/20). Therefore, the 12- hour time point used for assessment of steady state may have impaired the correct assessment of the steady state, since last drug intake on the day preceding the PK assessments may have been more or less than 12 hours, especially for subjects using a different treatment schedule than bid. The actual intake time of the last dose before study conduct has not been recorded.

The Applicant provided a re-evaluation of the results taking into account the assumed actual dose regimen of individuals (this was not pre-specified in the study protocol).

Table 2 Overview of steady state concentrations per patient

Subject nr	Usual daily dose[1]	Dose used for PK	Dose regimen	Time point for comparison	Conc. at through (ng/mL)	Conc. at steady state (ng/mL)
	1800 mg	900 mg	900 mg bid	12 h	96.6	91.2
	1500 mg	900 mg	900 mg – 600 mg bid	12 h	76.6	98.8
	1800 mg	600 mg	600 mg tid	8 h	90.4	134
	1800 mg	900 mg	900 mg bid	12 h	230	78.4
	1800 mg	600 mg	600 mg tid	8 h	32.2	33.7
	1800 mg	900 mg	900 mg bid	12 h	69.7	70.1
	1200 mg	600 mg	600 mg bid	12 h	148	93.4
	1500 mg	1500 mg	1500 mg qd	(24 h)	98.1	[2]
	2100 mg	600 mg	600 mg - 600 mg -900 mg tid	8 h	186	203
	2400 mg	600 mg	600 mg qid	6 h	385	310
	1800 mg	600 mg	600 mg tid	8 h	117	133
	2400 mg	600 mg	600 mg qid	6 h	120	214
	1500 mg	900 mg	900 mg – 600 mg bid	12 h	81.4	72.1
	900 mg	300 mg	300 mg tid	8 h	213	243
	1200 mg	600 mg	600 mg bid	12 h	82.7	57.0
	1200 mg	600 mg	600 mg bid	12 h	112	49.8
	1800 mg	600 mg	600 mg tid	8 h	87.6	155
	900 mg	300 mg	300 mg tid	8 h	54.1	73.2
	1200 mg	300 mg	300 mg qid	6 h	59.9	89.8
	1200 mg	600 mg	600 mg bid	12 h	193	122
				mean[3]	128.17	122.18

[1] according to listing 16.2.5 TR-001PK
[2] 24 h PK data not available, concentration at 12 h post dose was 263 ng/mL.

Results of this analysis indicate that the mean plasma concentration at the time-point for steady state assessment (122.18 ng/mL) is comparable to the mean pre-dose value (128.17 ng/mL), which would be expected in steady state conditions. Both, $C_{through}$ levels and the new 'concentration at steady state' levels seem to rather be values measured during the study TR-001 PK, than calculated variables (see table 14).

The baseline variabilities render comparisons of PK results between patients extremely difficult. The possible causes for the high variability of trientine exposure data are manifold and the most likely cause might not even be the high inter- and intra-patient variability of trientine PK per se; due to its poor design and absence of standardization during the study (see also discussion of the study above) the experiment was unlikely to suitably and sensitively evaluate possible inter- and intra- patient variability. This significantly hampers the interpretation of this data source as primary evidence for Cufence pharmacokinetics.

Overall, the design of Study TR-001 PK is not considered appropriate to robustly reveal or exclude any influences of demographic factors.

Bibliographical data

So far, only a few studies have been conducted investigating the PK of trientine in healthy volunteers as well as in patients. Thus, knowledge about the PK of trientine is rather limited and mainly based on the results of the two studies performed in

a) Healthy volunteers (Cho et al. 2009, Lu et al. 2010a)

Cho et al. (2009):

The population PK and pharmacodynamics (PD) of triethylenetetramine (TETA) dihydrochloride (trientine, GC811007) were determined in a prospective, randomized, double-blind, placebo-controlled, group-sequential, dose-escalating study in 40 healthy adult male and female volunteers (8 active subjects and 2 placebo subjects in each dose group). Trientine was administered orally as 100, 300, 600, or 1800 mg twice daily (daily doses of 200, 600, 1200 and 3600 mg) for 14 consecutive days. The PK profile, PD effects, PK/PD relationship, tolerability and safety of trientine was evaluated. Non-compartmental serum pharmacokinetic parameters were determined on Day 1 and Day 14, and the urinary excretion of copper was measured on Days 1, 7 and 14. The accumulation index is calculated as the AUC_{0-12} ratio for Day 14/Day 1. A two-compartment model was used for the PK analysis and a linear direct effect model for drug-induced copper excretion (PD). The population PK/PD model was applied using the NONMEM software. Covariates tested were glomerular filtration rate (GFR), body weight, and gender.

Results indicated that t_{max} was reached quickly (0.33-2 h after dosing) and there was subsequent bi-exponential decline in serum levels. Mean $T_{1/2}$ varied between days 1 (1.9 h), 7 (3.4 h) and 14 (5.1, 5.4, 10.4 and 14.2 h for the 200-, 600-, 1200- and 3600-mg daily doses, respectively).

Despite the longer half-life observed at higher doses there was no evidence of non-linearity of serum exposure over the dose range based on C_{max} or AUC. There was no notable accumulation of exposure upon repeated dosing. An increase in cupruresis occurred in all groups compared to baseline and placebo and was higher in the 0 to 12h interval compared to the 12 to 24-h interval suggesting a role of the circadian variation in the glomerular filtration rate (GFR) and of dietary intake. For the pooled trientine doses, cupruresis increased by 4- to 11- fold. The authors noticed a linear relationship between serum trientine concentrations and urine copper excretion rates.

The population PK absorption rate constant was estimated at 3.99 h^{-1} confirming that trientine is rapidly absorbed after a short lag time. Gender and body weight did not appear to influence any of the pharmacokinetic parameters. On the other hand, a sequential population PK/PD model which was developed with GFR, body weight and gender tested as covariates suggested that both GFR and gender may be helpful clinical covariates for individualizing trientine doses during chronic administration, although it was noted that additional long-term analysis in patients would be warranted.

Lu et al. (2010a):

These authors investigated whether the N-acetyltransferase (NAT) 2 phenotype has any effects on the pharmacological properties and safety profile of TETA. Twelve fast and 12 slow NAT2-phenotype healthy participants were recruited. Trientine was administered orally as a single 600 mg dose on Day 0, followed by twice daily doses of 600 mg on Days 2 to 6 and a single 600 mg dose on Day 7.

Non-compartmental analysis was used to determine the 24-hour plasma concentration-time profiles for trientine and two acetylated metabolites, N1-acetyltriethylenetetramine (MAT) and N1, N10-diacetyltriethylenetetramine (DAT) on Day 0 and Day 7. The PK parameters for fast and slow acetylators were compared using a 2-way analysis of variance to determine if there were any differences, and copper excretion in the same groups was compared by analysis of covariance. Comparison of drug/metabolite plasma concentrations with cupruresis was performed using a linear mixed effects model.

Since trientine was still detectable in plasma after 15 to 18 hours, the authors suggested that a non-compartmental approach did not provide the best estimates for half-life. No significant overall effect of acetylation status was found for the PK profiles of TETA, MAT, or DAT, and it was postulated that the trientine-metabolizing enzyme is spermidine/spermine acetyltransferase. Moderate accumulation of

trientine, MAT and DAT were apparent upon twice-daily dosing – the effect was more evident for the metabolites due to their longer half-lives.

Increased cupruresis was evident during the first 12 hours post-dose, with the highest rates occurring between 0 and 4 hours. There was no significant difference in cupruresis based on NAT2 acetylator phenotype. Comparison of drug/metabolite plasma concentrations with cupruresis indicated that the change in urinary copper excretion was more closely rated to trientine + MAT than to either trientine or MAT alone.

No differences were found in the safety and tolerability of trientine by acetylation status.

Detailed information of the test products (such as e.g. composition or dissolution properties) is not available for both studies and it is also not known if analytical analyses were adequate. However, both authors also studied trientine as dihydrochloride salt which is in accordance with the active moiety of Cufence.

b) Wilson's disease patients

Miyazaki et al. (1990): A sensitive and simple fluorometric method for the determination of trientine in human plasma by high-performance liquid chromatography is described. Plasma levels of trientine in 8 Wilson´s disease patients (4 male and 4 female patients) receiving treatment for excess copper were measured. The 8 patients received oral doses of approximately 8.3 mg/kg. Absorption rates of trientine were relatively slow and the peak levels were significantly different among patients. However, blood collection in that study was within the first 8 hours after dosing, and as PK parameters only C_{max} and t_{max} values were measured.

PK results were not tabulated but were plotted for individual subjects. These plots indicate that peak concentration occurred at 3 hours in 3 males and at 2 hours in the fourth, with C_{max} concentrations of approximately 0.35, 0.8, 1.4 and 16 µg/mL. In females, t_{max} was at 3 hours in 3 females and at 5 hours in the fourth with a C_{max} range of about 1.2 to 3 µg/mL. Free trientine - trientine that does not take part in chelation with metal ions - was not detected at any peak time in the 8 patients; the greatest part of trientine in plasma is thus probably chelated with metal ions (especially copper).

Tanabe (1996a): In this study the disposition behaviour of trientine and its metabolites in patients with Wilson's disease was studied. A high concentration of metabolites appeared in blood samples of patients soon after administration of trientine. Furthermore, large amounts of trientine metabolites were excreted into the urine of patients. These results suggest that trientine is subjected to a first-pass effect. The absorption process was determined an important factor for the behaviour of the substance. However, the metabolite(s) measured in that study were not identified or characterized; thus, it was unclear which metabolite(s) had been measured. Again, blood collection was within 8 hours following dosing, and most PK parameters were not reported, except for AUC_{0-6} values.

The mean ± SD AUCs of unchanged, metabolised and total trientine in 8 patients with Wilson's disease were 6.39 ± 3.07, 12.64 ± 4.02 and 19.03 ± 4.99 µg·h/mL, respectively. The AUC of the unchanged and metabolized trientine did not appear dependent on the administered dosage. However total trientine levels shown were consistent with dose proportionality. The mean ± SD urinary excretion of unchanged trientine expressed as a % of dose in patients with Wilson's disease was 2.11 ± 2.04 (n = 83) at 1 day and 1.64 ± 1.03 at 6 hours (n = 7) The corresponding percentages for total trientine were 27.08 ± 14.90 and 8.80 ± 3.34, respectively.

PK data from WD patients is particularly sparse. The studies of Miyazaki and Tanabe involved only very few subjects and reported few PK parameters. Interpretation of the results of these studies is difficult (uncontrolled trials, no information about the formulation of trientine, no information about the study populations concerning demographics, inclusion/exclusion criteria, concomitant therapies, time of drug

administration/ influence of food etc.) In addition, in both studies blood was only collected within the first 8 hours after dosing. Due to the outlined limitations, comparison of results with TR-001 PK is not feasible.

Comparison and Analyses of Results across Studies

Due to the limitations described above comparison of the results of Study TR-001 PK with the results of the four cited studies is difficult. The PK parameters measured in Study TR 001-PK could be considered comparable to those obtained in the two PK studies conducted in healthy volunteers with regard to their absolute values and variability. Also, the trientine AUC_{0-t} and C_{max} values in Wilson's disease patients were similar to those observed in healthy subjects, and the variability between subjects was also comparable. If dose-normalised, the mean exposure in healthy subjects upon repeat dosing was 6.93 (ng·h/mL)/(mg) [CV: 57.2%] compared with 7.62 (ng·h/mL)/(mg) [CV: 62.0%] in Wilson's disease patients.

For C_{max}, the mean dose-normalised values were 1.58 (ng/mL)/(mg) [CV: 69.4%] on Day 7 of repeat dosing in healthy subjects, and 1.94 (ng/mL)/(mg) [CV: 55.8%] at pharmacokinetic steady state in Wilson's disease patients. Other investigators have also noted variability of exposure to trientine, but without analysis of the variability due to the smaller number of subjects (Miyazaki et al, 1990; Cho et al, 2009). The mean half-life of trientine after repeat dosing was also found to similar between healthy subjects (3.28 ± 1.15 hours) (CV: 35.1%) and Wilson's disease patients (3.77 ± 1.28 hours) (CV: 33.9%). Thus, the Applicant concluded that the results obtained in the present PK study showed that the PK parameters (and their variability) for trientine observed in Wilson's disease patients were similar to those described in healthy subjects.

- **Influence of food**

TR-001 PK

In Study TR-001-PK, 17 patients were submitted to overnight fasting before dosing, 3 patients (all in the 0.6 g dose group) received their last meals in the morning 1.5 to 3 hours before dosing, whereas all other patients had previously eaten during the day before dosing. The Cmax/D range in the recently-fed patients (1.27 to 1.60 [ng/mL]/[mg]) was contained within the range for other patients of 0.843 to 5.63 (ng/mL)/(mg); the range of AUC0-t/D values (6.09 to 7.77 [ng/mL.h]/[mg]) was contained within the range in non-fed patients of 2.06 to 23.9 (ng/mL.h)/(mg). Thus, the Applicant concluded that there was no evident influence of food intake on trientine PK parameters based on data from these 3 patients.

This view is not fully supported. Food intake in this trial does not seem to have been standardised in terms of quality or quantity or timing of administration. Only limited information is given when patients received food after dosing ("approximately 30 min after dosing"), but basically food intake (or a critical beverage, like milk) was not restricted or sufficiently controlled after dosing during the study. This is not in line with available guidance for the evaluation of food effects.

Bibliographical Data

Available literature on trientine indicates that there is an interaction with food in animals and healthy volunteers. When taken together with food, the bioavailability of trientine was decreased by 1/8 in dogs compared to a fasted control group (Tanno et al. 2008). Following oral administration of 1500 mg TETA 2HCl in a fed healthy volunteer reduced C_{max} (from 3.8 to 1.5 mg/L), delayed t_{max} (from 2 to 4 h) and prolonged $t_{1/2}$ (from 4 to 8 h) (Nakano et al. 2009). This stands in contrast to the Applicant' results, however, the way the food effect was investigated in Study TR-001 PK was not state of the art.

Inclusion of information on a probable food effect in the PI is endorsed despite the lack of own clinical data (see above). As outlined in the section above ("Additional data – Dissolution profile") the conducted changes in dissolution could potentially increase the consequences of a food effect. Data from literature suggest that trientine will be absorbed throughout the length of the gastro-intestinal tract, with the rate of absorption linked to gut wall surface area (Kobayashi et al. 1990, Sakuma et al. 2007, Tanno et al.

2008). However, it remains unknown if these pre-clinical data can be extrapolated to Cufence capsules as different formulations of trientine were used in these studies and trientine was either administered already dissolved in water or in form of tablets.

Distribution

TR-001 PK

Distribution of trientine was not investigated.

Bibliographical data

Following oral administration and absorption in the gut, trientine is widely distributed in the human body with accumulation mainly in the liver and the kidney. Central and peripheral volumes of distribution were reported to be 393 L and 252 L, respectively (Cho et al. 2009; Lu 2010). This indicates wide distribution in the body and high tissue binding. While exhibiting a low distribution to brain, a high distribution of trientine to kidneys and liver was also reported in studies with rats (Tanabe 1996). An accumulation of trientine mainly in the liver and kidney as reported in the literature is likely to occur for Cufence as well.

Elimination

- **Excretion**

TR-001 PK

The terminal elimination half-life ($t_{1/2}$) of trientine ranged between 2.33 to 6.99 hours (the mean $t_{1/2}$ was 3.772 hours) and was calculated for 14 (out of 20) patients. There was no marked difference for $t_{1/2}$ between the child and adult patients. Interestingly, the highest $t_{1/2}$ of 6.99 hours was noticed for subject 05 receiving 0.6 g of trientine. This was the only Black or African American WD patient in the Study. As this patient also differed concerning the pre-dose and post-dose levels of trientine, influence of ethnicity could be possible but no conclusions can be drawn.

The terminal elimination half-life was found to be rather short which is in accordance with the literature which means that the drug is being rapidly removed from the body and therefore it may need to be administered several times a day to be effective. Dosing recommendations (2-4 doses/day) are therefore supported with this regard.

No relationship between dose administered and $t_{1/2}$ could be observed in the present study.

Bibliographical Data

The plasma elimination $t_{1/2}$ of TETA in healthy volunteers and Wilson's disease patients has been reported to range from 1.3 to 4 hours (Lu 2010), indicating fast elimination of the parent compound. The $t_{1/2}$ increases to approximately 3 to 5 hours after repeated dosing at 200 and 600 mg/ d (Cho et al. 2009; Lu et al. 2010a), and reaches 10 to 14 hours after repeated dosing at 1,200 and 3,600 mg/d (Cho et al. 2009).

Most oral TETA is not absorbed, but excreted unchanged in the feces (Gibbs and Walshe, 1986). Trientine that is systemically absorbed is said to be extensively metabolized, with the majority being excreted in urine as metabolite(s) (Lu 2010).

The urinary excretion of unchanged drug is approximately 1% of the administered dose and mostly occurs within the first 6 hours. Approximately 8% of such doses are excreted as two acetyl metabolites, monoacetyl-TETA (MAT) and diacetyl- TETA (DAT); their excretion occurs later than TETA excretion and continues for 26 hours or longer (Cho et al. 2009).

Little information was provided by the Applicant about the t1/2 of trientine´s two major metabolites, MAT and DAT (see section "Metabolism" below for further details). Lu et al. 2010a reported that both metabolites have much longer T1/2 than that of TETA itself. The MAT T1/2 is around 5.3 hours and DAT T1/2 is around 10.8 hours. After 7 days of repeated dosing at 600 mg/d, MAT T1/2 reached 9 hours and DAT T1/2 reached 14 hours.

- **Metabolism**

TR-001 PK

The metabolites of trientine were not measured in the present PK Study.

Bibliographical Data

Trientine is extensively metabolised in humans, as a number of metabolites have been found in urine in addition to the unchanged parent compound. Two major trientine metabolites have been identified from human urine, both of which are acetylation products of trientine: MAT and DAT (Lu 2010).

In plasma, the exposure to the monoacetylated metabolite is approximately twice that of unchanged trientine, which, in turn, is approximately three times that of the diacetylated metabolite (Lu et al. 2010a). Whereas DAT is most probably inactive, available studies (e.g. Lu et al. 2007) suggest that MAT is an active metabolite in humans with a contribution to overall urinary copper excretion. Lu et al. (2007) reported that most of the TETA excreted in urine was present as metabolites, and unchanged TETA only accounted for 22.8 ± 0.6% and 7.1 ± 0.8% of total excreted drug in healthy and diabetic subjects, respectively. The percentage of metabolites excreted via urine was much higher in diabetic subjects (92.9 ± 0.1%) than in healthy controls (77.2 ± 0.2%). This is in accordance with previous findings that more metabolite than parent compound is excreted in urine of humans and rats (Kobayashi et al., 1990; Kodama et al., 1993, 1997; Takeda et al., 1995).

Dose proportionality and time dependencies

Study TR-001 PK and bibliographical data

There is evidence from the literature (Cho et al. 2009) that trientine is dose proportional within the proposed dose range. There are no data available from the present study regarding dose proportionality of trientine. No dedicated single and multiple dose AUCs are available from Study TR-001 PK to elaborate on time-independency/dependency of the compound.

INTRA- AND INTER-INDIVIDUAL VARIABILITY

Study TR-001 PK and bibliographical data

Intra-individual variability:

Data regarding intra-subject variability of trientine PK/PD are sparse in literature and have only beengenerated in healthy volunteers so far. Cho et al. 2009 estimated in their PK/PD model the intra-individual variability for healthy volunteers to be 42.9 % (SE%:5.98) for PK sigma and to be 49.7 % (SE%: 10.6) for PD sigma. No data concerning intra-subject variability are available from Study TR-001 PK as the study was not designed to collect such data (single dose).

Inter-individual variability:

In Study TR-001 PK a high inter-individual variability of the different PK parameters between the 20 patients was noticed. This finding concurs with what is reported in the literature. There seems to be a large variablity of C_{max} and AUC among different individuals, in healthy volunteers and WD patients as well. Cho et al. 2009 suggested that C_{max} variance seems to be less profound in healthy volunteers and

that inter-subject variability could be even higher in the WD patients compared to healthy volunteers. The Applicant reported that if dose-normalised, the mean exposure in healthy subjects upon repeat dosing was 6.93 (ng·h/mL)/(mg) [CV: 57.2%] compared with 7.62 (ng·h/mL)/(mg) [CV: 62.0%] in the present study with Wilson's disease patients. For C_{max}, the mean dose-normalised values were 1.58 (ng/mL)/(mg) [CV: 69.4%] on Day 7 of repeat dosing in healthy subjects, and 1.94 (ng/mL)/(mg) [CV: 55.8%] at pharmacokinetic steady state in Wilson's disease patients. According to these results the inter-subject variability C_{max} was found to be lower in WD patients than in healthy volunteers, which is in contrast to the hypothesis of Cho et al. 2009.

Other investigators have also noted variability of exposure to trientine, but without analysis of the variability due to the smaller number of subjects (Miyazaki et al, 1990; Cho et al, 2009).

In clinical practice, high inter-individual variability might be compensated by titration to target. As exposure can vary between subjects, the starting dose should be selected conservatively so that all patients remain within a safe window of exposure.

Special populations

Influence of age, renal (or hepatic) impairment was not investigated in the present Study TR-001 PK. Information from bibliographical references is sparse. As regards PK results in children, please refer to previous sections of this report. No PK or PD data are available from literature in children.

Pharmacokinetic interaction studies

- **In vitro**

See safety section of this report.

Bibliographical Data

Trientine has been shown to chelate iron and zinc in vitro (Kodama et al. 1997). An interaction with iron and zinc, particularly if given at the same time, cannot be excluded. Appropriate recommendations to avoid interactions are given in the SmPC.

- **In vivo**

TR-001 PK

3 out of the 20 subjects in Study TR-001 PK concomitantly used zinc. One subject took iron as concomitant medication. A number of subjects concomitantly used calcium or magnesium containing medicines. Substance with presumed interactions with trientine could well have been discontinued for the time of treatment (including an appropriate wash out period) as long as patients were closely monitored. However, this was not done in Study TR-001PK.

The Applicant claims that concomitant medication did not influence the PK parameters based on the results of six patients, who were taking no medication at the time of PK sampling. The C_{max}/D range in the trientine-only patients (1.03 to 2.00 ng/mL]/[mg]) was contained within the range for other patients of 0.843 to 5.63 (ng/mL)/(mg); the range of AUC_{0-t}/D values (4.91 to 7.77 [ng/mL.h]/[mg]) was contained within the range in patients receiving other medications of 2.06 to 23.9 (ng/mL.h)/(mg). However, no thorough analysis to investigate the potential influence of concomitant medications was conducted, and the meaningfulness of such an analysis would have been questionable anyway, considering the small size of the trial and its other limitations.

No proper investigation regarding interactions of trientine with zinc was conducted by the Applicant.

Bibliographical Data

There is limited information on the use of trientine in combination with D-penicillamine to treat Wilson's disease patients.

Trientine as a chelating agent may reduce calcium and magnesium antacid effect. There is no evidence that calcium and magnesium antacids alter the efficacy of trientine but, as this cannot be excluded, it is recommended to separate administration of trientine and calcium and magnesium antacids by at least two hours (antacids should be taken after meals). This recommendation is made in the summary of product characteristics (SmPC).

Trientine also chelates iron, and co-administration of trientine and iron should be avoided because the complex with iron is toxic (Roberts and Schilsky, 2008, EASL, 2012, Trientine UK SmPC). Iron supplementation may be necessary in some cases and should be administered at a different time of the day to trientine. Trientine should not be taken concurrently with iron or other heavy metals with which it may form complexes. This recommendation is also made in the SmPC.

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. This recommendation is also made in the SmPC.

2.4.3. Pharmacodynamics

Mechanism of action

Trientine is a copper-selective chelator that enhances systemic elimination of divalent copper by forming a stable complex that is readily excreted by the kidneys. Trientine is a chelator with a polyamine-like structure and copper is chelated by forming a stable complex with the four constituent nitrogens in a planar ring. Thus, the pharmacodynamic action of trientine is dependent on its chemical property of chelating copper and not on its interaction with receptors, enzyme systems or any other biological system that might differ between species. Trientine may also chelate copper in the intestinal tract and so inhibit copper absorption.

Primary and Secondary pharmacology

Information on PD is derived from the literature and some pharmacodynamic parameters were collected as secondary objectives/endpoints in both of the submitted studies, study TR-001 PK and study UNV-TRI-002, respectively.

Primary pharmacology

Trientine is a copper-chelating agent which forms a stable complex with copper that is then eliminated through urinary excretion. Data from literature suggest that trientine may also inhibit absorption of copper from the intestinal tract (e.g. Hill et al. 1986, Fox 2008, Crisponi 2010, Siegemund et al. 1991).

Study TR-001 PK

The Applicant did not define PD objectives to describe PD dose response. Serum copper and serum ceruloplasmin levels were determined in Study TR-001 PK for evaluating the safety of Cufence after a single dose administration. According to the Applicant there were no clinically significant observations for any patient at any time point for either serum copper or ceruloplasmin. These results contributed to the Applicant´s overall conclusion that the single dose administration of Cufence was safe. Both parameters were only measured over a period of 8 hours.

Study UNV-TRI-002

Measurement of copper storage metabolism at each time point after initiation of trientine treatment was defined as an objective.

The change in 24-hour urine copper (24h-UCE) excretion over the course of trientine treatment (two measuring time points) was evaluated in 10 patients during a treatment-free period. 7 patients showed a decrease in copper excretion over time and 3 showed an increase, which the Applicant suggested to be linked to mobilisation of copper.

As patients were not under treatment at the time of measurement, it remains unknown what caused copper mobilisation. Both, an increase and a decrease of 24-hour urine copper excretion, are interpreted as beneficial trientine effects by the Applicant. During a treatment free period, patients would not be expected to have increased urinary copper excretion, however.

Secondary pharmacology

Studies investigating secondary pharmacological effects of trientine are listed below in Table 3.

Table 3 Secondary pharmacological effects of trientine

Table 15: Secondary pharmacological effects of trientine

Reference	Study Set-up / Use of Trientine	Species	Major Findings
Cardiovascular Diseases			
Baynes *et al.*, 2009	Citric acid or trientine (20 mg/day in drinking water) from week 10 to 32 of age	Zucker rats	• Prevention of end diastolic volume and pressure increase • Ejection fraction and myocardial relaxation ↑
Cheung *et al.*, 2015	1 mM trientine infusion after Cu^{2+} induced cardiac impairment	Diabetic Wistar Rats	• Cardiac function ↑
Lu *et al.*, 2013	Randomised, controlled study Trientine: 20 mg/day, orally, 8-week period	Diabetic Wistar Rats	• LVHbsa ↓ • 24h urinary Cu2+ excretion ↑, with a peak at 4 month
Cooper *et al.*, 2009	Randomised, placebo-controlled study Trientine: 600 mg, orally, 2x daily	Type 2 diabetic human patients	• LVHbsa ↓ • 24h urinary Cu2+ excretion ↑, with a peak at 4 months • Fe2+ levels were unaltered in serum
Reid *et al.*, 2017	Open-label, pilot study Trientine: initial dose of 300mg twice daily (dose was increased after 1 week to 600mg twice daily if tolerated) for six months	HCM patients with a LV ejection fraction ≥ 50%.	• LV Mass ↓ • Total Mass ↓ • T1 (ms) ↓ • ECV ↓

Reference	Study Set-up / Use of Trientine	Species	Major Findings
Anti-Cancer			
Moriguchi *et al.*, 2002	1500 or 3000 ppm of trientine	Nude mice	• ↓ growth of HuH-7 human hepatoma xenograft tumours • ↑ apoptotic potential, • ↓ microvessel density • ↓ production of IL-8
Yoshii *et al.*, 2001	1500 or 3000 ppm of trientine	BALB/c mice	• ↓ Growth of HCC tumors • ↓ CD31- immunopositive blood vessels • ↑ tumor cell apoptosis
Hayashi *et al.*, 2007	Dosage of 500 mg/kg twice a week; 5 to 10 weeks	C57BL/6 mouse fibrosarcoma-derived transplantable QRsp-11 cells	• ↓ Tumor growth compared to untreated mice • ↓ Increase of tumor volumes compared to untreated mice • ↑ tumor cell apoptosis
Lixia *et al.*, 2008	50 or 100 µM of trientine	MCF7 cells	• induction of cellular senescence phenotypes • ↑ population doubling • ↑ p53, ↑ p21
Liu *et al.*, 2008	≥ 50 µM of trientine 100 µM of trientine	MCF7 cells	• ↓ expression of human telomerase reverse transcriptase, inhibition of telomerase • ↑ antitumor activity of carboplatin, taxol, adriamycin
Kadowaki *et al.*, 2009	10 mM of trientine for 1 to 5 days	Mouse fibrosarcoma cells	• ↑p38 MAPK activity • ↑apoptosis
Crowe *et al.*, 2013	700 µg of trientine i.p. for 2 weeks	Mesothelioma bearing mice	• mesotheliomas sequestered Cu2+→ ↓Cu2+ by trientine: ↓mesothelioma growth • ↓tumor vessel diameter
Diabetes			
Gong *et al.*, 2008	34 mg/day of trientine	Diabetic Wistar Rats	• Normalisation of Cu levels in renal tissue • Urinary albumin:creatinine ratio ↓ • Total collagen ↓
Lu *et al.*, 2010	10 mg/ day; 20 mg/day; 50 mg/day of trientine	Diabetic Wistar Rats	• Cardiac afterload pressure ↑ • TGF-β1 ↓ • 24h urinary Cu2+ excretion ↑

Reference	Study Set-up / Use of Trientine	Species	Major Findings
Lu *et al.*, 2007	300, 600, 1200, and 2400 mg of trientine (orally)	Healthy volunteers and Type 2 diabetic human patients	• Healthy volunteers: Urinary trientine ↑ → Urinary Cu2+ ↑ • Diabetic patients: Urinary trientine - Urinary Cu2+ correlation differs in diabetic patients • Cu2+ values were more closely related to trientine + MAT
Hamada *et al.*, 2005	20 mg/kg per day of trientine (1 group) for 1 month	Diabetic Sprague–Dawley rats	• MG and 3-DG ↓ • Suppression of argpyrimidine • Suppression of SSAO activity
Alzheimer's Disease			
Wang *et al.*, 2013	60 or 180 mg/kg/day of trientine p.o. for 3 months	APP/PS1 transgenic AD mice**	• ↓ advanced glycation end products • ↓ Aβ deposits • ↓ Cu2+ and Zn2+ accumulation in brain amyloid plaques • Cu2+, Fe2+, Zn2+ levels unaltered in serum and brain

*by injection of 55 mg/kg streptozotocin
**β-Amyloid precursor protein and presenilin-1 double transgenic AD model mice

Trientine has complex interactions with dietary metals other than copper such as iron and zinc and they may inhibit one another's absorption and even cause deficiency states. Such interactions are difficult to explore and the literature is sparse. In practice, the problem represented by these interactions should be dealt with by careful timing of medications in relation to one another.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

For the description of Cufence´s PK this application relies partly on bibliographical data (predominately from healthy volunteers) and partly on data generated by the Applicant from a single dose, PK profiling study in 20 WD patients (TR-001 PK). In principle, this is considered an acceptable approach for a full mixed application.

Study TR-001 PK was conducted to fulfil requirements outlined in the EMA protocol assistance (2007 and 2012) in order to fulfil gaps on trientine PK documentation identified in the available literature. The aim was to establish a dose-exposure-response relationship and thereby support dosing recommendations in the PI, especially (but not exclusively) in special populations.

This study shows several deficiencies with regard to overall planning, conduct and reporting of the study hampering interpretation of the results (please refer to the above sections for details).

The patient population was inhomogeneous and no measures to take the differences into account were taken in the statistical plan and the evaluation of study results. The impact of age or food intake on the PK of Cufence cannot be properly assessed. Due to the lack of clinical data with regard to a possible food effect of Cufence, the Applicant proposes to bring the instructions on food effect in the SmPC in line with the current European guideline (to take Cufence 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). These

seem to be conservative and are considered acceptable. Thus, it is proposed that trientine should be taken 1 hour prior or two hours after meals.

It is however, noted that e.g. for a four times daily regimen these recommendations result in a very strict timetables for the patients concerning food intake and trientine dosing which may have an impact on compliance. A conclusion which can be drawn on the pharmacokinetic properties of Cufence is that, as previously reported in the literature, absorption seems to be low and variable in WD patients and healthy volunteers, with t_{max} occurring between 0.5 to 4 hours post-dose. Exposure is variable between subjects and elimination of trientine occurs rather fast ($t_{1/2}$ median 3.6 hours).

Available exposure data revealed also high variability across all age cohorts with a less pronounced inter-individual variability in the paediatric cohort. Large difference between the adult and paediatric patients were observed even for the dose normalized parameters. Thus, the C_{max} /D ranged from 1.03 to 2.16 (ng/mL)/(mg) (2.10-fold range) in the paediatric patients and from 0.843 to 5.63 (ng/mL)/(mg) (6.7-fold range) in the adult patients. The dose-normalised AUC_{0-t} ranged from 5.01 to 8.96 (ng/mL.h)/(mg) (1.8-fold range) in the paediatric patients and from 2.06 to 23.9 (ng/mL.h)/(mg) (11.6-fold range) in the adult patients. However, the CHMP acknowledged that the study design and the conduct of the study limit the assessment of this issue. Concerning t_{max} no marked difference between the paediatric and adult patients (but also high variability) was found: t_{max} ranged from 0.5 to 4.08 hours for children compared to 0.48 to 3 hours in adults (this is adequately reflected in the product information).

In conclusion, study TR-001 PK was not adequately designed to evaluate a dose response (as no relevant PD parameters were measured) and hence, results do not allow a thorough characterisation of the PK/PD profile of trientine/Cufence. Considering the limitations of the study, the Applicant has committed to further evaluate the dose response post marketing with a PK/PD (sub)-study in the planned PAES (see Section 4).

The absolute bioavailability of trientine is unknown and there is no mass balance study in humans to confirm that there are no other metabolism pathways or metabolites of importance formed. The Applicant summarized the available literature with this respect and adequately discussed the clinical context of the non-clinical oxidative metabolism pathway study APT-REP-01. The lack of a formal mass balance study in humans is still unaccounted for, yet is unlikely to have a clinical impact on the benefit/risk balance of the product.

It is expected that due to lack of interferences between trientine and biological processes, inhibition and induction of CYP450 isoenzymes will not occur. However, there is no literature data regarding the potential of trientine to inhibit or induce CYP450 isoenzymes. To partially address this issue, the Applicant submitted *in vitro* data in order to investigate the trientine´s potential to inhibit or induce CYP450 enzymes and cause potential drug-drug interactions (APT-REP-01 study). Trientine showed no *in vitro* inhibition or induction, which is consistent with it not being a substrate for CYP450. Given the absence of any evidence for the involvement of CYP450 in trientine metabolism from in vitro metabolism, inhibition and induction studies or from in vivo metabolite profiling, no further investigation is considered necessary, in accordance with the EMA Guideline on the Investigation of Drug Interactions.

The Applicant's claims based on literature data that MAT and DAT are both inactive metabolites which is not entirely supported. The statement is also not in line with information of another approved trientine product where it is stated that "MAT may also participate to the overall clinical activity of Cuprior, however the extent of MAT to the overall effect of Cuprior on copper levels remains to be determined." Thus, to further understand more the pharmacological properties of the drug, the pharmacokinetic profile of trientine (incl. N(1)-acetyltriethylenetetramine (MAT) and N(1),N(10)-diacetyltriethylenetetramine (DAT)) and the direct response of copper parameters after trientine exposure will be investigated in the PAES.

Bibliographical data

The overall extent and quality of available literature on trientine PK is limited.

Available literature on trientine indicates an interaction with food in animals and healthy volunteers. When taken together with food, bioavailability of trientine was decreased by 1/8 in dogs compared to a fasted control group (Tanno et al. 2008). Oral administration of 1500 mg TETA 2HCl in a fed healthy volunteer reduced the C_{max} (from 3.8 to 1.5 mg/L), delayed t_{max} (from 2 to 4 h) and prolonged $t_{1/2}$ (from 4 to 8 h) (Nakano et al. 2009) vs the fasted state.

This stands in contrast to the Applicant' own results (no influence of food was detected); however, the food effect was not investigated in Study TR-001 PK according to state of the art.

Some other reports that investigated trientine in healthy subjects and WD patients reported that the absorption rate in the gut after oral trientine administration is relatively low (8-30% according to Lu et al. 2010a). The reported t_{max} values range from 0.8 to 4 hours. A large variance of C_{max} has been seen among different individuals with Wilson's disease. C_{max} variability seems to be less profound in healthy volunteers (on the same dose of 600 mg trientine) (EASL 2012).

None of the historical investigations seems sensitive enough to reliably investigate the impact of intrinsic- or extrinsic factors on trientine PK.

Pharmacodynamics

Information on trientine's primary pharmacology is sparse. Available literature (e.g. Hill et al. 1986, Fox 2008, Crisponi 2010, Siegemund et al. 1991) indicates that trientine may have a dual mechanism of action; (i) by promoting urinary copper excretion and (ii) by reducing copper absorption from the gastrointestinal tract (and thus promoting faecal copper excretion). Based on the available data a precise quantification of the role of intestinal luminal chelation to the efficacy of trientine is not possible, but its contribution is considered rather low.

Non-clinical data indicates the existence of secondary pharmacological effects of trientine. The literature data on secondary pharmacodynamics was adequately discussed and summarized.

In both submitted clinical studies, only limited PD data was collected:

Study TR-001 PK:

The only PD parameters evaluated were serum copper and ceruloplasmin levels (measured for 8 hours primarily to support Cufence safety). Results do not allow evaluating trientine dose-proportionality and serum concentration-proportional effects on enhancing copper excretion and adequately describing the dose response relationship. Thus, available data from this study are not appropriate to support dose recommendations in the PI or adequately describe the dose response relationship for Cufence.

Study UNV-TRI-002:

Measurement of copper storage metabolism at each time point after initiation of trientine treatment was defined as an objective. An increase of urinary copper as a result of treatment with trientine would be a good indicator of effect and allow making assumptions on dose response relationship. Change in 24-hour urine copper excretion over the course of trientine treatment was evaluated in some selected patients, but did not show good correspondence with target ranges as outlined in relevant guidelines.

Trientine has complex interactions with dietary metals other than copper such as iron and zinc and they may inhibit one another's absorption and even cause deficiency states. The drug-interactions of trientine with zinc may cause adverse events in addition to altering its pharmacokinetics. Such interactions are difficult to explore and the literature is sparse with this regard. In practice, the problem is dealt with by careful timing of medications in relation to one another. Due to the limited data on concomitant use with

Zinc no specific dose recommendations can be made and the combination of trientine with zinc is not recommended. Concomitant oral iron or other heavy metals should be administered at a different time than trientine to prevent the formation of complexes as mentioned in the SmPC.

Trientine as a chelating agent may reduce calcium and magnesium antacid effect. There is no evidence that calcium and magnesium antacids alter the efficacy of trientine but, as this cannot be excluded, it is recommended to separate administration of trientine and calcium and magnesium antacids by at least two hours (antacids should be taken after meals). This recommendation is made in the summary of product characteristics (SmPC).

The effectiveness of trientine in removing excessive Cu from the body in WD patients is not questioned as it is substantiated by decades of experience in clinical practice.

2.4.5. Conclusions on clinical pharmacology

Dedicated studies to investigate the relationships between dose/titration schemes and relevant PD markers in patients (adult and paediatric) were not conducted. Cufence posology as proposed in the PI is therefore mainly based on the well-established use of the substance since more than 30 years and supported by recommendations in clinical treatment guidelines.

Clinical pharmacology data for trientine in the literature is sparse and Study TR-001 PK was not adequately designed to establish a dose-exposure-response relationship and thereby gaps in knowledge remain on dosing recommendations, especially (but not exclusively) in special populations. Therefore available data does not allow a thorough characterisation of the PK/PD profile of trientine/Cufence. Titration to target and expert prescription setting in this rare life threatening disease is taken into account for this marketing authorisation application and further PK/PD data needs to be provided post authorisation in particular on patients in the up-titration phase and in children where the current data is particularly limited in order to confirm or improve the dosing and titration recommendations in the PI. It is also noted that differences between the adult and paediatric patients were observed even for the dose normalized parameters and treatment in children might require lower (starting) doses or more conservative titration. There could be different requirements of copper (and thus trientine) in different age cohorts due to developmental status that might also require a relative adaption of doses for juvenile individuals. Therefore, also children from 5 years onwards should be included in the proposed PAES to further investigate the dose-exposure-response relationship in children. This study is imposed in line with Article 1(2)c of Commission Delegated Regulation (EU) No 357/2014.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

Post-Authorisation Efficacy Study (PAES): In order to further characterise the efficacy of trientine dihydrochloride in the treatment of Wilson's disease in patients with predominantly hepatic, neurologic or psychiatric symptoms as well as in paediatric patients, the MAH should conduct and submit the results of an open label, prospective study to investigate the clinical course of hepatic, neurological and psychiatric disease from the time of initiation of treatment with trientine dihydrochloride up to 24 months of therapy. The study will also contain a PK/PD sub-study to evaluate the dose-response relationship especially during the up-titration phase. The study should be conducted according to an agreed protocol.

Due date: Q4 2025 (Milestone for the PK/PD sub-study (Q4 2022)

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

There are no dedicated dose response studies available for trientine in Wilsons's disease.

The dosing regimen is 4-8 capsules; 1200 to 2400 mg (equivalent to 800-1600mg trientine base) daily divided in two to four doses. For children, a lower dose of 2-5 capsules; 0.6-1.5 grams (0.4-1 gram trientine base) was proposed for initiation of therapy. Adapted dosing according to the patient's clinical response is advised for patients and no separate proposal for maintenance therapy in children is made. This regimen is in line with the SmPC of the nationally licensed Trientine dihydrochloride 300 mg capsules (200 mg trientine base) in UK since more than 30 years.

It is stated that trientine is titrated to target albeit the dose recommendations are mainly based on clinical experience. The dose/exposure relationship was not thoroughly investigated in study TR-001 PK. Only one (individual) dose was applied under study conditions and no PD parameters useful to evaluate dose response were collected. The study has significant shortcomings in trial design and conduct and consequently provides little relevant information on pharmacokinetics. No Pop-PK was carried out, although this was recommended in the CHMP protocol assistance procedures.

The AASLD and EASL guidelines slightly differ in their dose recommendations; they are aligned with the posology of the product available in the respective area. In the EU, guidelines usually refer to titration in 300 mg TETA steps according to the UK-licensed Univar's trientine (a 300 mg TETA capsule), which has been the only available trientine product in the EU for many years. Cufence was developed in line with the UK product (i.e. 300 mg TETA per capsule corresponding to 200 mg trientine base). Treatment in children, who might require lower (starting) doses or more conservative titration steps, would benefit from lower capsule strengths/ appropriate formulation as outlined in previous CHMP protocol assistance.

The Applicant claims that trientine exposure is highly variable and thus dosing is highly individual. They also claim that respective PD parameters such as 24-h UCE or NCC are highly variable *within* patients. The possible causes for the observed high variabilities are however unknown and could also be due to the lack of applying standardisation measures for copper intake, food & beverages, concomitant zinc, measuring time points, etc., in the respective studies. It is however agreed that urinary copper excretion rates (UCE) and serum copper concentrations are not ideal parameters by which to monitor the benefit of trientine therapy alone, and that clinical parameters need to be taken into account.

However, some conclusions on the relationship of trientine and these PD parameters could be made based on the information provided in the dossier:

- Under trientine (and also D-PA) therapy, the 24-h urinary copper excretion (UCE) rates are higher when measured during treatment than after a 48-h dose interruption. This allows the conclusion that trientine promotes urinary copper excretion.
- Trientine is used in patients intolerant to D-Penicillamine. These patients are not necessarily fully de-coppered and this process can take many years. The behaviour of laboratory copper parameters such as 24-UCE or non-ceruloplasmin bound copper (NCC) in relation to trientine treatment seems influenced by the de-coppering status/total copper load of the patient. After long-term therapy, in patients that are thought to be de-coppered, copper excretion in urine is lower compared to earlier measuring time points.
- Availability of free copper in the serum and also the rate of copper excretion can significantly increase at initiation of therapy in patients with high copper loads (especially when receiving high trientine doses), which can result in negative clinical effects such as neurological deterioration and be reflected in worsening of laboratory parameters. According to the Applicant, in clinical practice patients with

higher copper loads are initially prescribed higher doses of trientine. Therefore, clear and precise titration rules for such cases would be desirable. For patients with neurological symptoms 'up-titration with moderation' and 'close monitoring' are recommended in the SmPC as these patients are at risk of neurological deterioration at treatment initiation, especially when the starting dose is high.

- To characterise the relationship between dose and PD-response, the 24-h UCE and NCC values measured in study UNV-TRI-002 (retrospective and prospective part) were analysed and put into context with the respective doses. These analyses reveal overall, that the 24-h UCE and NCC levels collected in UNV-TRI-002 did not show good correspondence with the proposed target ranges from the literature in the retrospective dataset; for reasons unknown, a slightly better correspondence was seen over a shorter time frame in the prospective dataset for reasons unknown. The 24-h UCE values were often below the lower proposed limit of 3 µmol per 24-h (and even more often below 3.2 µmol). The AASLD guideline states that values of UCE below 200 mg/day (3.2 mmol/day) may indicate either non-adherence to therapy or overtreatment and excess copper removal. NCC levels in the retrospective datasets are also rather low, which could also be interpreted as indicating overtreatment. Overall, the data on 24-h UCE and NCC from the retrospective dataset suggests that many patients might have been treated with too high doses.

Overall, it seems that 24-h UCE in study UNV-TRI-002 was not meant as a parameter for titration guidance and its meaningfulness for dose titration in clinical practice remains unclear. The same holds true for NCC measures. It seems that the clinical picture was more important for the treating practitioners. Taken together, these observations emphasize that the dose-exposure-response is not well understood and that there is a need for better data.

A prospective study under controlled circumstances (i.e. ensuring treatment compliance and copper intake) in patients at different levels of de-coppering (different copper loads), and investigation of parameters sensitive to depict treatment success (or failure) would be necessary to fully elucidate the exposure-response relationship of trientine in WD. The Applicant agreed to generate these data post-marketing within a PAES; an open label, multicentre, prospective study investigating efficacy and safety outcomes as well as PK and PD parameters in the first 24 months after initiation of treatment with trientine in 30-50 Wilson's Disease patients 5 years and older who have previously been treated with D-Penicillamine.

Currently the guidance on therapeutic monitoring as stated in the proposed Cufence PI reflects the recommendations from available treatment guidelines. It is emphasized that treatment should only be initiated by specialist physicians with experience in the management of Wilson's disease, and in clinical practice, these patients are usually closely monitored and followed in specialised centres.

2.5.2. Main study(ies)

Multicentre study to assess long-term outcomes of chelator-based treatment with trientine in Wilson's disease patients withdrawn from therapy with D-penicillamine

Methods

Study Participants

Inclusion Criteria:

1. Patients aged 1 year to 90 years of age

2. Physician-established diagnosis of Wilson´s disease based on a Ferenci Score >3

3. Documented treatment with D-penicillamine, withdrawal of treatment with D-penicillamine, followed by treatment with trientine for at least 6 months at date of informed consent

4. Able/willing to provide written informed consent.

Exclusion Criteria:

1. Incomplete history of medication use for trientine from initial diagnosis to last follow-up

2. Unavailable outcome data for hepatic and neurological course of disease at initiation of treatment with trientine and at least 1 time point post-initiation of treatment with trientine

Treatments

This was a retrospective study based on information obtained from the medical records of patients already attending major tertiary care centres for the treatment of Wilson disease. As such, no investigative products were managed or dispensed solely for the purpose of this part of the study. All patients have been prescribed treatment with trientine 300 mg capsules commercially available from Univar, UK (PL 41626/0001).

The approved daily dose of trientine, according to the current Summary of Product Characteristics (SmPC; UK SmPC, 2016), is 1,200 – 2,400 mg/day in 2-4 divided doses for adults, and a lower dose, typically 600 – 1500 mg/day, depending on age and body weight, for children.

The study medication was oral treatment with trientine (for at least 6 months as second line treatment after receiving D-penicillamine as first line). The given dose is highly patient-specific, variable and subject to constant review and change according to the patients' signs, symptoms and copper levels and was selected at the investigator's discretion according to the patient's needs.

Objectives

The objectives were to:

• Assess the clinical course of copper (Cu) stores, neurological disease, and hepatic disease following initiation of treatment with trientine following withdrawal of D-penicillamine. Retrospective data were collected from visits at 6, 12, 24, 36 and 48 months after initiation of treatment, and at the last available follow-up visit. Assessments were based on the Investigator's score (unchanged, improved but not normal, improved to normal, asymptomatic over duration of therapy, and worsened)

• Assess the safety of trientine treatment based on reported adverse events (AEs), including AEs leading to discontinuation of treatment with trientine

• Determine duration of treatment with second line therapy trientine, defined as time to discontinuation of treatment due to AEs and/or inadequate response.

Table 4 Data Collection Schedule

Table 9-1 Data Collection Schedule

	Baseline		Post Initiation of Trientine Treatment					
Data Collection/ Period	**Diagnosis**	**Initiation of trientine[a]**	**6 mo (± 2 mo)**	**12 mo (± 2 mo)**	**24 mo (± 2 mo)**	**36 mo (± 2 mo)**	**48 mo (± 2 mo)**	**Last Follow-up**
Informed Consent								X
Date of contact[b]		X	X	X	X	X	X	X
Family Screening	X							
ATP7B DNA analysis[c]	X							
Manifestation[d]	X	X						
Physical examination[e]	X	X	X	X	X	X	X	X
Clinical biochemistry[f]	X	X	X	X	X	X	X	X
Haematology[g]	X	X	X	X	X	X	X	X
Urinalysis[h]	X	X	X	X	X	X	X	X
Pathology[i]	X							
Treatment challenge test[j]	X							
Demography		X						
Height and Weight	X	X	X	X	X	X	X	X
Medical History		X						
Treatment History		X						
Treatment received[k] / Drug accountability		X	X	X	X	X	X	X
Hepatic Outcome[l]		X	X	X	X	X	X	X
Neurological Outcome[l]		X	X	X	X	X	X	X
Adverse Events			X[m]	X[m]	X[m]	X[m]	X[m]	X[n]
Concomitant medications		X[n]	X[m]	X[m]	X[m]	X[m]	X[m]	X[n]
Patient's Treatment Status								X
Date of Onset	X							

Note: Time of last follow-up could vary between patients.

a. Data not collected for the diagnosis
b. If applicable
c. DNA analysis or family screening
d. Pre-symptomatic; Symptomatic (Hepatic, Neurological, Both).
e. Tremor; drooling; rigid dystonia; dysarthria; dysphagia; depression; Kayser-Fleischer rings; ascites; oesophageal varices; encephalopathy; icterus; ataxia; other relevant symptoms as assessed by the Investigator; other relevant physical examination findings
f. Liver panel: ALT, AST, ALP, , total bilirubin, direct bilirubin, albumin; serum ceruloplasmin, and serum Cu. (Note that serum creatinine is available for > 80% of patients but not recorded on the patient's CRF.)
g. Hgb; platelet count; INR
h. 24-hour basal urinary Cu and proteinuria
i. Liver biopsy = liver Cu in µg/g dry liver weight
j. d-Penicillamine challenge; trientine challenge
k. T = trientine, D = d-Penicillamine
l. Outcome: 1 = unchanged, 2 = improved but not normal, 3 = improved to normal, 4 = asymptomatic over duration of therapy, 5 = worsened
m. Since the last visit
n. At this time point only

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase, CRF = Case Report Form, Cu = copper, DNA = deoxyribonucleic acid, GGT = gamma-glutamyltranspeptidase, Hgb = haemoglobin, INR = International normalised ratio, mo = months.

Outcomes/endpoints

Efficacy:

Clinical outcome for each time point after initiation of trientine treatment based on clinical course of neurological and hepatic disease

The clinical course of neurological and hepatic disease for each available time point after initiation of treatment (6, 12, 24, 36 and 48 months, and at the last available time point while taking second line trientine) was scored (Investigator's score) based on the status at the time of initiating trientine as:

1 = Unchanged

2 = Improved but not normal

3 = Improved to normal

4 = Asymptomatic over duration of therapy

5 = Worsened.

The following efficacy endpoints were assessed:

• The clinical course of hepatic disease at 6, 12, 24, 36 and 48 months, and at the last available time point while taking second line trientine, based on the Investigator's scores outlined above and based on hepatic status at the time of initiating trientine

• The clinical course of neurological disease at 6, 12, 24, 36 and 48 months, and at the last available time point while taking second line trientine, based on the Investigator's scores outlined above and based on neurological status at the time of initiating trientine

Cu storage and metabolism measurement at each time point after initiation of trientine treatment (see section on "Pharmacodynamics" of this report)

• Cu storage and metabolism measured at 6, 12, 24, 36 and 48 months and at the last available time point after initiation of trientine, by available tests, e.g. 24-hour urinary Cu excretion, serum ceruloplasmin (CPN), serum Cu, were compared to Cu storage values at the time of initiating trientine.

Time to discontinuation of treatment due to AE and/or inadequate response

The time to discontinuation of trientine due to AE and/or inadequate response was assessed as follows:

• Time to discontinuation of trientine due to AEs

• Time to discontinuation of trientine due to inadequate response measured by poor clinical outcome (failure to stabilise or reverse signs and symptoms) where:

- Inadequate hepatic response was defined by:
  - Progression to liver transplant
  - Increase of at least 2 of 3 liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyltranspeptidase [GGT]) ≥ 2 x normal or ≥ 2 x baseline
  - Increase of 24-hour urinary Cu excretion when collected in 2 consecutive measurements
- Inadequate neurological response was defined by neurological deterioration (physician's decision)

• Time to discontinuation of trientine due to AEs and/or inadequate response measured by poor clinical outcome

Patient treatment status at the last available time point

- Treatment status
- If trientine stopped:
    - Reason for discontinuing
    - When trientine discontinued
- Initiation of any new treatments for Wilson disease

Safety:

Adverse events related to trientine treatment and AEs leading to discontinuation of trientine were assessed at each available study time point.

Sample size

Number of Patients (Planned and Analysed):

The sample size was planned to comprise approximately 90 patients in total. The number of patients was dictated by the estimated size of the patient population to be studied and was an approximation based on the number of eligible patients in participating European Union centres.

A retrospective study examining the medical records on physician-confirmed Wilson disease cases from large tertiary care centres throughout Europe was expected to provide sufficient numbers of patients for analysis. The study is designed as a single group cohort study to include approximately 90 patients. The number of patients is dictated by the estimated size of the patient population to be studied and is an approximation based on the number of eligible patients in participating European Union (EU) centres. Inclusion criteria are in alignment with the proposed indication, defining the underlying population as D-penicillamine-intolerant patients. Due to the low disease incidence, adequate statistical power cannot be obtained, therefore only descriptive analysis will be performed on the safety and efficacy measures and changes will be compared with baseline values. The before/after single group cohort design is applied due to the lack of adequate comparison group.

Univar and investigators had the right to close a site at any time, although only after consultation between the involved parties. In case of site closure, the IEC and the competent regulatory authority were to be informed and all study materials were to be returned to Univar.

Univar had the right to terminate the entire study prematurely at any time.

It was allowed to stop recruitment at an individual site for reasons of particularly low recruitment, protocol non-compliance, non-compliance with Good Clinical Practice (GCP) according to the ICH-GCP, or inadequate data recording.

Randomisation

There was no comparator/control group and no randomisation carried out.

Blinding (masking)

No blinding was foreseen in this uncontrolled trial and neither patients nor treating physicians or other staff members were blinded and no central reading of findings/results from treatment visits is available.

Statistical methods

This was a non-randomised study. One single population was used for all data summaries and analysis presentations, corresponding to all patients who met the criteria for inclusion and exclusion.

No interim analysis was planned.

No primary endpoint was identified; conclusions from this study were based on the full extent of efficacy and safety results.

Analysis presentations in terms of summary statistics were focused on illustrating the efficacy, safety and tolerability of trientine chelator therapy in patients withdrawn from D-penicillamine treatment due to efficacy, safety, tolerability, or other reasons.

No formal statistical comparisons were performed and only descriptive methods were applied.

Continuous variables were summarised using n, mean, median, standard deviation, minimum, and maximum values. Categorical variables were summarised using counts and percentages. Time to event variables were based on Kaplan-Meier estimation. The baseline value for each patient to be presented in summary tables was defined to be the last non-missing assessment value for a patient for that particular parameter that was recorded prior to the initiation of trientine treatment.

All collected information as a minimum was included in patient listings. Any unscheduled visit results were included in patient listings only, noting that scheduled visit results corresponded to data collecting falling within the ± 2-month visit window.

For the time to discontinuation endpoints only, data was presented (summaries only, no statistical testing) for those patients who were symptomatic, as defined at baseline. Only treatment-emergent AEs (TEAEs) were considered for the safety endpoints of this study. All TEAEs were summarised and listed for this study. In addition, related TEAEs and AEs leading to discontinuation of treatment with trientine were summarised.

All other safety data were presented in patient listings only. With the listings of biochemistry, haematology, urinalysis and pathology data, any clinically significant abnormal laboratory values were identified within the listings against the parameter values.

Results

Participant flow

A total of 81 patients were enrolled into the retrospective part of the study. However, four patients were excluded from the intention to treat (ITT) population, as according to the dosage documented in the patient's medical record they had received non-Univar trientine at initiation of trientine instead of Univar's trientine.

Recruitment

Data were collected from dates between 15 Jul 2016 and 10 Apr 2017 in 4 centres in Germany, Greece, Italy and UK.

Conduct of the study

Data Management/ Data Collection

Data collection in the retrospective part of the study covered a historical time period of approximately 48 months. Data was collected at time points of 6, 12, 24, 36 and 48 months after initiation of treatment, as available. Data from the last available time point were also assessed.

Patient data were collected on CRFs (paper) and were substantiated by patient medical records and source documents at the clinical site. Where source documents (such as laboratory reports and medical records) or laboratory databases existed, all relevant data were transcribed into the CRF and transferred electronically with independent double entry to the study database by data entry personnel.

Completed CRFs were reviewed to ensure data accuracy, completeness, and consistency. Any discrepancies found during the CRF review were to be clarified by a corresponding query to the Investigator (or his/her designated staff). This included CRF reviews at the site by the Sponsor or its designee, or during quality assurance review of the data.

Case Report Form Completion

A CRF was completed for each patient from available source documents (e.g., laboratory reports and medical records). The CRF documented the laboratory tests and clinical features used to confirm diagnosis, summarised the history of treatment for Wilson disease, and listed the AEs as well as clinical laboratory and examination findings reported during treatment with trientine.

Data Processing

A database constructed from the CRFs was validated both manually and electronically. Clarification of data was requested from the study sites as required. The database was quality-assured and was available for statistical analysis.

Changes in the Conduct of the Study or Planned Analyses

The calculation of patient age differed from the planned analyses. Age was recorded based on the date of informed consent rather than at the start of treatment with trientine.

The following additional analyses were defined by the final SAP:

1) The following laboratory efficacy parameters were added:

• Proportion of patients with all transaminases (ALT, AST, GGT) within the normal range at each available time point

• Proportion of patients with all transaminases (ALT, AST, GGT) and all additional liver values (total bilirubin, albumin, INR) within the normal range at each available time point

• Proportion of patients with anaemia, defined as haemoglobin value below the lower limit of normal, at each available time point

2) Subgroup analyses by the following criteria were added for some of the analyses:

• Sex (male, female)

• Presentation at diagnosis (hepatic, neurologic, hepatic and neurologic, asymptomatic)

• Presentation at initiation of trientine (hepatic, neurologic, hepatic and neurologic, asymptomatic)

• Age group (age < 18 years, age ≥ 18 years)

• Presence of liver cirrhosis (present, absent) in patients with hepatic or mixed presentation at initiation of trientine.

3) The parameter non-CPN bound Cu (NCC) was added to the analysis of the Cu storage and metabolism.

4) For the clinical laboratory parameters of haematology and biochemistry, standard descriptive summary statistics were calculated at each scheduled measuring time point and for the change from baseline to each scheduled measuring time point after baseline.

5) Physical examination findings that were potentially related to Wilson disease were summarised by visit.

Baseline data

Descriptive statistics of demographics (age, sex, weight, height, ethnic origin) and baseline characteristics (relating to diagnosis) are presented.

The mean age (standard deviation [SD]) was 35.6 years (17.74 [range: 8 to 67 years]) and the majority (90.9%) of patients were Caucasian. There were more female patients than male patients (59.7% vs 40.3%). Of the 77 patients included in the ITT population, 16 (20.8%) patients were paediatric patients (aged <18 years). It should be noted that based on the year of birth provided there were 6 patients that were under the age of 8 at the start of trientine. Of these 6 patients, 3 patients were either 4 or 5 years of age.

The diagnosis of Wilson disease was supported by the results of the family screening in 18 (23.4%) patients. A total Ferenci Score of >3 confirmed Wilson disease diagnosis for this study. A Ferenci Score at baseline was available for 77 patients. All of these patients had a Ferenci Score of >3. Duration of Treatment with D-penicillamine was reported in 20 patients of the ITT population; mean duration was 10.3 (± 25.41) months. The most common reasons for withdrawal of D-penicillamine was due to AEs (58 [75.3%] patients) and no clinical improvement (12 [15.6%] patients).

Table 5 Summaries of demographic data at the time of signing the informed consent

Table 11-1 Age, Gender, Ethnic Origin (ITT)

Characteristic	Trientine (N=77)
Age (years)	
n	77
Mean (SD)	35.6 (17.74)
Median (min, max)	35.0 (8, 67)
Gender, n (%)	
Male	31 (40.3)
Female	46 (59.7)
Ethnic Origin, n (%)	
White Caucasian	70 (90.9)
Black	1 (1.3)
Asian	5 (6.5)
Other	1 (1.3)

Abbreviations: ITT = intention to treat, max = maximum, min = minimum, N = number of patients in the treatment group analysis set; n = number of patients in the specified category with non-missing values, SD = standard deviation.
Age was calculated as: year of informed consent – year of birth + 1.
Source: Section 14, Table 14.1.2.1.1

Table 6 Summaries of height, weight and body mass index (BMI) by sex

Table 11-2 Height, Weight and Body Mass Index by Sex (ITT)

Characteristic	Trientine (N=77)	
	Male (N=31)	Female (N=46)
Height (cm)		
n	18	18
Mean (SD)	142.73 (28.025)	154.47 (14.779)
Median (min, max)	134.85 (103.5, 192.0)	157.25 (124.0, 180.0)
Weight (kg)		
n	18	19
Mean (SD)	39.18 (21.579)	51.06 (18.682)
Median (min, max)	30.10 (16.0, 92.0)	47.00 (25.0, 89.0)
BMI (kg/m^2)		
n	18	18
Mean (SD)	17.86 (3.024)	19.86 (3.825)
Median (min, max)	17.15 (14.0, 25.0)	19.19 (13.6, 26.4)

Abbreviations: BMI = body mass index, ITT = intention to treat, max = maximum, min = minimum, N = number of patients in the treatment group analysis set; n = number of patients in the specified category with non-missing values, SD = standard deviation.
BMI was calculated as weight (kg) / (height (m)^2)
Source: Section 14, Table 14.1.2.1.2

Table 7 Demographic data by presentation at the time of diagnosis

Table 11-3 Demographics by Presentation at Diagnosis (ITT)

Characteristic	Trientine			
	Hepatic (N=32)	Neurologic (N=12)	Hepatic and Neurologic (N=9)	Asymptomatic (N=17)
Age (years)				
n	32	12	9	17
Mean (SD)	39.5 (16.64)	50.8 (11.40)	36.2 (16.70)	23.7 (14.24)
Median (min, max)	41.5 (15, 67)	53.5 (31, 67)	36.0 (11, 57)	18.0 (9, 59)
Gender, n (%)				
Male	11 (34.4)	4 (33.3)	6 (66.7)	8 (47.1)
Female	21 (65.6)	8 (66.7)	3 (33.3)	9 (52.9)
Height (cm)				
n	14	4	2	13
Mean (SD)	156.83 (21.311)	164.00 (12.193)	172.00 (24.042)	131.65 (19.585)
Median (min, max)	157.25 (128.5, 192.0)	163.50 (150.0, 179.0)	172.00 (155.0, 189.0)	130.00 (103.5, 165.0)
Weight (kg)				
n	15	4	2	13
Mean (SD)	54.57 (23.871)	53.03 (15.080)	49.60 (16.122)	33.09 (15.579)
Median (min, max)	58.00 (23.1, 92.0)	56.75 (31.6, 67.0)	49.60 (38.2, 61.0)	26.80 (16.0, 72.0)
BMI (kg/m^2)				
n	14	4	2	13
Mean (SD)	19.99 (4.086)	19.37 (3.647)	16.49 (0.832)	18.13 (3.420)
Median (min, max)	19.88 (13.6, 25.1)	20.58 (14.0, 22.3)	16.49 (15.9, 17.1)	16.57 (14.9, 26.4)

Abbreviations: BMI = body mass index, ITT = intention to treat, max = maximum, min = minimum, N = number of patients in the treatment group analysis set, n = number of patients in the specified category with non-missing values, SD = standard deviation.
Age was calculated as: year of informed consent – year of birth + 1. BMI was calculated as weight (kg) / (height (m)^2).
Source: Section 14, Table 14.1.2.1.3

Medical History

Seventy-three (73 [94.8%]) patients had at least 1 disease/event reported in their medical history. Splenomegaly was the disease recorded most often, i.e. in 19 (24.7%) patients. Osteopenia was recorded with second highest frequency, i.e. in 14 (18.2%) patients.

Concomitant medication:

Seventy-three (73 [94.8%]) patients reported intake of medication other than trientine. Drugs from the class of mineral supplements were named as concomitant medication most frequently (in 40 [51.9%] patients). The second highest frequency was found for the class of vitamins (in 35 [45.5%] patients). Intake of zinc acetate, zinc sulphate and zinc was reported by 17 (22.1%), 16 (20.8%) and 7 (9.1%) patients, respectively. In table below, drugs are listed by anatomical therapeutical chemical (ATC) Level 2 Classification and preferred term if they were used by at least 4 patients.

Table 8

Table 11-5 Summary of Concomitant Medication in ≥ 4 patients (ITT)

ATC Level 2 Classification Preferred Name	Trientine (N=77) n (%)
Patients with any Concomitant non-study Medications	73 (94.8)
Analgesics	13 (16.9)
Paracetamol	5 (6.5)
Anti-inflammatory and anti-rheumatic products	17 (22.1)
Penicillamine	10 (13.0)
Ibuprofen	7 (9.1)
Beta blocking agents	5 (6.5)
Propranolol hydrochloride	4 (5.2)
Bile and liver therapy	6 (7.8)
Ursodeoxycholic acid	5 (6.5)
Diuretics	5 (6.5)
Spironolactone	4 (5.2)
Drugs for acid related disorders	22 (28.6)
Omeprazole	10 (13.0)
Pantoprazole sodium sesquihydrate	9 (11.7)
Ranitidine	6 (7.8)
Drugs for obstructive airway diseases	6 (7.8)
Salbutamol	5 (6.5)
Mineral supplements	40 (51.9)
Zinc sulfate	16 (20.8)
Lekovit CA	13 (16.9)
Magnesium	12 (15.6)
Zinc	7 (9.1)
Other alimentary tract and metabolism products	20 (26.0)
Zinc acetate	17 (22.1)
Psychoanaleptics	9 (11.7)
Citalopram	4 (5.2)
Thyroid therapy	15 (19.5)
Levothyroxine sodium	12 (15.6)
Vitamins	35 (45.5)
Pyridoxine hydrochloride	16 (20.8)
Colecalciferol	12 (15.6)
Pyridoxine	7 (9.1)
Tocopherol	5 (6.5)

Abbreviations: ATC = Anatomic Therapeutic Chemical, ITT = intention to treat, N = number of patients in the treatment group analysis set, n = number of patients in the specified category with non-missing values, WHO DD = World Health Organization Drug Dictionary.
Note: Classifications of concomitant medications were based on the WHO DD version March 2016.
Source: Section 14, Table 14.1.6

Ferenci Score

A total Ferenci Score of >3 confirmed Wilson disease diagnosis for this study. A Ferenci Score at baseline was available for all 77 patients of the ITT group. All of these patients had a Ferenci Score of >3. More details are provided in Table 9.

Table 9

Table 11-6 Ferenci Score at Baseline (ITT)

Characteristic	Trientine (N=77)
Liver Copper (in Absence of Cholestasis), [Sub-score], n (%)	
Unknown	47 (61.0)
Normal (<50 µg/g), [-1]	0 (0.0)
≤ 5×ULN (50-250 µg/g), [1]	6 (7.8)
> 5×ULN (250 µg/g), [2]	23 (29.9)
Serum Ceruloplasmin, [Sub-score], n (%)	
Unknown	16 (20.8)
Normal (> 0.2 g/L), [0]	5 (6.5)
0.1 – 0.2 g/L, [1]	20 (26.0)
< 0.1 g/L, [2]	36 (46.8)
Rhodanine Stain (in Absence of Quantitative Liver Copper Determination), [Sub-score], n (%)	
Unknown	61 (79.2)
Absent, [0]	11 (14.3)
Present, [1]	1 (1.3)
Kayser-Fleischer Rings, [Sub-score], n (%)	
Unknown	14 (18.2)
Absent, [0]	32 (41.6)
Present, [1]	31 (40.3)
Mutation Analysis, [Sub-score], n (%)	
Unknown	10 (13.0)
No Mutation Detected, [0]	3 (3.9)
1 Chromosome Mutation, [1]	21 (27.3)
2 Chromosome Mutations, [4]	43 (55.8)
Neurological Symptoms, [Sub-score], n (%)	
Unknown	16 (20.8)
Absent, [0]	40 (51.9)
Mild , [1]	7 (9.1)
Severe, [2]	13 (16.9)
Urinary Copper (in Absence of Acute Hepatitis), [Sub-score], n (%)	
Unknown	26 (33.8)
Normal (< 0.9 µmol/d or < 100 mg/d), [0]	4 (5.2)
1-2×ULN, [1]	9 (11.7)
> 2×ULN, [2]	25 (32.5)
Normal but > 5× Upper Limit of Normal after d-Penicillamine, [2]	12 (15.6)
Coomb's Negative Haemolytic Anaemia, [Sub-score], n (%)	
Unknown	45 (58.4)
Absent, [0]	29 (37.7)
Present, [1]	3 (3.9)
Total Score	
n	77
Mean (Standard Deviation)	6.7 (2.24)
Median (Minimum, Maximum)	6.0 (4, 14)

Abbreviations: ITT = intention to treat, N = number of patients in the treatment group analysis set, n = number of patients in the specified category with non-missing values, ULN = upper limit of normal.
Source: Section 14, Table 14.1.2.3.1

Numbers analysed

A total of 81 patients were enrolled into the study, however 4 patients (4.9%) did not meet the inclusion criteria. Therefore, a total of 77 (95.1%) patients were included in the ITT population.

Outcomes and estimation

Clinical course of hepatic disease

Over the course of trientine treatment, hepatic symptoms 'improved to normal' in 17 (22.1%) patients and were 'improved but not normal' in 21 (27.3%) patients, leading to a total of 38 (49.4%) patients showing improved hepatic symptoms, with 27 (35.1%) patients 'asymptomatic', 8 (10.4%) patients 'unchanged' and 4 (5.2%) patients with 'worsened symptoms'. Hepatic outcome was generally similar after 6, 12, 24, 36 and 48 months of treatment.

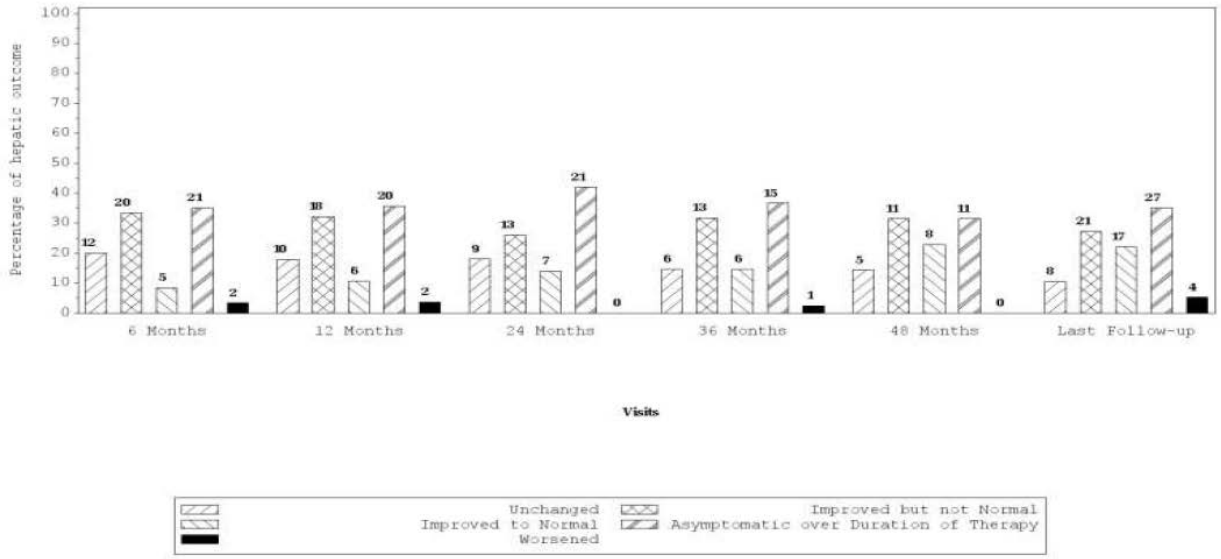
Table 10 Hepatic outcome

Table 2.7.3-2: Hepatic Outcome (ITT) in Study UNV-TRI-002

	6 Months	12 Months	24 Months	36 Months	48 Months	Last Follow-up
Hepatic Outcome, n (%)[1]						
n	60	56	50	41	35	77
Unchanged	12 (20.0)	10 (17.9)	9 (18)	16 (14.6)	5 (14.3)	8 (10.4)
Improved but not normal	20 (33.3)	18 (32.1)	13 (26.0)	13 (31.7)	11 (31.4)	21 (27.3)
Improved to normal	5 (8.3)	6 (10.7)	7 (14.0)	6 (14.6)	8 (22.9)	17 (22.1)
Asymptomatic over duration of therapy	21 (35.0)	20 (35.7)	21 (42.0)	15 (36.6)	11 (31.4)	27 (35.1)
Worsened	2 (3.3)	2 (3.6)	0	1 (2.4)	0	4 (5.2)
Inadequate hepatic response since last available time point, n (%)[1]						
n	59	55	49	41	35	76
Yes	2 (3.4)	2 (3.6)	1 (2.0)	1 (2.4)	0	2 (2.6)
No	57 (96.6)	53 (96.4)	48 (98.0)	40 (97.6)	35 (100.0)	74 (97.4)
Reason for inadequate hepatic response, n (%)[2]						
Increase of at least two of three liver enzymes (AST, ALT, GGT) ≥twice normal range or ≥twice baseline and increase of 24-hour urinary Cu excretion when collected in two consecutive measurements	1 (50.0)	0	0	1 (100)	0	0
Other	1 (50.0)	2 (100.0)	1 (100.0)		0	2 (100)

Source study UNV-TRI-002, Table 11-10
Abbreviations: ALT=alanine aminotransferase, AST=aspartate aminotransferase, Cu=copper, GGT=gamma-glutamyltranspeptidase, ITT=intention to treat, n=number of patients in the specified category with non-missing values.
Note: Months were months post initiation of treatment with trientine.
1 Percentages were based on the number n of patients with assessment of hepatic outcome/hepatic response.
2 Percentages were based on the number of patients with inadequate hepatic response.

Figure 11-1 Hepatic Outcome Over Time (ITT)



Abbreviations: ITT = intention to treat.

Source: Section 14, Figure 14.2.1

Figure 3 Hepatic Outcome over time (ITT)

Clinical course of neurological disease

Neurological symptoms 'improved to normal' in 2 (2.6%) patients and were 'improved but not normal' in 9 (11.7%) patients, leading to a total of 11 (14.3%) patients showing improved neurological symptoms, with 36 (46.8%) patients 'asymptomatic', 28 (36.4%) patients 'unchanged' and 2 (2.6%) patients with 'worsened symptoms'. Overall, neurological outcome was similar after 6, 12, 24, 36 and 48 months of treatment.

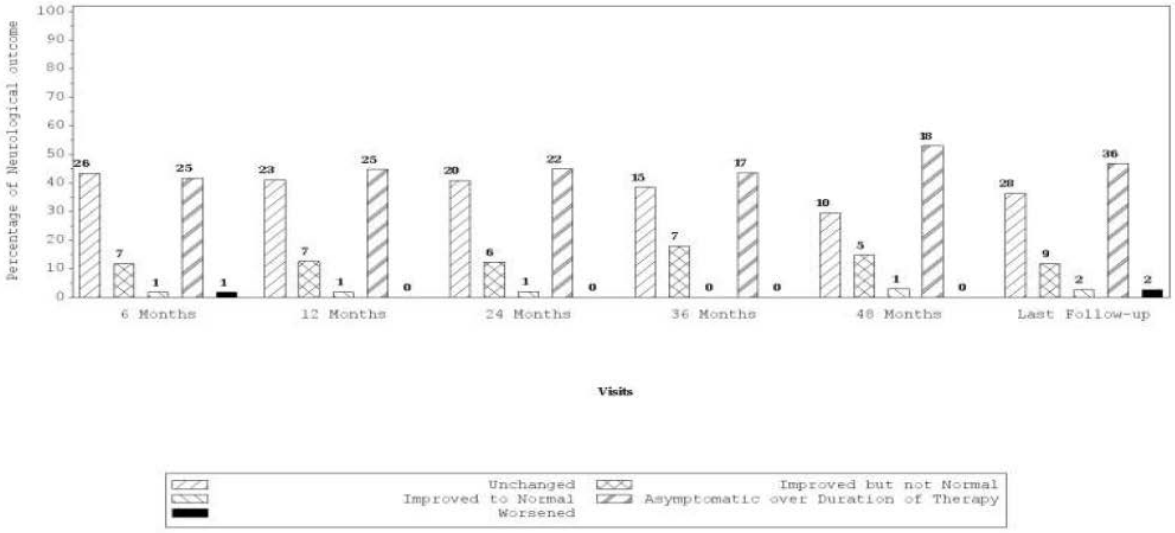
Table 11 Neurological outcome (ITT)

Table 11-9 Neurological Outcome (ITT)

	6 Months	12 Months	24 Months	36 Months	48 Months	Last Follow-up
Neurological Outcome, n (%)						
n	60	56	49	39	34	77
Unchanged	26 (43.3)	23 (41.1)	20 (40.8)	15 (38.5)	10 (29.4)	28 (36.4))
Improved but not Normal	7 (11.7)	7 (12.5)	6 (12.2)	7 (17.9)	5 (14.7)	9 (11.7)
Improved to Normal	1 (1.7)	1 (1.8)	1 (2.0)	0	1 (2.9)	2 (2.6)
Asymptomatic Over Duration of Therapy	25 (41.7)	25 (44.6)	22 (44.9)	17 (43.6)	18 (52.9)	36 (46.8)
Worsened	1 (1.7)	0	0	0	0	2 (2.6)
Inadequate Neurological Response since Last Available Time Point, n (%)						
n	59	55	48	39	34	76
Yes	1 (1.7)	0	0	0	0	1 (1.3)
No	58 (98.3)	55 (100)	48 (100)	39 (100)	34 (100)	75 (98.7)

Abbreviations: ITT = intention to treat, n = number of patients in the specified category with non-missing values.
Note: Months were months post initiation of treatment with trientine.
Percentages were based on the number n of patients with assessment of neurological outcome/neurological response.
Source: Section 14, Table 14.2.2

Figure 11-2 Neurological Outcome Over Time (ITT)



Abbreviations: ITT = intention to treat.

Source: Section 14, Figure 14.2.2

Figure 4 Neurological outcome Over Time (ITT)

General laboratory parameters

Although the majority of patients did not have ALT, AST, GGT or all transaminases (ALT, AST, GGT) and total bilirubin, albumin and INR within normal range at the 6, 12, 24, 36, 48 month and follow up visits; the majority of values outside of the normal range were not considered clinically relevant by the Applicant. These values were considered to reflect acceptable findings in patients with chronic liver disease. There were no observable trends over time in biochemistry and haematology.

Values are available from a fraction of patients at each time point and no reference values are stated. Observed reduction in alanine aminotransferase (and to a lesser degree aspartate aminotransferase) could be considered a treatment success. , No relevant changes were observed on other laboratory parameters.

Copper storage and metabolism

A change in 24-hour urine Cu excretion over the course of trientine treatment could only be determined for 10 patients, with 7 showing a decrease, indicating efficacy, and 3 showing an increase, which could be linked to mobilisation of Cu. Although the method used in derivation of the non-ceruloplasmin bound Cu (NCC) concentration limits the value of this parameter in interpretation of efficacy, overall the median NCC concentration showed a decrease from baseline on each testing time point, with the exception of 48 months.

A patient's Cu burden can be evaluated by 24-hour urine Cu excretion during a treatment-free period, whereas urine Cu excretion measured whilst patients are receiving trientine treatment will reflect the trientine dose. Much of the retrospective urine Cu data was collected whilst patients were receiving trientine treatment and in many cases dose levels changed over the duration of treatment. Treatment-free urine Cu data are available on more than one time point for only 10 patients. Of these

patients, 7 showed a decrease in 24-hour urine Cu excretion between the 2 time points, indicating efficacy, whereas 3 showed an increase, which could be linked to mobilisation of Cu.

Serum ceruloplasmin and total serum Cu are not, in themselves, indicative of efficacy, although both are likely to be below normal levels in Wilson disease patients. Concentrations of serum ceruloplasmin and total serum Cu are used to derive the concentration of NCC using the following equation:

NCC (µmol/L) = Serum Copper (µmol/L) – [47.2 x Serum Ceruloplasmin (g/L)].

As a derived parameter, NCC has limitations, particularly with the low serum ceruloplasmin concentrations in Wilson disease patients being close to the limit of quantification of the assay method. As a result, it is acknowledged that approximately 20% of NCC results will be theoretically impossible negative values [Twomey et al. 2005]. Although the limitations of the derived NCC concentration mean this parameter should be treated with caution, the median NCC concentration showed a decrease from baseline on each testing time point, with the exception of 48 months. Subgroup analyses of the results from parameters of Cu storage and metabolism by gender, diagnosis, initiation of trientine, age group and presence of liver cirrhosis for patients with hepatic or mixed presentation at initiation of trientine are provided. No clear trend was seen in the subgroup analyses.

Table 12

Table 11-13 Copper Storage and Metabolism (ITT)

	Baseline	6 Months	12 Months	24 Months	36 Months	48 Months	Last Follow-up
24-hour Basal Urine Copper Excretion (µmol/24 h)							
n	49	38	34	32	32	28	58
Mean (SD)	4.526 (6.6898)	3.410 (3.2636)	2.839 (1.9684)	2.511 (1.7612)	2.630 (2.1080)	3.010 (2.0214)	12.128 (61.7660)
Median (min, max)	1.963 (0.25, 32.80)	2.226 (0.61, 19.07)	2.615 (0.75, 10.31)	2.205 (0.28, 8.46)	2.002 (0.63, 10.53)	2.525 (1.08, 10.85)	3.465 (0.46, 474.00)
Serum Ceruloplasmin (g/L)							
N	56	30	34	28	22	24	57
Mean (SD)	0.100 (0.0961)	0.076 (0.0493)	0.077 (0.0618)	0.085 (0.0658)	0.081 (0.0610)	0.087 (0.0570)	0.069 (0.0549)
Median (min, max)	0.055 (0.01, 0.52)	0.050 (0.01, 0.18)	0.050 (0.01, 0.29)	0.050 (0.01, 0.26)	0.050 (0.02, 0.23)	0.085 (0.02, 0.23)	0.060 (0.01, 0.23)
Serum Copper (µmol/L)							
N	45	30	30	29	22	23	60
Mean (SD)	5.573 (3.9211)	4.269 (3.2853)	4.459 (3.1362)	5.009 (3.4760)	4.746 (3.5884)	6.676 (3.5057)	4.630 (3.4921)
Median (min, max)	5.200 (0.40, 21.90)	3.650 (0.40, 11.90)	3.700 (0.04, 11.78)	4.400 (1.00, 15.00)	3.721 (0.40, 14.00)	6.500 (1.57, 13.19)	3.100 (0.40, 15.30)
Non-Ceruloplasmin Bound Copper (µmol/L)							
N	42	27	30	28	21	23	57
Mean (SD)	2.142 (2.0502)	1.324 (1.6364)	1.211 (1.3600)	1.074 (1.1222)	1.562 (1.3843)	2.658 (2.0715)	1.300 (1.3649)
Median (min, max)	1.614 (0.00, 8.60)	0.940 (0.00, 5.74)	1.048 (0.00, 5.17)	0.962 (0.00, 4.48)	1.440 (0.00, 4.56)	2.037 (0.22, 8.34)	0.996 (0.00, 8.22)

Abbreviations: ITT = intention to treat, max = maximum, min = minimum, n = number of patients in the specified category with non-missing values, NCC = non-ceruloplasmin bound copper, SD = standard deviation

Note: Months were months post initiation of treatment with trientine.

NCC was calculated as NCC (µmol/L) = Serum Copper (µmol/L) – [47.2 x Serum Ceruloplasmin (g/L)].

Derived NCC values < 0 are imputed by 0 in the calculation of summary statistics.

Source: Section 14, Table 14.2.4.1

Bibliographical data

Detailed PD data is sparse, but in the study by Cho et al. (2009), increased cupruresis compared to baseline and placebo was observed following single and multiple doses of 200, 600, 1200 and 3600 mg/day of TETA 2HCl (Protemix). Doses of 1200 mg/day (salt) or above produce a marked and consistent increase in urine copper excretion. Copper was excreted at the highest rate in the 0- to 2-hour interval following dosing, and the excretion decreased in each subsequent 2-hour interval. The mean 0- to 4-hour

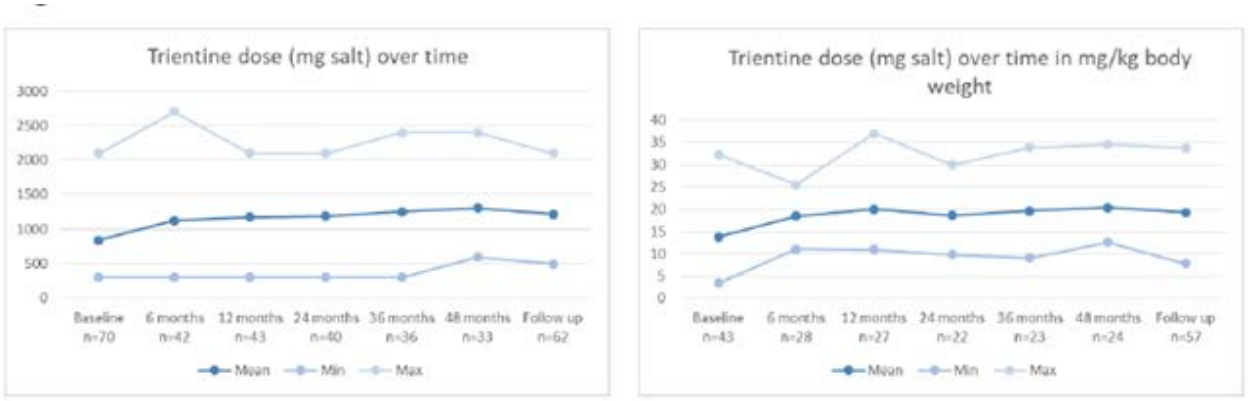
cumulative urine copper excretion accounted for approximately 72% of the mean total 24-hour urine copper excretion. Urinary copper excretion showed a similar pattern on days 1, 7, and 14. Following the first dose of TETA on day 1, total urinary copper excretion increased in a dose-proportional manner.

It also increases urinary excretion of zinc and iron. Urinary copper excretion is proportional to the dose of Trientine taken and varies significantly depending on glomerular filtration rate and sex (EASL 2012).

Dosing/Titration curve over time and Treatment compliance

Complete data sets from all predefined time points (6, 12, 24, 26, 48 months) are available only from a minority of the patients. The Applicant states that 'Due to the nature of this retrospective study, treatment compliance could not be determined in detail'. All available data on trientine dose were used to generate an overview of the trientine dose per time point, which is presented in figure below.

Figure 5 Trientine dose over time



Based on data from table 1.1 of the additional analysis for study UNV-TRI-002

Figure 5 indicates the following:

1. Mean starting doses were in general lower than mean maintenance doses and up-titration to maintenance doses occurred within the first 6 months.

2. Maintenance doses are relatively stable over time

3. Doses between 300mg TETA and 2700mg TETA were used in the study, but it is unknown how many patients received each dose (e.g. 300mg TETA doses and 2700mg TETA doses), why especially low or high doses were used (these doses were outside of the range of the SmPC of the UK product) or why the dose was not up-titrated in some patients initially receiving 300mg TETA.

4. Mean starting doses are below 20mg/kg indicating that the proposed paediatric dose/kg is higher than what is used for starting doses in adults.

It was noticed that the maximum doses reported in figure 3 were not in line with what was reported as maximum doses in this study in the initial submission. The Applicant clarified that the maximum dose of 2100 mg presented in Table 14.1.3.1 of the CSR of Study UNV-TRI-002 was the maximum dose used at the beginning of trientine treatment. The dose of 2700 mg, as displayed in figure 3 was the maximum dose observed during the 48 months period.

EASL GL states that typical doses of trientine are 900–2700 mg day in two or three divided doses, with 900–1500 mg/day used for maintenance therapy. This seems to indicate that higher doses of trientine can be used at treatment initiation, and would somewhat contradict the findings from study UNV-TRI- 002

discussed above and the Applicant's postulated: 'start low and go slow' approach. It remains unknown in what situations doses on the upper end of the proposed dose range (Cufence SmPC or EASL) are indicated. The current dosing proposal is in line with what is approved in the SmPC for the nationally approved Trientine dihydrochloride 300mg capsules (200mg trientine base) in UK since more than 30 years, however.

Analyses of temporary treatment discontinuation for all included patients were not provided. This is because no exposure data are available from the study participants to inform on treatment compliance.

Treatment compliance is a known issue for trientine therapy (patients have to take up to 4 doses a day and the product should be stored in a refrigerator) appropriate precautionary statements were included in the product information.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13 Summary of Efficacy for trial UNV-TRI-002

Title: Multicenter, Retrospective Study to Assess Long-term Outcomes of Chelator-based Treatment with Trientine in Wilson Disease Patients Withdrawn from Therapy With D-penicillamine			
Study identifier	unknown		
Design	This study was a retrospective review of Wilson disease patients' medical records and aimed to assess the efficacy, safety, and tolerability outcomes of trientine chelator-based treatment after withdrawal of D-penicillamine in a multicenter study. Patients had been receiving treatment as directed by their physician.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		15.6.2016 to 10.4.2017 (data processing) not applicable not applicable
Hypothesis	Outcomes were exploratory and descriptively prepared (no inferential statistics were applied) with no hierarchy of endpoints		
Treatments groups	Oral treatment with trientine as second line treatment after receiving D-penicillamine as first line.		Cufence capsules in the patient's usual dose for a minimum of 6 months
Endpoints and definitions	Exploratory		Clinical outcome for each time point (6, 12, 24, 36 and 48 months) after initiation of trientine treatment based on clinical course of neurological and hepatic disease
	Exploratory		Cu storage and metabolism measurement at each time point after initiation of trientine treatment
	Exploratory		Safety of trientine and time to discontinuation of treatment due to AE and/or inadequate response
Database lock	Presumably 10.4.2017		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Intent to treat, 6, 12, 24, 36 and 48 months and last available follow-up time point.			
Descriptive statistics and estimate variability	Treatment group	Cufence	N/A	N/A
	Number of subject	77	N/A	N/A
	Clinical course of hepatic disease (descriptive)	improved to normal in 17 (22.1%) patients, improved but not normal in 21 (27.3%) patients, 27 (35.1%) patients asymptomatic, 8 (10.4%) patients unchanged and 4 (5.2%) patients worsened	N/A	N/A
	N/A	N/A	N/A	N/A
	Clinical course of neurological disease (descriptive)	improved to normal in 2 (2.6%) patients, improved but not normal in 9 (11.7%) patients, 36 (46.8%) patients asymptomatic, 28 (36.4%) patients unchanged and 2 (2.6%) patients worsened	N/A	N/A
	N/A	N/A	N/A	N/A
Notes	Efficacy was estimated based on a non-validated 5-category scoring system (improved to normal, improved but not normal, asymptomatic, unchanged and worsened), the underlying source data are unknown and so is the way the clinical data were translated into the score. The analysis indicate a 'comparison to baseline' but no baseline data are reported. Efficacy results based on this analysis are not considered reliable.			
Analysis description	**N/A**			

Clinical studies in special populations

No dedicated studies in special populations are available. Of the 77 patients included in UNV-TRI-002, 16 (20.8%) patients were paediatric patients (aged <18 years). There were 6 patients under the age of 8 at the start of trientine. Of these 6 patients, 3 patients were either 4 or 5 years of age. The oldest included patient was 67. The proposed lower age limit for Cufence is 5 years.

The majority of WD patients are suffering from impaired hepatic function. No information on patients with renal impairment is available. There is only very limited data for elderly patients. According to the SmPC no specific dose adjustment is required in these patients.

Supportive studies

Prospective part of study UNV-TRI-002

The study report of the prospective part of the study was submitted during the course of the procedure. This investigation is a continuation of the retrospective part of UNV-TRI-002; the objectives and designs are similar in both parts, apart from an additional QoL objective included in the prospective part.

Enrolment in the prospective part of the study was for 12 months, with data collection at 'baseline' and at 6 and 12 months. 'Baseline' was defined as the last non-missing assessment value from the retrospective trial, and was thus variable for individual patients.

All 52 included patients had also been enrolled in the retrospective part of the study, and were continued to be observed in a prospective fashion. The prospective part of the study was conducted in 1 centre in Germany in patients that gave consent. The total amount of patients studied in UNV-TRI-002 does not increase.

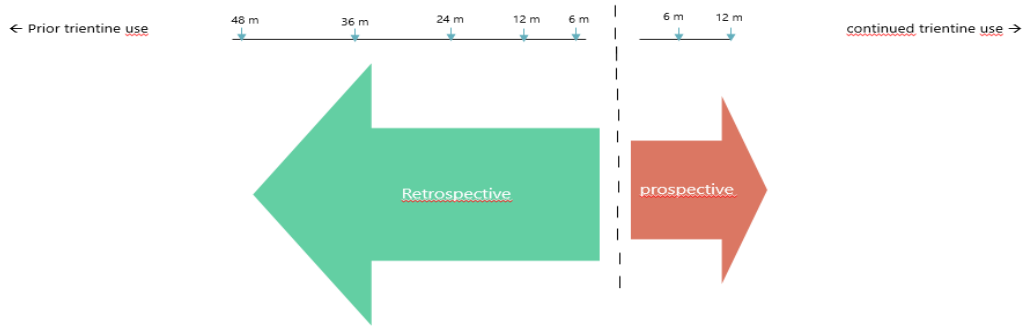


Figure 6 ***(made by the assessor): Study UNV-TRI-002 observation scheme***

The clinical results were described by the same 5-point score as was applied in the retrospective part (see Discussion of efficacy below).

PD parameters of interest measured in the prospective part are assessed in depth in the D180 JRAR and also discussed together with PD results from the retrospective part in the section 'Dose-response studies and main clinical studies' in this report.

The only additional measure in this prospective part of the study was collection of QoL data; Index values for the EQ-5D-3L questionnaire and their changes from baseline were measured at baseline, month 6 and month 12.

Clinical course of neurological disease

Of the 51 patients included in the prospective analysis, the neurological symptoms improved but not to normal in eight patients (15.7 %), and improved to normal in one patient (2.0%). In 12 patients (23.5%) symptoms remained unchanged and there was one patient (2.0%) with worsening of neurological symptoms. A total of 29 (56.9%) patients were asymptomatic over the duration of therapy.

The patient with the worsening neurological symptoms used a stable dose of 1200 mg/day trientine. This patient was asymptomatic at baseline, and neurological symptoms were increased at 12 months.

UWDRS - Neurologic Subscale

The mean score of the total neurological subscale of the UWDRS was 11.3 at baseline and decreased to 9.7 in month 6 and 8.8 in month 12. This decrease was mainly due to changes in the subscore II (sum of

all items of part III, the neurological part of the UWDRS), which decreased from 9.6 at baseline to 8.0 in month 6 and to 7.1 in month 12. The subscore I (sum of all items of parts I on consciousness and part II on disability of the UWDRS) remained virtually the same during the study (1.7 at baseline, 1.6 in month 6 and 1.7 in month 12).

The results of the neurological subscale of the UWDRS indicates a neurological improvement during treatment with trientine.

Quality of Life – Anxiety/depression question

Of the 51 patients 34 were not, 15 were moderately and two were extremely anxious or depressed at baseline. The number of extremely anxious or depressed patients remained the same during the 12 month prospective study. The number of patients with moderate anxious or depressed state decreased from 15 to 11 at month 6 and to 9 at month 12, while the number of patients without anxiety or depression increased from 34 at baseline to 38 at month 6 and to 40 at month 12. These data indicate that overall, the anxiety and depression improved during treatment with trientine

Adverse events

Four patients (7.7%) reported a psychiatric adverse event; adjustment disorder, aggression, depression and drug abuse were each reported by one patient (1.9%). All four adverse events were considered to be unrelated to the study treatment.

Note: The described doses are expressed as mg of trientine dihydrochloride salt (i.e. not in mg of the trientine base).

Literature data

Literature data on trientine (in WD) is one major cornerstone for this mixed marketing application. Therefore, particular attention is given to the provided literature search and identified publications.

This application includes 133 literature references dated 1958-2017 to support clinical and preclinical parts of the dossier. Approximately 12 clinical studies were identified on the use of trientine in Wilson's disease, as well as more than 12 reported case studies and more than 20 reviews on the use of trientine in the management of Wilson's disease. However, no real rating of the relevance of individual publications for the present applications was made by the Applicant; identified literature considered relevant for clinical aspects was only listed under the heading 'key studies'. In the course of the assessment of this procedure, further (older and also recent) relevant publications on WD were identified.

Controlled trials with active or placebo comparison or trials testing different doses (apart from one study four Japanese patients who received increasing doses from 1.0 to 2.0 g/day to 2.5 to 3.0 g/day, (Saito et al., 1991)) or titration schemes are not included within the list of historical trials and such data might not be available. Only retrospective, single arm reviews and case reports are included.

Studies from the Literature – Adults

Identified literature has shortly been summarized to provide an overview of available data.

Baseline characteristics for the populations included in the 6 retrospective cohort studies (Weiss et al., 2013; Weiss et al., 2011a; Hölscher et al., 2010; Merle et al., 2007; Rodrigo Agudo et al., 2008, Sini et al., 2013) were described and from the information provided (no Ferenci scores are available) they seem to adequately reflect the target population of WD patients, apart from the fact that a part of included patients has used trientine as first line treatment. The same holds true for the patients from the case reports (five reports: Walshe, 1982: Scheinberg et al., 1987; Dahlman et al., 1995; Dubois et al., 1990; Saito et al., 1991). The total number of adult patients (using trientine for WD, first or second line) included in the 6 historical reviews is about 231, and 63 such patients were studies in the case reports.

Altogether the literature database contains information from around 300 WD patients using trientine. Data on trientine second line use compiles around 200 patients. However, significant patient overlap between publications is assumed.The Applicant acknowledges the risk that data from some patient cohorts or individuals may have been reported more than once. This could be suspected for the following references (including, but not limited to): Weiss et al. 2013 and Weiss et al. 2011 and Merle et al., 2007, for Hölscher et al. 2010 and another Hölscher et al. 2010 publication as well as for the two publications from Scheinberger et al., both published 1987.

The most significant of the submitted literature references is the publications by Weiss et al., 2013 as it included the vast majority of patients and reports the most details. There are suspected overlaps with the study population from study UNV-TRI-002.

In Weiss et al. 2013 data on the effects on hepatic and neurologic symptoms and AEs were collected for a median of 13.3 years. Follow-up at 48 months showed that in symptomatic hepatic patients approximately 90% of patients improved, regardless of 1st line treatment received; additionally, when chelators were given as 2nd line therapy, rates of improvement were not statistically different between groups. D-penicillamine was associated with a higher incidence of AEs leading to discontinuation. Both drugs were not as effective in treating neurologic symptoms as in treating hepatic symptoms, which is in line with other observations on the topic. For evaluation of effect, the same 5 point evaluation score as used for assessment of UNV-TRI-002 results was used. The aim of this study was to evaluate safety of chelator therapy and respective long term outcomes. No formal objective or endpoint was defined.

In Weiss et al., 2011a chelator therapy was compared to zinc in WD patients and zinc was found out to be less effective when looking at hepatic results and also survival. Effectiveness was mainly evaluated according to analyses of nonresponse to therapy and treatment discontinuations (including respective reasons). No objective or endpoint was defined. Some literature references indicate that a combination of therapies (trientine and zinc) could be beneficial.

Another rather large cohort was observed by Merle et al., 2007, who also reviewed long term outcomes of WD patients. Side effects while under treatment where recorded and compared between D-penicillamine, trientine and zinc with trientine and zinc being significantly better tolerable. For evaluation of hepatic and neurological symptoms over time it was not distinguished between the respective treatment options, but symptoms improved in the majority of patients. The authors claim that results show a similar survival of patients with Wilson's disease when compared with a control population matched for age and sex.

The number of WD patients treated with trientine as second line option from the other publications is small and not many details are available, however, the overall impression is that trientine does improve WD symptoms while appearing better tolerable than D-penicillamine.

The quality of the provided historical investigations is low and often there is no information on the trientine product used, no information on applied dose was provided e.g. by Weiss et al. 2013 and 2011). Many patients received concomitant medications together with trientine (D-penicillamine or zinc) or used trientine as first line treatment. However, it is acknowledged that most of the trientine patients from these historical references used trientine for long periods (many years).

Treatment outcomes, while not investigated by state of the art measures, were overall reported favorably for trientine as second line treatment. While the investigations were mostly not suitable to allow exact estimation of the treatment effect, they support the assumption that trientine is a recognized treatment that is widely used and well tolerated and improves survival. Trientine is mentioned in relevant treatment guidelines as state of the art therapy in Wilson's disease (see table 2.7.3-7 (Table 14) for a summary of guideline recommendations).

Table 14 Recommendations for Treatment

Table 2.7.3-7 Recommendations for Treatment

Recommendation	Guideline	Strength of Evidence	Reference
Initial treatment for symptomatic patients with Wilson's disease should include a chelating agent (D-Penicillamine or trientine). Trientine may be better tolerated	EASL	GRADE II-1, B, 1*	EASL, 2012
	AASLD	Class I**, Level B	Roberts and Schilsky, 2008
Treatment of presymptomatic patients or those with neurological disease on maintenance therapy can be accomplished with a chelating agent or with zinc	EASL	GRADE II-1, B, 1*	EASL, 2012
	AASLD	Class I**, Level B	Roberts and Schilsky, 2008
Treatment is lifelong and should not be discontinued, unless liver transplantation is performed	EASL	GRADE II-1, B, 1*	EASL, 2012
	AASLD	Class I**, Level B	Roberts and Schilsky, 2008

Source Roberts and Schilsky, 2008; EASL, 2012
Abbreviations EASL= European Association for the Study of Liver; AASLD=American Association for the Study of Liver Diseases
*Strong recommendation: Factors influencing the strength of recommendation included the quality of evidence, presumed patient-important outcomes and costs;
**Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.

Guideline recommendations suggest that trientine may be better tolerated than D-penicillamine. It is noted that the two stated guideline documents (EASL and AASLD) discuss trientine primarily as treatment alternative to D-penicillamine rather than as second line treatment.

Studies from the Literature - Children

As for adults, the amount of data for second line use of trientine in paediatric WD patients is quite small and the quality of the publications is limited. The total number of patients (using trientine for WD) included in the 7 historical reviews cited above is about 50. It is acknowledged that paediatric patients were often included in the publications for adults, and thus, the actual extent of exposure might be a little bit larger. However, patient overlap cannot also be excluded for the paediatric references.

Baseline characteristics for the paediatric populations included in the seven submitted studies (Arnon et al., 2007; Taylor et al., 2009; Avinashi and Ling, 2009; Dhawan et al., 2005; Manolaki et al., 2009; Sarles et al., 2001; Millard et al., 2015) indicated that from the information provided (no Ferenci scores are available) they adequately describe the target population (paediatric WD patients), apart from the fact that a part of included patients has used trientine as first line treatment. First line trientine use seems to be more common in paediatric patients compared to adults, probably due to the better tolerability compared to D-penicillamine.

The symptoms of the observed children mostly improved under treatment and, if used as second-line after discontinuation of D-penicillamine, respective D-penicillamine side effects mostly resolved with trientine. Paediatric data confirm what has been seen in adults with this regard. For some children observed in these literature references observational periods of decades up to 37 years (Dhawan et al., 2005)) are available. Considering that untreated WD is universally fatal, these life spans support the notion that chelation therapy improves survival in paediatric WD patients. Doses used are not always stated in the individual reports but seem to have been applied over a wide dose range.

2.5.3. Discussion on clinical efficacy

The evidence base to support Cufence efficacy consists of post-hoc review of available data from various primary data sources, Study UNV-TRI-002 with a prospective and retrospective part and a review of bibliographical references. This is an acceptable approach in view of the applied legal basis (full mixed marketing application). This is also in line with the protocol assistance issued in 2012, where CHMP stated that a retrospective study and review of clinical experience, together with PK and PK/PD data, might be sufficient for a second-line indication.

Design and conduct of clinical studies

UNV-TRI-002

The retrospective part of study UNV-TRI-002 was a multicenter review based on information obtained from the medical records of 77 patients that were already attending major tertiary care centers for the treatment of Wilson's disease. Assessments were performed for 6, 12, 24, 36 and 48-month time points, as available. No control, blinding or randomization measures were introduced in the trial, which makes the design susceptible to confounding factors and bias. The number of paediatric patients included (n=16 (20.8%)) is considered borderline sufficient to assess efficacy of Cufence in children with WD.

Overlaps with the study population reported by Weiss et al. 2013, who studied WD patients in the same geographic area as the applicant cannot be excluded. Information flow between study centers and sponsor might have driven center selection, subject selection or time frame selection prior to protocol setup and selection of patients for study UNV-TRI-002 might have been data driven No evidence based selection of planned sample size (n=90) was performed. While the Applicant argues that all available patients that gave consent for participation in the study and met the inclusion and exclusion criteria were included for participation, it seems that there were no measures introduced in the data processing steps to protect against such bias (e.g. a selection after protocol setup).

The prospective part of the study was conducted in one single centre in Germany and was a continuation of the retrospective part of UNV-TRI-002, including 52 patients that gave consent. The switch from the retrospective to the prospective observation part and its impact on the results is difficult to interpret.

Enrolment in the prospective part of the study was for 12 months, with data collection at 'baseline' and at 6 and 12 months. 'Baseline' was defined as the last non-missing assessment value from the retrospective trial, and was thus variable for individual patients.

Treatments

Patients were treated with trientine according to their usual regimen. While this is not optimal from a methodological point of view (as it introduces variability), it is one suitable option for a long-term investigation of trientine in WD patients. There was no control group (and no randomisation/blinding) in the trial. While placebo control would likely not have been ethically defendable, comparison with other treatment options (e.g. zinc or DPA) would have been feasible in principle. As a second line label is sought, direct comparison with D-penicillamine as active control was not studied.

Inclusion and exclusion criteria are deemed largely suited to identify the target population. Although no validation work seems to have been done (or was submitted) for the Ferenci score, this appears to be an established algorithm to diagnose Wilson's disease in clinical practice. According to Roberts EA, Schilsky ML (2008) it has been subjected to preliminary validation in children, but no detailed data are available. Patients with a Ferenci score of 4 or higher were included which means that the diagnosis of WD is highly likely. It is unknown if a higher Ferenci score indicates a more severe form of disease, however some of the criteria included are suited to change in response to effective treatment and could thus also be interesting to measure treatment success.

The female predominance is rather surprising as a male predominance would rather have been expected (see Litwin et al. 2012; they observed a male predominance in a large population of WD patients included in a registry between 1958 and 2010 (327 males vs. 290 females; $p<0.05$). The Applicant did not comment on this issue, but it seems that more female patients were included in all of the submitted literature reviews. Differences in reaction to treatment (efficacy and safety) between genders seem however unlikely.

The youngest children were 4 years of age. Though the majority of patients with Wilson disease are diagnosed at an age between 5 and 35 (mean 13) years (Lin et al. 2014), WD may be diagnosed in younger patients. In a study of 143 children with WD, 21 children (15 percent) presented with symptoms or abnormal liver function tests before the age of five years (Wiernicka et al. 2017). But the age range of included patients is considered appropriate for claimed indication.

Endpoints, objectives

No primary endpoints were defined for study UNV-TRI-002. In such a situation, all evaluated endpoints could be considered exploratory or all measures could be interpreted as one composite endpoint and no inferential statistical methodology was applied according to the retrospective protocol. Therefore information regarding importance of specific endpoints, or rigor of evidence generated by the corresponding data collections is challenging to be interpreted.

The primary objectives (hepatic and neurological symptom progression under treatment) were assessed by applying a score of 5 categories; Unchanged, improved but not normal, improved to normal, asymptomatic over duration of therapy and worsening. Due to the not validated status of the score methodological concerns will need to be considered in the assessment. The 5-point scale was not applied in a standardized and comprehensive way. It is thus not a fully reliable basis to inform on trientine's influence on hepatic- or neurological symptoms in WD.

Patients were allocated to one of the categories based on the physician's decision and this decision was based on clinical measures from the patients (at a time). The clinical measures available could have been diverse and and the process translating them into the score was not standardized

It can however be considered as a reliable finding from this study that patients survived for many years under trientine treatment which, when comparing to what is known from the natural course of the disease indicates a relevant beneficial treatment effect. Taken all the above deficiencies into account, the efficacy data based on the applied score can only serve as supportive data.

Concomitant medications seem to have been unrestricted in the study and included D-penicillamine (DPA) and zinc preparations, which could have influenced the outcomes.

The WD population using trientine 2nd line can be divided in three groups: Patients who show intolerance during the 24-h D-penicillamine stress test (patients characteristics are those of a 1st line treatment); patients developing side effects early after the start of D-penicillamine treatment switching to trientine while they have not yet been fully de-coppered (more comparable to the characteristics of patients on 1st line treatment); and 'real' 2nd line patients who have developed an intolerance after prolonged treatment with D-penicillamine or show insufficient response. It seems likely that the de-coppering status should have influence on the determination of (starting) doses and titration schemes.

The information on how long patients were pre-treated with DPA or another chelating agent allowed CHMP to estimate the de-coppering status of the individual patient, as accumulation in the tissues cannot easily be estimated from clinical investigations/PD results alone. If patients hadn't had received chelating treatment for an extended period, they would likely be in a status comparable to a treatment naïve WD patient as copper accumulates again in tissues over time. The lag time between cessation of

D-Penicillamine and trientine treatment in the retrospective study UNV-TRI-002 was > 1 year in 17 patients (22% of ITT). The duration of D-Penicillamine treatment before trientine initiation was < 30 days in 9 patients (overlaps between the two categories are not reported). A considerable number of patients were therefore likely treated with trientine before 'initial de-coppering' had been completed.

While after in depth assessment of the respective data an influence of D-PA on study outcomes seems unlikely (both compounds were not used concomitantly, but previous D-PA use has been recorded in the concomitant drugs section for some patients) at least 27 patients received zinc in addition to trientine during long periods of time which could probably have affected related efficacy (and safety) outcomes as well as the trientine dose.

Impact of dissolution on clinical efficacy (and safety)

At some time during the study, the manufacturer of the product changed and a new trientine capsule with poorer dissolution properties was introduced. That the formulation of the product could have influence on the absorption and thus exposure of Cufence (and consequently on the dose) cannot be completely ruled out based on the provided data.

The comparison of patients receiving the one or the other formulation over the majority of time in UNV-TRI-002 revealed no obvious differences in observed safety and efficacy parameters. However, weaknesses of the applied evaluation measures were evident.

Time to Discontinuation of Treatment Due to Adverse Event or Inadequate Response

The time to discontinuation of treatment due to an adverse event or inadequate response is discussed in the context of the evaluation of efficacy in this application, as it was defined as efficacy objective. For discussion on the extent of exposure please refer to the respective section in the efficacy and safety part of this report.

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. Overall study results indicate that patients usually stay on trientine treatment for quite a long time (several years) before switching to an alternative.

Efficacy data and additional analyses

Patients were assessed for a maximum treatment duration of up to 48 months. The results of the 5-point outcome scale indicate a certain beneficial effect of Cufence on WD symptoms (hepatic and – to a lesser extent - neurological) can be assumed. Only a minority of patients worsened in disease status according to the provided results and no fatalities were reported. As WD is a chronic, progressive disease, stabilisation of symptoms could be considered a treatment success. Described weaknesses of the score and the study design need to be taken into consideration in this interpretation.

There was a constant decrease of analysed patients over time. However, 'last follow up'- data are available for all included patients, or rather only patients with information available from at least two time points were included in the trial ('6- months visit' and 'last follow up visit'). It is noted that a comparison of two (or three) time points only is considered less meaningful than a continuous analysis including many time points, also considering the variability of disease and the many confounding factors that could have influenced outcomes.

The Applicant argues that due to the challenges of evaluating a drug's performance in WD, patient's general well-being should also be taken into account. This is agreed upon, however, neither ‚QoL' nor 'survival' have been considered as objectives in the retrospective part of the study. In the prospective part of the study QoL data were collected. Index values for the EQ-5D-3L questionnaire (and their

changes from baseline) were measured at baseline, month 6 and month 12. Overall, the five dimensions of the EQ-5D-3L (mobility, self-care, usual activities, pain/discomfort, anxiety /depression) were relatively stable over the 12 months duration. This is not surprising in treated, stabilised WD patients and given the rather short time-period.

The way trientine was titrated in the study according to clinical parameters or disease symptoms was not reported systematically. Therefore gaps remain in the knowledge on the dose/exposure/response relationship of Cufence in WD patients.

Availability of free copper in the serum and also the rate of copper excretion can significantly increase at initiation of therapy in patients with high copper loads (especially when receiving high trientine doses), which can result in negative clinical effects such as neurological deterioration and be reflected in worsening of laboratory parameters. According to the Applicant, in clinical practice patients with higher copper loads are initially prescribed higher doses of trientine. Therefore, clear and precise titration rules for such cases would be desirable. For patients with neurological symptoms 'up-titration with moderation' and 'close monitoring' are recommended in the SmPC as these patients are at risk of neurological deterioration at treatment initiation, especially when the starting dose is high. However better characterisation of efficacy and PK/PD needs to be generated in a PAES in particular in patients with predominantly hepatic, neurologic or psychiatric symptoms as well as in paediatric patients.

Laboratory values are available only from a fraction of patients at each time point and no reference values are stated. Apart from a reduction in alanine aminotransferase (and to a lesser degree aspartate aminotransferase), which could be considered a treatment success, no relevant changes were observed. It could be assumed that laboratory parameters were investigated rather in patients with clinical symptoms than in asymptomatic patients (patients with complaints/deteriorating of symptoms are more likely to go into hospital for medical examination), which could have biased the outcome. However, this would more likely have resulted in an outcome not favouring trientine.

Cufence capsules are manufactured in 200 mg (trientine base) capsules only. The proposed lower age limit for Cufence (5 years) is justified based on the claimed appropriateness of the 200mg capsule for this age and weight category. However, lower strengths may be needed to accommodate a more appropriate initial dose and dose titration in children. Therefor the applicant is recommended to develop lower capsule strengths.

Literature data

Retrospective, single arm reviews and case reports are available.

The extent of WD patients studied within this bibliographical database is small. The number of WD patients referred to in historical studies relevant for this application (trientine second line use) is around 200 adults and 50 children, not considering patient overlap in different publications. Many patients received concomitant medications together with trientine (D-penicillamine or zinc) which may have impacted on treatment outcomes.

However, it is acknowledged that most patients used trientine for long periods (many years/decades). Also, treatment outcomes, while not investigated by state of the art measures, were overall reported favourable for trientine. Overall survival has not been evaluated in a systematic manner but despite the modest quality of the available literature and study data it can be derived with reasonable certainty that trientine treatment improves survival in WD patients, if they are compliant to treatment.

Chelating agents are used for various conditions in adults and also in paediatric patients (e.g. for treatment of iron overload). As for chelators in general, also trientine's mechanism of action is rather straightforward and most likely the same in children as in adults. There is no reason to believe that copper

binding and promotion of urinary copper excretion would not work similarly in children with WD compared to adult patients.

Bibliographical data on trientine use in children support these assumptions and are considered important for this application. The current Cufence SmPC recommends for paediatric patients 400-1000 mg trientine base at initiation of therapy and should be subsequently be adapted according to the patient's clinical response and based on free copper levels in plasma and the urinary copper excretion during maintenance therapy.

Identified gaps on the use of trientine in children and adolescents from the clinical study UNV-TRI-002 pertain to the lack of justification for (starting) dose and titration steps as well as for appropriate target parameters. According to the proposed SmPC and available publications, the dose for children should be reduced compared to adults, accounting for a lower body weight. However, there are no PK or PD data in children to support the proposed dose. There could be different requirements of copper (and thus trientine) in different age cohorts due to developmental status that might also require a relative adaption of doses for juvenile individuals. Therefore, children from 5 years onwards should be included in the proposed PAES to further investigate the dose-exposure-response relationship in children.

2.5.4. Conclusions on the clinical efficacy

Trientine has the ability to chelate metal ions and eliminate copper from the body. These effects have been shown in non-clinical and clinical studies as well as during decades of trientine use in clinical practice.

Study *UNV-TRI-002* indicates 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.

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.

The provided bibliographic references support the notion that trientine has been used in the condition since decades with success as to life expectancy but lack sufficient quality to fill identified evidence gaps.

The proposed posology is in line with the posology of the nationally authorised UK trientine product, which is on the market for more than 30 years. The therapy is known to be effective and essential for WD patients intolerant to D-Penicillamine. Moreover, WD patients are treated by specialised physicians, who are familiar with the disease and treatment, as also clearly stated in the product information. Therefore, considering the totality of evidence in this rare and life threatening disease the efficacy is considered demonstrated.

However, no dedicated dose-response studies are available for trientine and the quality of the data provided with study UNV-TRI-002 is considered limited due to shortcomings in designs, conduct and reporting of the submitted investigations (e.g. sample size selection, protection against bias and not validated 5-point outcome scale).

The treatment effect/effect size of Cufence in WD patients with predominantly hepatic, neurologic or psychiatric symptoms cannot be determined based on the provided data, very limited data is available for patients in the up titration phase and paediatric patients. Uncertainties particularly in these sub-populations require further clinical evidence.

Therefore, in order to confirm or improve the dosing and titration recommendations in the PI for relevant subgroups of the target population and to characterise the dose-exposure-response relationship of WD patients, especially in the up-titration phase (first 6 months of therapy) a PAES is made condition to the market authorisation. The applicant is highly recommended to discuss protocol details in a scientific advice procedure. This study is imposed in line with Article 1(2)c of Commission Delegated Regulation (EU) No 357/2014.

The CHMP considers the following measures necessary to address issues related to efficacy:

PAES: In order to further characterise the efficacy of trientine dihydrochloride in the treatment of Wilson's disease in patients with predominantly hepatic, neurologic or psychiatric symptoms as well as in paediatric patients, the MAH should conduct and submit the results of an open label, prospective study to investigate the clinical course of hepatic, neurological and psychiatric disease from the time of initiation of treatment with trientine dihydrochloride up to 24 months of therapy. The study will also contain a PK/PD sub-study to evaluate the dose-response relationship especially during the up-titration phase. The study should be conducted according to an agreed protocol.

Due date: Q4 2025 (Milestone for the PK/PD sub-study Q4 2022)

2.6. Clinical safety

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 (see Table 15) and one retrospective, observational review conducted by the Applicant.

Table 15

Table 2.7.4-5: Reported Trientine Dose in the Treatment of Adults and Children With Wilson's Disease - Key Publications

Study Design	N	Age at Diagnosis (Years)	Trientine Administered Dose	Follow- up Period (Years Unless Otherwise Stated)	Reference
Adults					
Retrospective analysis of patients with WD in one European tertiary care centre (2002 – 2005)	163	20.4 (mean) 25.3 months after first symptoms	Trientine (n=9)/ 900 to 2100 mg per day;	16.7 (mean)	Merle et al., 2007
Retrospective descriptive review analysing the clinical characteristics, treatment, and follow-up of a cohort of patients in Spain	29	Data not shown	Trientine (with or without zinc): 750 to 1000 mg per day (zinc 150 to 250 mg per day)	9.68 ± 8.68 (range: 1 to 34)	Rodrigo Agudo et al., 2008
A retrospective analysis of a cohort of Italian patients with WD treated with zinc and/or D-Penicillamine	60	23.0 ± 2.0 years	Trientine: 600 mg/day and a gradual increase to a daily dose at 1200 mg/day thereafter for the first year	25.0 ± 9.0	Sini et al., 2012
Case reports	20	Previously untreated patients 13 to 30 (n=8)	Trientine: 400 to 800 mg three times daily	14 to 120 months (n=8)	Walshe, 1982
Case reports	13	Range 14 to 47[1]	Trientine:1 to 1.5 g per day	2 to 15	Scheinberg et al., 1987
Case reports	19	Range 10 to 58	Trientine: 1 to 1.8 g per day	Trientine: 4 months to 17.5 years (mean 8.5 years per patient)	Dahlman et al., 1995
Case reports (age range 13 to 33 years)	7	Not presented	Trientine: 0.5 to 2 g per day	6 weeks to 16 years	Dubois et al., 1990
Case reports (Japanese patients)	4	Range 17 to 43	Trientine: in increasing dose from 1.0 to 2.0 g/day to 2.5 to 3.0 g/day	2 months	Saito et al., 1991

Study Design	N	Age at Diagnosis (Years)	Trientine Administered Dose	Follow- up Period (Years Unless Otherwise Stated)	Reference
Retrospective review of 16/96 (17%) children with WD (1981 – 2006)	16	Median 10.5 (range 6.6 to 15.6)	Trientine: 0.6 g per day <12 years) or 1.2 g per day (>12 years) increasing to 1.5 or 2.4 g per day if side effects continued	Median 6.43 (range 0.78 to 18.6)	Taylor et al., 2009
Retrospective review of the medical records of children with WD treated at a Paediatric Liver Service, UK (between 1967 and 2000)	57	Median 11.9 (range, 5.9 to 17.9; for n=57 symptomatic children)	Trientine: 10 mg/kg twice daily	Children on long-term chelation (n=32): Median 11.78 (range, 1.45 to 34.2)	Dhawan et al., 2005
Retrospective review of the medical records of children with WD treated at a Paediatric Liver Service, UK (between 1967 and 2000)	17	Median 10.4 (range, 2.6 to 16.9; for n=17 asymptomatic siblings)	Trientine: 10 mg/kg twice daily	Asymptomatic siblings: Not stated	Dhawan et al., 2005
Retrospective review of patient medical records for patients with diagnosis of WD between 1983 and 2004 in a tertiary care unit in Greece	57	Mean 9.27, SD ± 3.6 years (range 4 months to 18 years); Median age 9	Trientine/250 to 750 mg/day	Not stated	Manolaki et al., 2009
Case reports (9 were prospective reports)	10	Mean 9.2 (range 3 to 15 years)	Trientine: Initial mean dose 30 ± 5 mg/kg/day	Mean 71 months (range 20 to 120 months)	Sarles et al., 2001

Source: Table 2.7.3-1 in module 2.7.3
Abbreviations: AE=adverse event; N/n=number of patients; SD=standard deviation; WD=Wilson's disease.
1 Age at onset

The single dose PK trial TR-001 PK is considered of little value for safety assessment (no AEs were recorded although symptomatic patients were included; the applied safety monitoring system seems therefore not reliable).

'Safety' was one objective of the main study (UNV-TRI-002), but no hierarchy of endpoints is applied.

Patient exposure

Wilson's disease 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 table 2.7.4-5 (see above) is that most of the patients received Cufence for many years/decades. For a MA for a chronic treatment a one year treatment exposure would usually be a minimum requirement in a study setting. While patient numbers from UNV-TRI-002 alone would not be sufficient to fulfil regulatory requirements; in the light of the rarity of the disease and the supportive literature data, the overall extent of exposure could be acceptable for the assessment of safety.

UNV-TRI-002

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 (629.7mg TETA). The maximum doses as recommended in the PI (2400 mg TETA for adults and 1500mg TETA for children) were hardly ever reached. One patient received 2100mg TETA/day and 5 received 1800 mg TETA/day according to the information in the original dossier. 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.

Table 16

Table 2.7.4-4: Treatment with Trientine (ITT Population) - Study UNV-TRI-002

	Trientine (N=77)
Duration of treatment with trientine (months)	
n	33
Mean (SD)	73.3 (74.76)
Median (minimum, maximum)	56.7 (5, 307)
Total dose per day at initiation of trientine (mg)	
n	71
Mean (SD)	852.1 (539.01)
Median (minimum, maximum)	600.0 (300, 2100)
Total dose per day during treatment (mg)	
n	19
Mean (SD)	1005.7 (425.32)
Median (minimum, maximum)	881.3 (481, 1728)
Ongoing at last available time point	65 (84.4)
Time to discontinuation for patients that withdrew trientine (months)	
n	8
Mean (SD)	52.193 (27.7423)
Median	45.894
Minimum, maximum	18.43, 92.31

Source: Study UNV-TRI-002, Table 11-16, Table 12-1
Abbreviations: ITT=intention to treat; N=number of patients in the treatment group analysis set; n=number of patients in the specified category with non-missing values; SD=standard deviation.
Note: Duration of treatment with trientine=(Date of withdrawal/death/last contact - Date of initiation of trientine + 1)/30.44

Complete data sets from all predefined time points (6, 12, 24, 26, 48 months) are available only from a minority of the patients. The Applicant states that 'Due to the nature of this retrospective study, treatment compliance could not be determined in detail'. All available data on trientine dose were used to generate an overview of the trientine dose per time point. In contrast to the numbers given in table 2.7.4-4, new data from these additional analyses reveal that maximum doses were indeed 2700mg TETA.

Literature

Please also see respective discussion in the efficacy section with this regard.

The estimated extent of exposure (trientine second line use) in key publications on trientine is difficult to assess because of presumed significant patient overlap, but could be around 250 patients, including adult and paediatric patients. Studied patients are mostly long-term users, however.

Many publications restricted the safety analysis to adverse events leading to discontinuation of the respective drug or did not report AEs at all. Whether this is due to the deficient collection/reporting

measures or an actual reflection of a benign safety profile cannot be said with certainty. Weiss et al. 2013 an 2011 a, b as well as Hölscher et al. 2010 did not state respective applied trientine doses.

When looking at trientine doses reported. it is noted that the maximum recommended dose according to the SmPC was never reached (apart from in 4 patients, Saito et al. 1991, who received increasing doses up to 3g/day over 2 months), as was already observed in study UNV-TRI-002. Trientine safety in high doses can therefore not be assessed. It is noted that only publications using trientine in a monotherapy setting seem to have been included in the safety review.

Post marketing experience

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 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). A fifth periodic benefit-risk evaluation report/PSUR for trientine dihydrochloride is available summarising the safety data received by Univar for trientine dihydrochloride from 01 April 2012 to 31 March 2015 inclusive. During this 3-year reporting period, Univar distributed 53,848 bottles of trientine dihydrochloride (300 mg capsules), each containing 100 capsules, were, thus equating to 820 patients with Wilson's disease 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 Wilson's disease, 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 17.

Table 17 Cumulative Patient Exposure

Table 2.7.4-18: Cumulative Patient Exposure (2001 to 2014)

	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

Source: Periodic Safety Update Report (01 April 2012 to 31 March 2015)

The data indicates an overall increase of patients treated with trientine over time. The significant increase in the years 2011/2012 is not comprehensively explained. It is assumed that the number of WD patients throughout the world remains relatively stable. The data pictured also support that WD is a rare disease; 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 is available.

Collection of trientine AEs from the post-marketing setting was provided during the procedure: The Applicant carefully reviewed cases of hepatic toxicity and discussed possible relation to trientine treatment. While a connection cannot fully be excluded based on the available data, it is 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 is ambiguous and there is no clear indication that trientine causes hepatic toxicity. Therefore, hepatic reactions are currently not included as adverse drug reaction in the PI. Liver enzymes are monitored regularly in WD patients and changes in hepatic status are recorded by treating physicians.

Adverse events

UNV-TRI-002

According to the data collection schedule, AEs were recorded at trientine initiation, after 6, 12, 24, 36, 48 months of treatment and at the 'last follow up'. At each of the visits, patients were asked about 'AEs since the last visit'. This covers a time-period of 6 to 12 months or longer for patients that missed occasional visits, which is true for most of included patients. It seems rather unlikely that precise and detailed AE records could be obtained in this way since significant recall bias must be assumed. In conclusion, the safety monitoring was not sufficiently sensitive to reliably depict the safety profile of chronic trientine use in WD patients.

In addition to the unspecific questioning, a catalogue of physical findings considered related to Wilson's disease was queried at each of these visits, including tremor, drooling, rigid dystonia and other symptoms. These were, however, not considered AEs, but seem to have been used for the evaluation of efficacy (see respective section above). Results from this query are available only for a fraction of included patients at each time point. No development over time can be assessed based on the presentation of these data.

Table 18

Table 2.7.4-13: All Treatment-Emergent Adverse Events (Preferred Term) in at Least Four Patients in Study UNV-TRI-002 (ITT Population)

System Organ Class Preferred Term	Trientine (N=77) n (%)
Patients with any TEAE	48 (62.3)
Blood and lymphatic system disorders	5 (6.5)
Splenomegaly	4 (5.2)
Endocrine disorders	7 (9.1)
Hypothyroidism	5 (6.5)
Gastrointestinal disorders	20 (26.0)
Abdominal pain	4 (5.2)
Nausea	4 (5.2)
Infections and infestations	9 (11.7)
Nasopharyngitis	4 (5.2)
Musculoskeletal and connective tissue disorders	15 (19.5)
Osteopenia	5 (6.5)
Psychiatric disorders	9 (11.7)
Depression	4 (5.2)

Source: Study UNV-TRI-002, Table 14.3.1.2
Abbreviations: AE=adverse event; ITT=intention to treat; MedDRA=medical dictionary for regulatory activities; N=number of patients in the treatment group analysis set; n=number of patients in the specified category with the observation; TEAE=treatment-emergent adverse event.
Note: Classifications of AEs were based on MedDRA (Version 19.1).
An AE was defined as treatment-emergent (TEAE) if its onset date is on or after the date of initiation of trientine.
Patients were only counted once per treatment for each row.

Table 19

Table 2.7.4-14: All Treatment-Emergent Adverse Events Related to Trientine in Study UNV-TRI-002 (ITT Population)

System Organ Class Preferred Term	Trientine (N=77) n (%)
Patients with any TEAE related to trientine	19 (24.7)
Blood and lymphatic system disorders	1 (1.3)
Anaemia	1 (1.3)
Endocrine disorders	1 (1.3)
Autoimmune thyroiditis	1 (1.3)
Gastrointestinal disorders	7 (9.1)
Nausea	4 (5.2)
Abdominal pain	3 (3.9)
Abdominal discomfort	1 (1.3)
Diarrhoea	1 (1.3)
Intestinal obstruction	1 (1.3)
Tongue dry	1 (1.3)
General disorders and administration site conditions	1 (1.3)
Asthenia	1 (1.3)
Investigations	3 (3.9)
Hepatic enzyme increased	1 (1.3)
Transaminases increased	1 (1.3)
Weight increased	1 (1.3)
Metabolism and nutrition disorders	1 (1.3)
Hypomagnesaemia	1 (1.3)
Iron deficiency	1 (1.3)
Musculoskeletal and connective tissue disorders	1 (1.3)
Muscle spasms	1 (1.3)
Nervous system disorders	4 (5.2)
Dizziness	1 (1.3)
Dysgeusia	1 (1.3)
Dystonia	1 (1.3)
Tremor	1 (1.3)
Psychiatric disorders	1 (1.3)
Insomnia	1 (1.3)
Skin and subcutaneous tissue disorders	3 (3.9)
Acne	1 (1.3)
Alopecia	1 (1.3)
Rash	1 (1.3)

Source: Study UNV-TRI-002, Table 14.3.1.3
Abbreviations: AE=adverse event, ITT=intention to treat, MedDRA=medical dictionary for regulatory activities, N=number of patients in the treatment group analysis set, n=number of patients in the specified category with the observation, TEAE=treatment-emergent adverse event.
Note: Classifications of AEs were based on MedDRA (Version 19.1).
An AE was defined as treatment-emergent (TEAE) if its onset date was on or after the date of initiation of trientine.
Patients were only counted once per treatment for each row.

Overall, the amount of reported AEs, TEAEs and trientine related AEs is very low (considering the relatively long observational period). Whether this is due to the deficient collection/reporting measures or an actual reflection of a benign safety profile cannot be said with certainty. Gastrointestinal disorders (26.0% of patients), musculoskeletal and connective tissue disorders (19.5% patients) and nervous system disorders (14.3% patients) were the most common reported events attributed to the drug in UNV-TRI-002. Observed events more or less match with what would be expected according to literature and information from other licensed trientine products (see section on literature below).

Possible dose dependency of adverse reactions cannot be assessed based on the available data as AEs are not discussed in view of respective doses. Moreover, maximum doses (2.4 g/day as stated in the PI) were not used in this study. The Applicant provided an overview of reports of high trientine doses from the literature, which suggests dose dependency of AEs. Nevertheless, the Applicant concludes that the safety

window for trientine is large and that a dose recommendation up to 2400 mg/day (1600 mg/day active moiety) is in line with the recommendations for the nationally licensed trientine product and also conservative, regarding the European guidance document on the matter. The risk for over-chelation is not discussed in this context, however.

From the available data it seems that higher doses are used rather for initiation of treatment than for maintenance, which contradicts the Applicant's approach of 'start low and go slow'. The Applicant argues that a slow increase in dose to reach the recommended therapeutic dose should be considered in patients with neurological symptoms due to the risk of neurological deterioration at the initiation of treatment; this is also stated in the PI. In UNV-TRI-002, at initiation of the trientine treatment the mean dose was approximately 800 mg TETA and the dose was up titrated to reach a maintenance dose of around 1200 mg per day at month 6.

AEs of paediatric patients were outlined and discussed compared to adult data.

Table 20

Table 27: Summary of adverse event by body system and age group

System Organ Class	Paediatric population (N=28)		Adult population (N=49)	
	n	(%)	n	(%)
Patients with Any TEAE	9	(32.1)	39	(79.6)
Blood and lymphatic system disorders			5	(10.2)
Cardiac disorders	1	(3.6)	3	(6.1)
Ear and labyrinth disorders			3	(6.1)
Endocrine disorders	1	(3.6)	6	(12.2)
Eye disorders			1	(2.0)
Gastrointestinal disorders	7	(25.0)	13	(26.5)
General disorders and administration site conditions	1	(3.6)	6	(12.2)
Hepatobiliary disorders			1	(2.0)
Infections and infestations	2	(7.1)	7	(14.3)
Injury, poisoning and procedural complications			3	(6.1)
Investigations	1	(3.6)	3	(6.1)
Metabolism and nutrition disorders	1	(3.6)	4	(8.2)
Musculoskeletal and connective tissue disorders	1	(3.6)	14	(28.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			7	(14.3)
Nervous system disorders	3	(10.7)	8	(16.3)
Pregnancy, puerperium and perinatal conditions			2	(4.1)
Psychiatric disorders			9	(18.4)
Renal and urinary disorders	1	(3.6)	2	(4.1)
Reproductive system and breast disorders			2	(4.1)
Respiratory, thoracic and mediastinal disorders			3	(6.1)
Skin and subcutaneous tissue disorders			3	(6.1)
Surgical and medical procedures			7	(14.3)
Vascular disorders			3	(6.1)

The data indicate good tolerability also in paediatric patients. For study UNV-TRI-002 a summary of height and weight gain over the course of treatment in paediatric patients did not indicate impairment of normal development.

Adverse Events - Literature Data

From other trientine products licensed in the EU it is known that possible AEs comprise gastrointestinal disorders (included in the Cufence PI), iron deficiency anaemia (included) and skin conditions such as rash (included), pruritus (not included), erythema (not included) and urticaria (not included).

The FDA approved 'Syprine' in addition mentions systemic lupus erythematosus (included), muscular spasm (included) and myasthenia gravis (not included).

There have been reports of neurological deterioration in Wilson's disease patients treated with copper chelators including trientine, with symptoms of, for example, dystonia, rigidity, tremor and dysarthria (all included). 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. The Applicant attributed this event to other causes than the use of trientine.

Copper deficiency as possible adverse reaction comes to mind when thinking about trientine's mechanism of action. '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) and is included in section 4.8 of the SmPC.

The Applicant states that treatment guidelines recommend that treated Wilson's disease 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. This is adequately covered in the PI.

It was not discussed how the "known AEs from literature" have been identified, whether a dedicated literature search on trientine tolerability has been conducted.

A comparison of the safety profiles of trientine and D-penicillamine conducted by the Applicant shows that trientine seems better tolerable. This is in line with reports from several publications and with statements in respective treatment guidelines, even if use of trientine after D-penicillamine withdrawal is not specifically considered. It could be assumed that patients intolerant to one chelator (D-penicillamine) might be at higher risk of intolerance to another (trientine). The Applicant argues that a cross-sensitivity between D-penicilamine and trientine is unlikely; while this is not justified in depth and no clinical data are available to support the statement, the rationale can be followed.

Non-clinical data did not raise any particular concerns from a safety point of view.

Adults

Short summary overviews of available safety data from key publications are presented in the clinical AR. Safety data from the largest retrospective cohort study to date, of patients with Wilson's disease in European tertiary care centres and patients recorded in the EuroWilson registry (Weiss 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).

However, possible patient overlap between the population from study UNV-TRI-002 and the population studied by Weiss et al. 2013 (and probably Weiss et al. 2011, see efficacy section) renders the significance of this publication relative. Deficiencies regarding AE collection and reporting are believed to be the same as for UNV-TRI-002. No doses were reported by Weiss et al. 2013 and thus a possible dose dependency of adverse reactions could not be assessed. The majority of significant events were gastrointestinal complaints, skin- and musculoskeletal issues. One patient withdrew from trientine due to nephropathy, a rather unexpected event that was not further discussed by the Applicant. Nephropathy is an AE reported in some publications, but mostly in connection with D-penicillamine treatment.

Children

The medical records of children diagnosed with Wilson's disease at a single European centre between 1981 and 2006 and converted from D-penicillamine to trientine, were retrospectively reviewed (Taylor et al., 2009). Trientine was discontinued in three of 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.

A retrospective review of the medical records of children with Wilson's disease evaluated and treated in a paediatric liver/liver transplant program (Arnon et al., 2007) 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.

Tolerance and efficacy were investigated in case studies of 10 children with Wilson's disease, nine of whom were prospectively treated with trientine (Sarles et al., 2001). 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.

A review of medical records of patients who received a diagnosis of Wilson's disease between 1983 and 2004 in a tertiary care unit in Greece has been published (Manolaki et al., 2009). 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.

A retrospective review of the medical records of 74 children with Wilson's disease treated at the Paediatric Liver Service, King's College Hospital between 1967 and 2000 has been reported (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.

Serious adverse event / deaths / other significant events

Study UNV-TRI-002

In study UNV-TRI-002 serious TEAEs were reported from 17 (22.1%) patients (Table 21). Serious TEAEs considered related to trientine were reported from two patients (Anaemia [led to discontinuation of trientine] and Intestinal obstruction were reported from one patient, and Hepatic enzyme increased [Study medication was reduced from 1800 mg to 1200 mg daily due to this event] was reported from one patient). The other recorded serious TEAEs were not considered related to treatment by the Applicant which seems acceptable. The SAEs, considered related to trientine, resolved. The majority of SAEs resolved, resolved with sequelae or improved.

Table 21

Table 2.7.4-15: All Serious Treatment-Emergent Adverse Events in Study UNV-TRI-002 (ITT Population)

System Organ Class Preferred Term	Trientine (N=77) n (%)
Patients with serious TEAE	17 (22.1)
Blood and lymphatic system disorders	1 (1.3)
Anaemia[1]	1 (1.3)
Endocrine disorders	1 (1.3)
Pituitary-dependent Cushing's syndrome	1 (1.3)
Gastrointestinal disorders	2 (2.6)
Haemorrhoids	1 (1.3)
Intestinal obstruction[1]	1 (1.3)
Infections and infestations	2 (2.6)
Chronic sinusitis	1 (1.3)
Pneumonia	1 (1.3)
Pyelonephritis	1 (1.3)
Injury, poisoning and procedural complications	1 (1.3)
Wrist fracture	1 (1.3)
Investigations	1 (1.3)
Hepatic enzyme increased[1]	1 (1.3)
Musculoskeletal and connective tissue disorders	2 (2.6)
Intervertebral disc protrusion	2 (2.6)
Spinal column stenosis	1 (1.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (6.5)
Bowen's disease	1 (1.3)
Breast cancer	1 (1.3)
Breast cancer recurrent	1 (1.3)
Cholesteatoma	1 (1.3)
Leiomyoma	1 (1.3)
Nervous system disorders	2 (2.6)
Cerebral infarction	1 (1.3)
Syncope	1 (1.3)
Vertebral artery dissection	1 (1.3)
Pregnancy, puerperium and perinatal conditions	1 (1.3)
Stillbirth	1 (1.3)
Reproductive system and breast disorders	1 (1.3)
Endometriosis	1 (1.3)
Respiratory, thoracic and mediastinal disorders	1 (1.3)
Pneumothorax	1 (1.3)
Surgical and medical procedures	5 (6.5)
Cholecystectomy	1 (1.3)
Foot operation	1 (1.3)
Hysterectomy	1 (1.3)
Intramedullary rod insertion	1 (1.3)
Nasal septal operation	1 (1.3)
Osteotomy	1 (1.3)

The reported data on SAEs do not raise particular concern.

Other sources

For the majority of cases the primary source of information on adverse safety events are retrospective narrative reviews and studies reported in the literature. In these publications, the reported safety events are not presented or reported in a predefined and consistent way, which would allow them to be reliably categorised as non-serious or serious or integrated and examined for frequency over time.

Death

No fatalities were reported in studies UNV-TRI-002 or TR-001PK and no death attributed to trientine use was reported in the provided literature. On the contrary, what can be derived with relative good certainty

from available literature data despite their poor quality is an improvement in survival in WD patients compliant to treatment. Reported fatalities are usually related to progression of the underlying disease or non-compliance to treatment.

Untreated Wilson´s disease is universally fatal (EASL). Copper accumulation in the liver eventually leads to development of cirrhosis, and among patients with neurologic forms of the disease it 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 from progressive neurologic disease.

The prognosis of WD patients who receive treatment and are adherent 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).

Laboratory findings

In UNV-TRI-002 no laboratory findings (not even if clinically significant) were reported as AEs, unless clinical signs or symptoms were present in addition. It is unknown if samples were taken as part of clinical routine measures or if clinicians triggered them based on the clinical appearance of the patient. Therefore, laboratory findings are discussed in the efficacy section of this report. Apart from a reduction in alanine aminotransferase (and to a lesser extent aspartate aminotransferase) no relevant changes were observed.

No data on laboratory parameters is available from the literature. In Weiss et al. 2013 one case of neutropenia was recorded in one patient under trientine treatment.

Safety in special populations

The Applicant states that dosing is highly patient-specific, variable and subject to constant review and change according to the patients' signs, symptoms and copper levels. Efforts to provide clear guidance on how to monitor patients (including which parameters to monitor and how often) and how to titrate upon signs, symptoms and laboratory have proven rather futile in light of the poor data situation. Currently, the proposed dosing recommendations need further substantiation by appropriate PK/PD data.

Currently available data does not allow to conclude that PK/PD or dose/exposure/ response relationship between adults and children are similar and if there are different copper requirements (and thus, need for different trientine doses) in different age cohorts due to their developmental status.

No information on patients with hepatic impairment or elderly patients seems available. Large inter-individual variability in exposure was observed, but differences between populations could still be relevant for defining the appropriate (safe) starting dose and treatment targets. Literature data indicates that differences in PK could occur depending on intrinsic patient factors (e.g., trientine bioavailability was higher in patients with type II diabetes). However, as trientine is titrated to target, small differences will likely not become apparent.

The difficulty of studying subgroups in a small population is acknowledged, but more PK/PD data especially in paediatric patients is needed and should be collected post-marketing in the frame of the PAES.

Adverse Events by Age

Table 22

Table 30: Adverse Event by System Organ Class and Preferred Term by Age Data

MedDRA Terms	Age < 18 number (percentage)	Age < 65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+ number (percentage)	Age unknown (percentage)	Grand total
Total AEs	33 (25%)	78 (58%)	2 (1%)	0	1 (0.7%)	20 (15%)	134
Serious AEs – Total	28 (33%)	51 (59%)	2 (2%)	0	0	5 (6%)	86
- Fatal	1 (50%)	1 (50%)	0	0	0	0	2
- Hospitalization/ prolong existing hospitalization	4 (8%)	40 (80%)	2 (4%)	0	0	4 (8%)	50
- Life-threatening	0	2 (100%)	0	0	0	0	2
- Disability/incapacity	0	6 (100%)	0	0	0	0	6
- Other (medically significant)	23 (77%)	6 (20%)	0	0	0	1 (3%)	30
AE leading to drop-out	0	1 (100%)	0	0	0	0	1
Psychiatric disorders	0	0	0	0	0	0	0
Nervous system disorders	7 (35%)	6 (30%)	0	0	0	7 (35%)	20
Accidents and injuries *	1 (11%)	5 (56%)	1 (11%)	0	0	2 (22%)	9
Cardiac disorders	0	1 (100%)	0	0	0	0	1
Vascular disorders	2 (40%)	3 (60%)	0	0	0	0	5
Cerebrovascular disorders **	0	0	0	0	0	0	0
Infections and infestations	0	5 (100%)	0	0	0	0	5
Anticholinergic syndrome	0	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0	0

MedDRA Terms	Age < 18 number (percentage)	Age < 65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+ number (percentage)	Age unknown (percentage)	Grand total
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	0	1 (syncope) 1 (wrist fracture) 2 (dizziness) (67%)	1 (radius fracture) (17%)	0	0	1 (dizziness) (17%)	6
Other AE appearing more frequently in older patients ***	0	0	0	0	0	0	0

*Injury, poisoning and procedural complications SOC
** Cerebrovascular disorder PT

A total of 134 patients are available for allocation to age cohorts in the provided table.
Most AEs are recorded in the largest group of patients aged <65 years. The data does not indicate a higher risk of AEs in paediatric patients.
The amount of patients in the >65 years group is extremely limited and thus reliable comparisons to other age groups are difficult. However, there is no indication that the safety profile differs significantly in older patients. Close monitoring also in older patients is recommended to allow timely up- or down titration of trientine dose in reaction to the patient's status. The current wording in the PI is acceptable with this regard.

Immunological events

Information from the submitted literature is rare. Immunogenicity was investigated by Weiss et al. 2013. Results indicate a good immunogenetic profile of TETA 2HCL as compared to D-penicillamine:

		No. of event (incidence rate, %)		
		TETA 2HCl	D-Penicillamine	Zinc
Increase of ANA antibodies	Weiss 2013	1 (0.7%)	22 (6.7%)	N/A

ANA: antinuclear antibody

Safety related to drug-drug interactions and other interactions

In line with requirements outlined in the protocol assistance 2012, the Applicant conducted in vitro CYP450 interaction studies with trientine in human liver microsomes and human hepatocytes. Results do not indicate a clinically relevant risk for DDIs: a small dose response in CYP1A2 (with 3.2-fold as the highest response) was less than 5% of the fold induction with the positive control omeprazole – as such considered unlikely to mediate drug-drug interaction.

In the study report of UNV-TRI-002, concomitant medication with trientine is listed. Zinc was used quite frequently together with trientine, but it is not recommended due to likely interactions. A warning on concomitant intake of iron (where interaction with trientine is highly likely) is included in section 4.5 of the SmPC.

Discontinuation due to adverse events

Assessment of the safety of trientine treatment based on *AEs leading to discontinuation of treatment with trientine* and *time to discontinuation of treatment due to AEs and/or inadequate response* were two objectives of the main trial UNV-TRI-002. The respective results are discussed in the efficacy section of this report.

Overall, results indicate that patients usually stay on trientine treatment for quite a long time (several years or even decades) before switching to an alternative. The data supports a benign safety profile, especially compared to the first line therapy D-penicillamine.

2.6.1. Discussion on clinical safety

For the evaluation of Cufence safety in this “full mixed” application, published references on trientine use in WD patients from different sources were submitted as well as a retrospective observational review conducted by the Applicant (study UNV-TRI-002). This study also had a prospective part, basically observing the same patients as in the retrospective part.

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.

Shortcomings in designs, conduct and reporting of the submitted investigations must be balanced against the longstanding experience with trientine, which is available on the marked since decades and considered state-of-the-art therapy for WD according to relevant guidelines.

Trientine´s tolerability seems widely recognised. Though patients are not thoroughly documented, the exposure periods are very long. Overall, the amount of reported AEs, TEAEs and trientine-related AEs is very low. Whether this is due to insufficient collection/reporting measures or is an actual reflection of a

benign safety profile cannot be said with certainty. The safety profile of trientine is also considered favourable when compared to D-penicillamine. Finally, non-clinical data did not raise any particular concerns from a safety point of view.

It is acknowledged that WD is a very rare disease and that the amount of potential study subjects is therefore limited. Data on trientine use from the post-marketing setting using sales numbers was provided and supports regular use of the product, even if no details on dose or duration of exposure are available.

Not in all of the included literature was trientine used as a second line option after D-penicillamine. The Applicant states in several sections that initial de-coppering can take many months up to years and it seems likely that patients (receiving trientine 2nd line) were included in the database also if initial de-coppering was not yet completed. Trientine will likely be used in these patients in clinical practice. Patients at different stages of the de-coppering process were included in the safety database and thus data provides a rather comprehensive picture, likely corresponding to later clinical use. The Applicant further argues that a cross-sensitivity between the two compounds (D-penicilamine and trientine) is unlikely and that therefore there is no reason to assume that patients intolerant to D-Penicillamine could be more at risk of being intolerant to trientine, which can be followed.

In study UNV-TRI-002 (uncontrolled, unblinded), patients were enrolled if they were previously treated with trientine for at least 6 months. Patients that withdrew from treatment within these first six month were not included in the study population. Thus, there is an identified lack of information on safety of trientine within the first 6 month of treatment, which has to be considered as an uncertainty. No statement about the amount of patients with immediate intolerability or non-responsive to treatment can be made. However, the proposed PAES will study patients directly after switching from D-Penicillamine and will address this gap.

From the originally submitted data, it is obvious that doses over 2.4 g/day are not used in clinical practice and doses of 2100mg are very rarely used. Thus, safety at higher doses cannot be properly assessed but the recommended dose is 800 – 1,600 mg (4 – 8 capsules) daily in 2 to 4 divided doses.

From the available data and information on other licensed trientine products it is known that possible trientine AEs compile primarily gastrointestinal disorders, nervous system disorders and skin conditions. Results from different sources largely agree in this regard. There is a certain risk for drug-drug interactions with iron, zinc and D-penicillamine and appropriate information in this regard is included in the SmPC.

No fatalities attributed to trientine use were reported in the provided literature. Despite the rather poor quality of the available literature data, it can be derived with reasonable certainty that trientine treatment improves survival in WD patients, if they are compliant to treatment. Reported deaths are usually related to progression of the underlying disease or non-compliance to treatment.

Assessment of paediatric data on clinical safety

WD is usually diagnosed rather early and the share of paediatric patients included in the documentation is relatively large. There are no relevant differences in the quality or quantity of reported AEs of paediatric patients compared to adults in study UNV-TRI-002. According to data from other literature sources (e.g. Taylor et al., 2009, Arnon et al., 2007, Manolaki et al., 2009), good tolerability can be assumed for trientine also in paediatric patients.

It seems that in paediatric patients, trientine is often used as a first line option (instead of D-penicillamine) rather than in second line, probably due to the more favourable safety profile. Results are overall in line with results from adult patients; however, the data situation (extent and quality) is poor for the paediatric cohorts and concerns with trientine treatment (or in general – chelator treatment)

pertaining to the paediatric population could be a certain risk of copper deficiency with over-treatment that could impair juvenile developmental processes.

In this light the proposed dosing regimen particularly in children is poorly supported by PK/PD data and the dose/exposure/response (safety) relationship is not well characterised. Dosing recommendations for all age groups are largely based on the SmPC of the long-standing nationally licensed Univar's trientine product and require further substantiation in the imposed PAES.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics

2.6.2. Conclusions on the clinical safety

Amount and quality of the available data is limited. Nonetheless, longstanding experience with the substance in clinical practice as well as the data provided support a benign safety profile of trientine in the treatment of with Wilson's disease in patients intolerant to D-penicillamine therapy, in adults, adolescents and children aged 5 years or older.

2.7. Risk Management Plan

Safety concerns

Important identified risks	None
Important potential risks	None
Missing information	Drug exposure during pregnancy Use of drug in lactation and in neonates

Pharmacovigilance plan

Routine pharmacovigilance activities are proposed for all safety concerns.

As part of routine pharmacovigilance activities beyond adverse reactions reporting and signal detection, targeted pregnancy follow-up forms for both ongoing and completed pregnancies are used as part of routine pharmacovigilance activities.

Risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Drug exposure during pregnancy	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC section 4.6. *PL section 2.* Additionally, the pregnancy should be 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. Babies born to mothers being treated with trientine should be monitored for serum copper and ceruloplasmin levels where appropriate. Additional risk minimisation measures: None	and signal detection: Pregnancy Report Form A Pregnancy Report Form B Additional pharmacovigilance activities: None
Use of drug in lactation and in neonates	Routine risk minimisation measures: *SmPC section 4.6.* Additionally, babies born to mothers being treated with trientine should be monitored for serum copper and ceruloplasmin levels where appropriate. It is unknown definitively whether trientine is excreted in human breast milk during breastfeeding. *PL section 2.* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The Applicant applies for the following indication: *"Cufence is indicated for the treatment of Wilson's disease in patients intolerant to D-penicillamine therapy, in adults, adolescents and children aged 5 years or older."*

Wilson's disease, also known as hepatolenticular degeneration, is a rare autosomal recessive disorder of copper metabolism caused by an autosomal recessive inheritance of ATP7B gene mutations. Wilson's disease 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 Wilson disease 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.

3.1.2. Available therapies and unmet medical need

Treatment of patients with Wilson's disease 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). D-penicillamine is licensed both as first line treatment for the de-coppering phase in treatment naïve patients and as maintenance therapy. It is regarded as a more potent, but also less tolerable chelator (as compared with trientine).

Trientine is used as second line treatment after D-penicillamine. Univar is the MAH and commercial supplier for trientine dihydrochloride in the UK, also exporting the product widely. In the US, trientine hydrochloride 250 mg capsules are approved (Syprine). Trientine in the form of TETA 4 HCL (Cuprior) has been approved in the EU via the centralised procedure in 2017 in the same indication as claimed by the applicant.

Zinc is another treatment option, centrally approved for the treatment of Wilson's disease since 2004 (Wilzin).

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 et al. 2005), with poorer outcomes in patients with neuropsychiatric symptoms.

3.1.3. Main clinical studies

The main clinical study is a phase IV, multicentre, observational trial, UNV-TRI-002. It is a retrospective review of historical WD patient data. A prospective observation following patients included in the retrospective study, if they consented, was conducted in one of the centres. In the retrospective part, 77 WD patients were observed for a maximum duration of 48 month during their regular treatment with trientine. The objective was to assess long-term outcomes of treatment with trientine in WD patients, who had withdrawn from therapy with D-penicillamine. No primary endpoint was defined, but a 5-point assessment score was applied to evaluate neurological and hepatic outcomes (classified as unchanged, improved but not normal, improved to normal, asymptomatic over duration of therapy or worsened).

The bibliographical database consists of reports of patient outcomes recorded over fairly long periods of time (years to decades); for some patients (children at initiation of treatment) observational periods lasted for up to 37 years (Dhawan et al. 2005). The main literature references are authored by Weiss (Weiss et al, 2013, 2011a and b), with study objectives and settings comparable to UNV-TRI-002. The Applicant also conducted a Phase I, single dose PK study (Study TR-001 PK) in 20 adult and paediatric WD patients treated with trientine dihydrochloride.

3.2. Favourable effects

Trientine has the ability to chelate metal ions and eliminate copper from the body. These effects have been shown in non-clinical and clinical studies as well as during decades of trientine use in clinical practice.

Study *UNV-TRI-002* indicates 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.

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.

While the quality of the respective literature references is moderate, they serve to support recommendations regarding posology, optimal treatment timing and duration, as well as data sources to judge upon consistency of results across trials.

3.3. Uncertainties and limitations about favourable effects

No dedicated dose-response studies are available for trientine. Dosing information was mainly obtained from clinical experience, outside controlled/ experimental study settings. To date, there is no optimal parameter or combination of parameters identified with which to monitor treatment success of chelator therapy in WD patients. Characterisation of the relationship between dose and PD-response according to PD parameters measured in study UNV-TRI-002 is only possible to a limited degree but management of dose titration in adults, paediatric patients, different disease subgroups (hepatic, neurologic, psychiatric) or in patients with different de-coppering status lies within the remit of specialised practitioners.

Study design and conduct of PK study TR-001 were not appropriate to provide meaningful results and the batch of trientine dihydrochloride used in study TR-001 PK had demonstrated faster *in vitro* dissolution behaviour than the to-be-marketed capsules, therefore PK and PD characterisation of Cufence in WD patients is fragmentary.

No specific food interaction studies in humans have been performed with trientine. However as trientine is poorly absorbed following oral intake, food may inhibit absorption. This uncertainty has been addressed in the SmPC advising to take trientine 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. The most relevant PD data (i.e. 24-h UCE and NCC) collected in UNV-TRI-002 in the retrospective study did not show good correspondence with the proposed target ranges from the literature (for reasons unknown, a slightly better correspondence is seen over the shorter time frame of the prospective dataset). The quality of the data provided with study UNV-TRI-002 is considered limited due to shortcomings in designs, conduct and reporting of the submitted investigations (e.g. sample size selection, protection against bias and not validated 5-point outcome scale).

Suspected overlaps between the study population included in study UNV-TRI-002 and the study population of the main literature reference, Weiss et al. 2013, may render the latter study to be of limited value (respective results can only be considered once) and the overall amount of patients studied on second line trientine use in WD in the literature is small (it compiles around 200 adults and 50 children without considering patient overlaps).

The influence of trientine on the mental state of WD patients cannot be determined based on the provided data and the dossier will need further substantiation from the planned PAES.

Treatment of patients with renal impairment, hepatic impairment/cirrhosis and potential drug-interactions with Zinc have not been fully investigated and precautionary statements were included in the SmPC. Whilst concomitant use of zinc is not recommended in the SmPC, it is common in clinical practice and regular concomitant intake of zinc was recorded for 27 patients in UNV-TRI-002.

3.4. Unfavourable effects

In study UNV-TRI-002 overall, the amount of reported AEs, TEAEs and trientine related AEs was very low (considering the relatively long observational period). Nineteen (19) TEAEs that were considered related

to treatment were reported. Gastrointestinal disorders (26.0% of patients), musculoskeletal and connective tissue disorders (19.5% patients) and nervous system disorders (14.3% patients) were the most common reported events attributed to trientine in UNV-TRI-002. Hepatic symptoms worsened in 5.2% of patients and neurologic symptoms worsened in 2.6% of patients. Observed events match more or less what is expected from trientine use according to available literature and information from other licensed trientine products.

The adverse events listed in the PI include anaemia (as trientine may reduce serum iron levels), nervous system disorders, gastrointestinal disorders and skin disorders, all of them mostly mild. Iron supplementation might become necessary under trientine therapy. There have been reports of neurological deterioration in Wilson's disease patients treated with copper chelators including trientine, which is also stated in the PI.

One case of 'hepatic toxicity', was reported by Arnon et al. 2007 (in a child), and another case of hepatic toxicity were reported in study UNV-TRI-002. Nephrosis/nephropathy is described in some publications, but mostly in connection with D-penicillamine treatment. The SmPC advises that 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.

3.5. Uncertainties and limitations about unfavourable effects

The overall safety database is small. Seventy seven (77) patients have been studied in study UNV-TRI-002 and around 250 WD patients using second line trientine are reported in the literature. Altogether, the amount of reported AEs, TEAEs and trientine related AEs is low (considering the relatively long observational period). Whether this is due to the deficient collection/reporting measures or an actual reflection of a benign safety profile cannot be said with certainty based on this data. The way safety was monitored in the historical references is unknown, but will likely not have been done in a systematic manner. Some literature references do not report safety findings at all.

The safety monitoring in study UNV-TRI-002 is not considered sufficiently sensitive to reliably depict the safety profile of chronic trientine use in WD patients or to investigate differences between adult and paediatric patients. At each visit, patients were asked about the occurrence of 'AEs since the last visit'. This covers a time period of 6 to 12 months (or longer for patients that missed occasional visits). It seems rather unlikely that precise and detailed records could be obtained in this way and significant recall bias must be assumed.

However, the committee acknowledges the clinical use of trientine 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. Also, the fact that the nationally approved trientine product has been marketed for decades and went through several PSUR assessments and renewals also speaks for an established safety profile.

Patients withdrawing from treatment within the first six months were not included in study UNV-TRI-002 and no statement can be made about the proportion of patients with immediate intolerability or unresponsive to treatment. The imposed PAES will aim to characterise the dose-exposure-response relationship of WD patients, especially in the up-titration phase (first 6 months of therapy) and therefore, also complement the safety information.

3.6. Effects Table

Table 1. Effects Table for Cufence indicated for the treatment of Wilson's disease in patients intolerant to D-Penicillamine therapy, in adults, adolescents and children aged 5 years or older.

Effect	Short Description	Unit	Treatment	Control	Strength of evidence	References
Favourable Effects*						
Hepatic Symptom	Improvement in clinical performance	% of patients	49.4	none	limited	UNV-TRI-002
Neurol. symptoms	Improvement in clinical performance	%	14.3	none	limited	UNV-TRI-002
Hepatic symptoms	Improvement in clinical performance	%	30.1	none	limited	Weiss et al. 2013
Neurol. symptoms	Improvement in clinical performance	%	25.2	none	limited	Weiss et al. 2013
Unfavourable Effects*						
Hepatic worsening	Deterioration of symptoms	% of patients	5.2	none	limited	UNV-TRI-002
Neurol. worsening	Deterioration of symptoms	%	2.6	none	limited	UNV-TRI-002
Hepatic worsening	Deterioration of symptoms	%	3.9	none	limited	Weiss et al. 2013
Neurol. worsening	Deterioration of symptoms	%	7.8	none	limited	Weiss et al. 2013

Abbreviations:

*second line trientine

TEAE: treatment emerged adverse event

sTEAE: serious treatment emerged adverse event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Trientine is known to decrease blood copper levels in Wilson's disease patients, its mechanism of action is well known; chelation has shown useful in removing toxic metals from the body in many indications. Trientine has been in use for this purpose since more than 30 years and is recommended in relevant treatment guidelines (EASL and AASL), based on evidence of 'moderate quality' (EASL). Notably, its efficacy has never been evaluated in a randomised controlled trial.

Whereas Wilson's disease is universally fatal if untreated, the prognosis for patients who receive and are adherent to treatment is excellent, even in those patients 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).

Trientine may have a better safety profile when compared to the first line treatment, D-penicillamine, though D-penicillamine could be more effective. Trientine in the form of TETA 4 HCL (Cuprior) has been approved in the EU via the centralised procedure in 2017 in the same indication as claimed by the applicant. According to literature, trientine causes fewer side effects and D-penicillamine´s side effects mostly resolve during trientine treatment. The fact that the nationally approved trientine product has

been marketed for decades and went through several PSUR assessments and renewals also speaks for an established safety profile.

The documentation in the clinical part of the dossier is fragmentary and aspects of trientine's characteristics have not been properly addressed: Dose response has not been characterised and dose recommendations and respective titration schemes in the PI (including all subgroups of interest) rely on clinical experience as laid down in the *EASL and AASL* treatment guidelines. Particularly in paediatric WD patients the PK data is limited. Thus, there is presently a risk that some patients may not be optimally treated.

3.7.2. Balance of benefits and risks

In the EMA protocol assistance issued in 2012, the CHMP stated that a retrospective study and review of clinical experience, together with PK and PK/PD data, might be sufficient to support a second-line indication. The Applicant submitted results from a PK study and a retrospective review, but gaps in knowledge remain related to food effect and possible interactions (mainly with zinc), the dose- and exposure-response relationship or the PK of trientine in the paediatric population mainly due to the limited quality of the provided data (both literature and own data).

The dose and titration regimen for Cufence is based on long-standing clinical experience of expert physicians with trientine in this rare disease and based on the submitted data including literature there is little doubt that trientine is an effective treatment that may increase the life span of WD patients. The remaining uncertainties are considered outweighed taking into consideration that Cufence will be used by specialists (as mandated in the SmPC), who are familiar with the disease and chelator treatment, and treatment will be titrated mainly according to clinical symptoms, which should minimise the risk of inappropriate dosing.

Whilst there is lack of knowledge about a food effect and interactions of trientine with zinc these issues have been addressed with appropriate recommendations and precautionary wordings in the product information, Uncertainties on the product's benefit-risk with regards to the effect size, in particular in patients with hepatic, neurological and psychiatric disease, and on the dose exposure response relationship particularly in patients in the up-titration phase and in children remain. These uncertainties require the generation of further clinical evidence from an imposed PAES based on a protocol agreed by the CHMP.

3.8. Conclusions

The overall B/R of Cufence is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Cufence is favourable in the following indication:

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Description	**Due date**
PAES: In order to further characterise the efficacy of trientine dihydrochloride in the treatment of Wilson's disease in patients with predominantly hepatic, neurologic or psychiatric symptoms as well as in paediatric patients, the MAH should conduct and submit the results of an open label, prospective study to investigate the clinical course of hepatic, neurological and psychiatric disease from the time of initiation of treatment with trientine dihydrochloride up to 24 months of therapy. The study will also contain a PK/PD sub-study to evaluate the dose-response relationship especially during the up-titration phase. The study should be conducted according to an agreed protocol.	Final report: Q4 2025 (main study) Q4 2022 PK/PD sub-study

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable