Doc. Ref: CMDh/200/2007 Rev.9
July 2020

Decentralised Procedure

RMS Final Assessment report

OVERVIEW AND LIST OF QUESTIONS

Trientin Waymade 200 mg Hartkapseln
Trientine Dihydrochloride

DE/H/6991/001/DC

Applicant: Waymade B.V

Reference Member State	DE
Start of the procedure:	12.03.2021
End of procedure:	08.07.2022

TABLE OF CONTENTS

ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Trientin Waymade 200 mg Hartkapseln
Name of the drug substance (INN name):	Trientine Dihydrochloride
Pharmaco-therapeutic group (ATC Code):	A16AX12
Pharmaceutical form(s) and strength(s):	Capsule, hard
Reference Number(s) for the Decentralised Procedure	DE/H/6991/001/DC
Reference Member State:	DE
Concerned Member States:	AT, DK, EL, ES, FI, FR, IT, NL, NO, PT, SE
Legal basis of application:	Generic Art 10.1 and 10.2 Dir 2001/83/EC
Applicant (name and address)	Waymade B.V Herikerbergweg 88 1101CM Amsterdam
Names and addresses of all proposed manufacturer(s) responsible for batch release in the EEA	Drehm Pharma GmbH Hietzinger Hauptstraße 37/2, Wien, 1130 Austria AcertiPharma B.V. Boschstraat 51 4811 GC, Breda Netherlands
Names and addresses of all proposed manufacturer(s) of the medicinal products	Waymade PLC, Sovereign House, Miles Gray Road, Basildon, Essex, SS14 3FR, United Kingdom (Secondary Packaging) Waymade PLC, Josselin Road, Burnt Mills Industrial Estate, Basildon, Esse United Kingdom (Secondary Packaging) Apothecon Pharmaceuticals Pvt. Limited. Plot No.1134 to 1137,1138-A&B,1143-B,1144-A&B, Padra Jambusar Highway, Tal. Padra, P.O. Dabhasa, Pin - 391 440, District - Vadodara, State – Gujarat, India. (Manufacturing, testing, primary and secondary packaging) DSG Biotec GmbH Institut für Pharma-Analytik Kirchstr. 10 83229 Aschau im Chiemgau Germany (QC Testing: Chemical/Physical)

	MikroBiologie Krämer GmbH Primsaue 7 66809 Nalbach Germany (QC Testing: Microbiological - non-sterility) Malta Life Science Park, LS2.01.06 Industrial Estate, San Gwann, SGN 3000 Malta (EEA Control Testing Site: Physical/Chemical, Microbiological – non sterility)
Names and addresses of all proposed manufacturers of the active substance	[redacted]
Names and addresses of all proposed ASMF holders (if different from manufacturer of active substance)	N/A
Names and addresses of all proposed CEP holders (if different from manufacturer of active substance)	N/A
Names and addresses of contract companies used for clinical trials (CRO(s))	[redacted] Clinical study and bioanalytical, pharmacokinetic, and statistical analysis
RMS contact person	**Name** [redacted] Tel: Email:
Names of the assessors:	**Quality**: **Name(s)** [redacted] Email: **Name(s)** [redacted] Tel: Email: **Non-clinical**: **Name(s)** [redacted] Tel: Email: **Clinical**: **Name(s)** [redacted] Tel: Email:

	Name Review: **Name(s)** [redacted] Tel: Email: **Pharmacovigilance System**: **Name(s)** [redacted] Tel: Email: **Risk Management Plan**: **Name(s)** [redacted] Tel: Email:

I RECOMMENDATION

Based on the review of the data on quality, safety, and efficacy, the RMS considers that the application for Trientine Waymade 200 mg Hartkapseln in the treatment of patients ≥ 5 years of age with Wilson's disease and being intolerant to D-penicillamine therapy,

is approvable.

II EXECUTIVE SUMMARY

II.1 Problem statement

Not applicable

II.2 About the product

In line with the reference medicinal product, trientine capsules are indicated for the treatment of Wilson's disease in patients ≥ 5 years of age and intolerant to D-penicillamine therapy; the ATC code is A16AX12.

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 PD action of trientine is dependent on its chemical property of chelating copper and not on an 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 thus inhibit copper absorption.

Treatment with trientine should only be initiated by physicians specialised and with experience in the management of Wilson's disease.
The starting dose would usually correspond to the lowest recommended dose and the dose should subsequently be adapted according to the patient's clinical response.
In adults, the recommended dose is 800 – 1,600 mg (4 - 8 capsules) daily expressed as mg of trientine base (i.e. not in mg of the trientine dihydrochloride salt) divided in 2 to 4 doses. There is insufficient clinical information available whether differences in responses between the elderly and younger patients exist for trientine and thus the dose selection should be cautious. There is also limited information in patients with renal or hepatic impairment and therefore, the recommended dose in these patients is not adjusted.
In the paediatric population, the dose is lower than for adults and depending on age and body weight. At the initiation of therapy 400 – 1,000 mg (2 - 5 capsules) have been used and the dose should be adjusted according to clinical response. The safety and efficacy of trientine in children ≤ 5 years of age have not yet been established; no data are available.
The capsules should be swallowed whole with water and it is important that trientine is given at least one hour before or two hours after meals on an empty stomach and at least one hour apart from any other medicinal product, food, or milk.

As regards special warnings and precautions for use, caution is advised when switching a patient from another trientine formulation since different trientine salts are available which may have a different trientine content (base) and a different bioavailability. Dose adjustment may be required. Patients receiving trientine should remain under regular medical supervision and be monitored using all available clinical data for an appropriate control of clinical symptoms and copper levels in order to optimise treatment. The monitoring frequency is recommended to be at least twice a year; more frequent monitoring is advised during the initial phase of treatment and during phases of disease progression or when dose adjustments are made.
As trientine is a chelating agent, it may also reduce serum iron levels and iron supplementation may be necessary in some cases. If oral iron is given, this should be administered at a different time than

trientine.
The combination of trientine with zinc is not recommended; as there are only limited data on the concomitant use available, no specific dose recommendations can be made.
In patients who were previously treated with D-penicillamine, lupus-like reactions have been reported during subsequent treatment with trientine, but it is not clear whether there is a causal relationship with trientine.
Patients with renal and/or hepatic impairment receiving trientine should remain under regular medical supervision for appropriate control of symptoms and copper levels and close monitoring of renal and/or liver function is also recommended.
Worsening of neurological symptoms may occur at the beginning of chelation therapy due to an excess of free serum copper during the initial response to treatment; this effect may be more evident in patients with pre-existing neurological symptoms. It is recommended to monitor patients closely for such signs and symptoms and to consider careful titration to reach the recommended therapeutic dose and to reduce the dose when necessary.
Trientine dose adjustments should be considered in case of signs of reduced efficacy such as persistent increase in liver enzymes and worsening of tremor. If needed, trientine dose adjustments should be done in small steps. The trientine dose may be reduced in case of side effects such as gastrointestinal complaints and haematological changes; doses may be increased again once side effects have been resolved.

The bioavailability of trientine in humans has not been established. Based on preclinical data, the mechanism of absorption, and the high first pass effect, it is expected that the bioavailability of trientine is low and highly variable following oral administration. Clinical studies showed that trientine is absorbed with a t_{max} occurring between 0.5 and 6 hours post-dose in healthy volunteers and patients. Exposure to trientine is highly variable between subjects, with a variation of up to 60%. The intake of food within 30 minutes prior to trientine administration delays t_{max} by 2 hours and reduces the extent of absorption of trientine by approximately 45%.
Trientine has low human plasma protein binding and it is widely distributed in tissues with relatively high concentrations measured in liver, heart, and kidney in the rat.
Trientine is acetylated in two major metabolites, N(1)-acetyltriethylenetetramine (MAT) and N(1),N(10)-diacetyltriethylenetetramine (DAT). Clinical data in healthy subjects indicate that the plasma exposure to the MAT metabolite is approximately 3-times that of unchanged trientine while exposure to the DAT metabolite is slightly lower compared to trientine. The trientine metabolites have Cu-chelating properties but the stability of these Cu-complexes is low due to the introduction of the acetyl groups. Clinical data in healthy volunteers suggest limited contribution of chelating activity by the MAT and DAT metabolites.
Trientine is metabolised by acetylation via spermidine / spermine N-acetyltransferase and not via N-acetyltransferase 2.
After absorption trientine and its metabolites are rapidly excreted in the urine, either bound to copper or unbound. The unabsorbed fraction of orally administered trientine is bound to intestinal copper and eliminated through faecal excretion.
The elimination half-life of trientine is approximately 4 hours (mean $t_{½}$ 3.8 ± 1.3 hours at steady state in patients; 4.4 ± 4.7 hours after single dose in healthy volunteers). The elimination half-lives of the two metabolites were 14.1 ± 3.7 and 8.5 ± 3.0 hours for MAT and DAT, respectively, after single dose administration of trientine in healthy subjects.
Data from clinical studies conducted in adult healthy subjects indicate that age, gender, and body weight do not influence the pharmacokinetics of trientine. No pharmacokinetic analysis has been performed on interethnic differences.

II.3 General comments on the submitted dossier

The application is submitted in accordance with Article 10 (1) of Directive 2001/83/EC (generic application) as amended. The submitted documentation in relation to the proposed product is of sufficient quality and consistent with the current EU regulatory requirements from a non-clinical and clinical point of view.

This decentralised application concerns a generic version of trientine dihydrochloride under 1 trade name. The originator product is Trientine dihydrochloride capsules 300 mg (trientine dihydrochloride)

by Univar Solutions BV, registered in the UK since 08 August 1985. Thus, trientine dihydrochloride is not considered a new active substance

With DE as the Reference Member State (RMS) in this Decentralised Procedure (DCP) Waymade BV is applying for the Marketing Authorisations (MA) for Trientine Waymade 200 mg hard capsule in AT, DK, EL, ES, FI, FR, IT, NL, NO, PT, and SE.

The clinical overview has been written by Alex Kudrin MD, PhD, MBA, MRCP, FFPM, Chief Medical Officer and Managing Director, Biotech Consultancy, London, UK and is dated 14 December 2020. The report refers 43 publications up to the year 2020.

To support the application, the Applicant has submitted a report of 1 bioequivalence study titled 'An open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of Trientine Dihydrochloride Capsules 300 mg of Waymade Plc, UK comparing with that of Cufence 200 mg hard capsules (equivalent to 300 mg of Trientine hydrochloride) of Univar BV Schouwburgplein 30-34, 3012 CL Rotterdam, The Netherlands in healthy, adult, human subjects under fasting conditions'.

The Applicant received Scientific Advice by the MHRA in January 2020 (Scientific advice letter 2191, Medicines & Healthcare products Regulatory Agency (MHRA), 9 January 2020), but in contrast to the Applicant's statement not all aspects have been followed (see below).

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

GMP

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, Apothecon Pharmaceuticals Private Limited, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, issued by the inspection services of MHRA (inspection at 2019-12-03) that acceptable standards of GMP are in place at those non-Community sites (GMP-Certificate for manufacture of drug products only).

GMP active substance

Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer responsible for batch release situated in the EU.

GLP

In line with the type of Application the Applicant does not submit nonclinical studies.

GCP

A statement on the application of appropriate GCP standards in the submitted bioequivalence study (code 62420) has been provided. According to the Applicant the latest inspection of the clinical,

bioanalytical, pharmacokinetic, and statistical analysis site (all identical address) has been conducted in 2019 by the MHRA (UK).

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The active substance is Trientine dihydrochloride. There is no Ph. Eur. monograph available. A monograph for Trientine dihydrochloride (USP-name "Trientine hydrochloride") is included in the USP. In the dossier, the Applicant has submitted full information on the Active Substance in Module 3.2.S.

Trientine dihydrochloride is synthesised in three stages (chemical reaction, salt formation and purification), starting from 1,2-dichloroethane and ethylenediamine. The choice of the starting materials is justified.

Characterisation of one process validation batch has been provided.

A discussion on possible impurities is presented.

The drug substance is controlled by an in-house specification. The specification includes description, solubility, Identification of Trientine (IR, GC) and of chloride, loss on drying, assay (titrimetry), pH, residue on ignition, chromatographic purity (TLC), assay (GC), residual solvents (GC), related substances (GC), chloride content (titrimetry), thermal analysis (DSC), particle size distribution, bulk density, tapped density and microbial purity.
Batch analysis data for overall six commercial scale batches (three smaller scale batches and three larger scale batches) showed compliance with the specification.

The stability studies include three commercial scale batches, which were stored for 48 months at 5°C ± 3°C and for 6 months at 25°C±2°C, 60±5% RH. For only one full production scale batch (batch with larger batch size), stability data over 6 months under accelerated storage conditions (25°C±2°C, 60±5% RH) and over 12 months under long-term conditions (5°C ± 3°C) of an ongoing long term stability study are provided. The presented three batches with smaller batch size are considered pilot scale. According to the "Guideline on stability testing: Stability testing of existing active substances and related finished products" (CPMP/QWP/122/02, rev 1 corr), a commitment is provided, to place the next two full production scale batches (batches with larger batch size) on long term stability studies through the proposed re-test period.

Drug Product

The drug product contains 300 mg of Trientine dihydrochloride (equivalent to 200mg of Trientine base) per hard capsule for oral use.

The only excipient of the capsule fill is stearic acid, which serves as lubricant. The capsules are made of gelatine with white colouring agent titanium dioxide and are printed with black ink. The excipients are well known in the formulation of capsules and the quality complies with the requirements of the corresponding Ph. Eur. monograph where applicable.

An in-vivo bioequivalence study was carried out on one process validation batch of the proposed generic product and the reference product Cufence 200 mg hard capsules.

Comparative in-vitro dissolution profiles of the clinical batches are presented, showing significant different dissolution behaviour between test and reference product at pH 1.2, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and in water. A discussion is provided.

The manufacturing process consists of sifting, lubrication, capsule filling and packing. Process validation has been performed with three validation batches of a batch size of 10.300 kg (33,333 Capsules), which is also the commercial batch size.

The product specifications cover relevant parameters for this dosage form. Validation results of the analytical methods have been presented.
Batch analysis results are provided for the three process validation batches. The specified parameters were met.

The capsules are packed in HDPE bottles, containing silica gel strip, and closed with polypropylene screw cap. One bottle contains 100 hard capsules.

The conditions used in the stability study are in accordance with the ICH stability guideline. For the three validation batches, results of a stability study over 6 months under accelerated conditions (25 ±2ºC/60±5% RH) and over 24 months of a long-term stability study (5°C ±3ºC) are available, meeting the specifications.

Conclusion

With the day 160 response all deficiencies in pharmaceutical quality are solved and in view to pharmaceutical quality the grant of a marketing authorisation can be recommended.

III.2 Non clinical aspects

Pharmacodynamic, pharmacokinetic, and toxicological properties of trientine are well known. As trientine is a widely used, well-known active substance, the Applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview has been written by Anders Neil, PhD, Independent Consultant, Owner of Neil Konsult AB, Uppsala Sweden and dated Decmber 14th, 2020. Report refers to 39 publications up to year 2020.

In response to a request the non-clinical overview was amended with further information on possible impurities in the medicinal product under review. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

Environmental Risk Assessment (ERA)

Since Trientine Waymade 200 mg Hartkapseln is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Clinical aspects

Pharmacokinetics bioequivalence study P-62420

To support the application, the Applicant has submitted a report of 1 bioequivalence study titled ‘An open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of Trientine Dihydrochloride Capsules 300 mg of Waymade Plc, UK comparing with that of Cufence 200 mg hard capsules (equivalent to 300 mg of Trientine hydrochloride) of Univar BV Schouwburgplein 30-34, 3012 CL Rotterdam, The Netherlands in healthy, adult, human subjects under fasting conditions’.

As this MAA concerns only one dose strength and trientine needs to be taken at least one hour before

or two hours after meals on an empty stomach and at least one hour apart from any other medicinal product, food, or milk, one bioequivalence study under fasted conditions is adequate for this generic application and the open label, balanced, randomised, two-treatment, two-period, two-sequence, single-dose, crossover, fasted, oral design is acceptable. Also, the reference products Cufence 200 mg hard capsule is adequate. Treatment phases were separated by a washout period of 10 days which is appropriate considering the moderate terminal $t_{½}$ of approximately 5.5 hours according to the literature. Also, the sampling period is considered long enough and the sampling scheme adequate to estimate the relevant pharmacokinetic parameters.

The chosen study population is considered acceptable.

The analytical method is considered appropriate and adequately validated. Handling of samples is also considered adequate. A statement on GLP compliance has been provided. The method is therefore considered acceptable for the sample analyses.

Standard pharmacokinetic variables have been assessed and standard statistical methods for the assessment of bioequivalence have been applied.

Results

All 46 subjects enrolled and randomised in the study completed both periods of the clinical phase, were analysed, and considered for pharmacokinetic and statistical analyses.

Trientine

Analyses of the pharmacokinetic data of the test and the reference product for trientine in study 62420 showed that the predefined bioequivalence criteria of 90% confidence intervals for log-transformed parameters of AUC_{0-t} and C_{max} to be within the acceptance range of 80.00% to 125.00% were met.

Pharmacokinetic data and resulting statistical analyses are summarised in the following tables. The comparison for t_{max} between test and reference products is based on median and ranges.

Parameters	Test (T)			Reference (R)		
	Mean ± SD	CV (%)	N	Mean ± SD	CV (%)	N
C_{max} (ng/mL)	758.24 ± 330.39	43.573	46	762.54 ± 369.27	48.427	46
AUC_{0-t} (hr*ng/mL)	3383.652 ± 1730.715	51.149	46	3358.961 ± 1739.391	51.784	46
AUC_{0-inf} (hr*ng/mL)	3524.692 ± 1793.701	50.890	46	3498.249 ± 1793.168	51.259	46
t_{max}* (hr)	1.25 (0.17 – 4.00)	60.92	46	2.00(0.50 - 4.50)	45.74	46
$t_{1/2}$ (hr)	7.29 ± 4.31	59.14	46	7.48 ± 4.76	63.54	46
K_{el} (hr^{-1})	0.1325 ± 0.0759	57.2843	46	0.1350 ± 0.0819	60.6508	46
Residual Area	0.041 ± 0.018	42.494	46	0.042 ± 0.020	46.407	46
AUC_{0-t}/AUC_{0-inf}	0.959 ± 0.018	1.827	46	0.958 ± 0.020	2.049	46

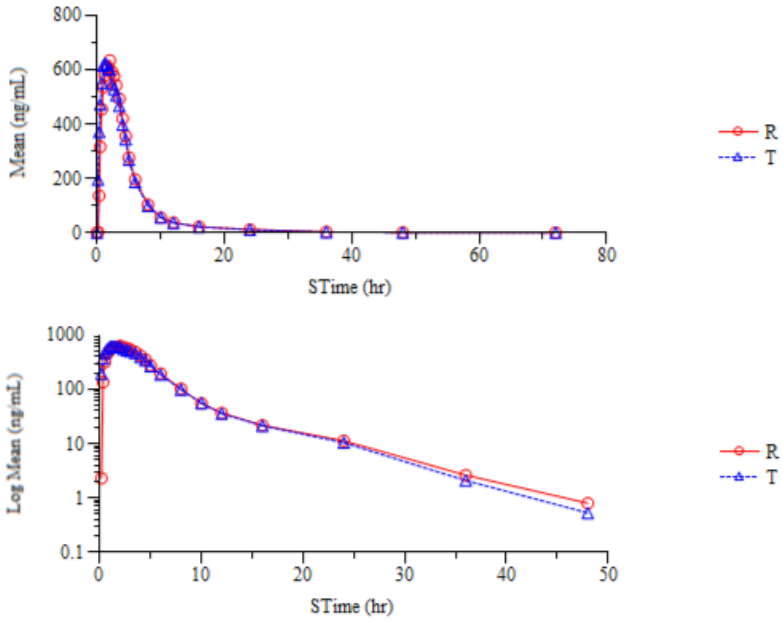
*t_{max} is represented as median (range)

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

The p-values derived from the analyses of variance (ANOVA) for the assessment of the main effects treatment, period, and sequence are given in the following table.

Main effects	Ln(C_{max})	Ln(AUC_{0-t})	Ln(AUC_{0-inf})
Sequence	0.4961	0.0668	0.0689
Period (group)	0.9638	0.8145	0.9025
Treatment	0.6791	0.7289	0.7397

The linear and the semi-log plot for trientine mean plasma concentrations versus time for all subjects are given in the figures below.



N1-acetyl triethylenetetramine (MAT) and N1,N10-diacetyltriethylenetetramine (DAT)

Furthermore, supportive pharmacokinetic data for the metabolites N1-acetyl triethylenetetramine (MAT) and N1,N10-diacetyltriethylenetetramine (DAT) were in line with the primary finding. Analyses for both metabolites met the predefined acceptance limits of 90% confidence intervals for AUC_{0-t} and C_{max} (80.00% to 125.00%).

Pharmacokinetic data for MAT and resulting statistical analyses are summarised in the following tables. The comparison for t_{max} between test and reference products is based on median and ranges.

Parameters	Test (T)			Reference (R)		
	Mean ± SD	CV (%)	N	Mean ± SD	CV (%)	N
C_{max} (ng/mL)	661.56 ± 193.96	29.319	46	646.91 ± 234.85	36.303	46
AUC_{0-t} (hr*ng/mL)	6947.169 ± 2020.625	29.086	46	6742.006 ± 2371.960	35.182	46
AUC_{0-inf} (hr*ng/mL)	7291.659 ± 2139.351	29.340	46	7069.224 ± 2478.792	35.065	46
t_{max}* (hr)	5.00 (3.00 - 6.00)	16.42	46	5.00 (3.50 – 6.00)	13.06	46
$t_{1/2}$ (hr)	15.69 ± 8.10	51.64	46	16.11 ± 7.20	44.70	46
K_{el} (hr^{-1})	0.0553 ± 0.0242	43.7486	46	0.0521 ± 0.0225	43.2373	46
Residual Area	0.047 ± 0.017	35.867	46	0.047 ± 0.016	32.879	46
AUC_{0-t}/AUC_{0-inf}	0.953 ± 0.017	1.751	46	0.953 ± 0.016	1.628	46

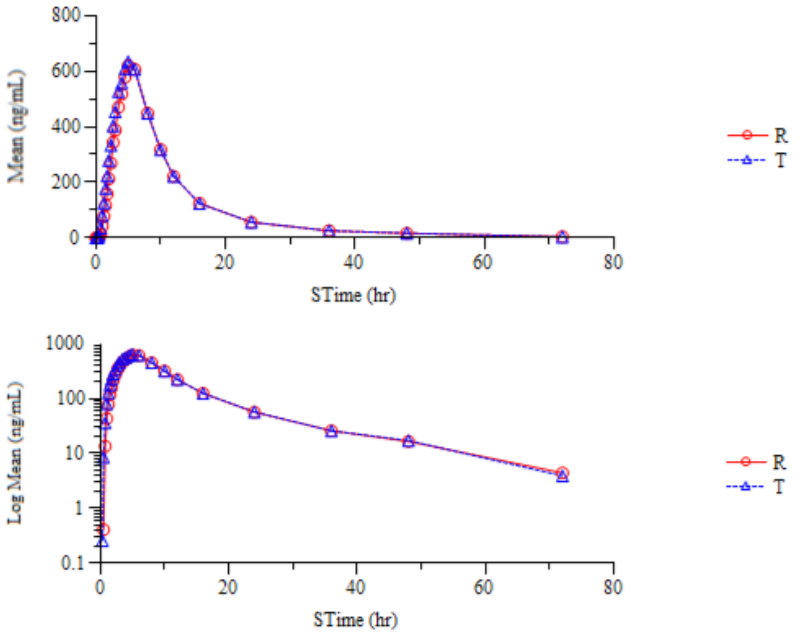
*t_{max} is represented as median (range)

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

The p-values derived from the analyses of variance (ANOVA) for the assessment of the main effects treatment, period, and sequence are given in the following table.

Main effects	Ln(C_{max})	Ln(AUC_{0-t})	Ln(AUC_{0-inf})
Sequence	0.5981	0.0722	0.0763
Period (group)	0.8204	0.9178	0.9179
Treatment	0.3274	0.2926	0.3019

The linear and the semi-log plot for mean plasma concentrations versus time for all subjects are given in the figures below.



Pharmacokinetic data for DAT and resulting statistical analyses are summarised in the following tables. The comparison for t_{max} between test and reference products is based on median and ranges.

Parameters	Test (T)			Reference (R)		
	Mean ± SD	CV (%)	N	Mean ± SD	CV (%)	N
C_{max} (ng/mL)	188.06 ± 108.87	57.893	46	176.26 ± 102.62	58.222	46
AUC_{0-t} (hr*ng/mL)	2594.133 ± 1018.001	39.242	46	2494.804 ± 1028.088	41.209	46
AUC_{0-inf} (hr*ng/mL)	2736.281 ± 1040.045	38.009	46	2638.964 ± 1058.200	40.099	46
t_{max}* (hr)	6.00 (3.50 – 10.00)	22.67	46	6.00 (3.50 – 10.00)	23.95	46
$t_{1/2}$ (hr)	11.59 ± 4.60	39.66	46	11.21 ± 3.37	30.03	46
K_{el} (hr^{-1})	0.0653 ± 0.0153	23.4546	46	0.0659 ± 0.0145	22.0475	46
Residual Area	0.056 ± 0.022	39.236	46	0.058 ± 0.018	30.886	46
AUC_{0-t}/AUC_{0-inf}	0.944 ± 0.022	2.340	46	0.942 ± 0.018	1.918	46

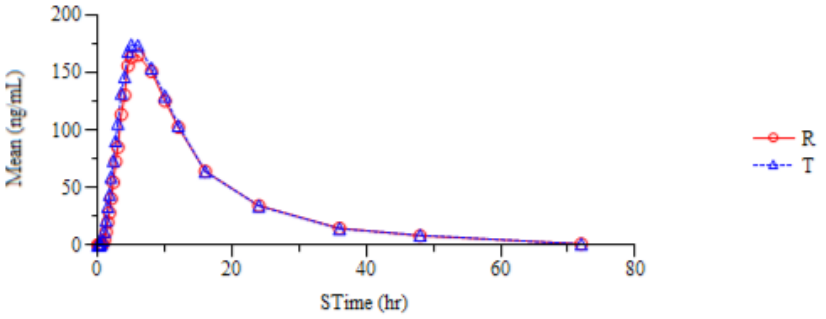
*t_{max} is represented as median (range)

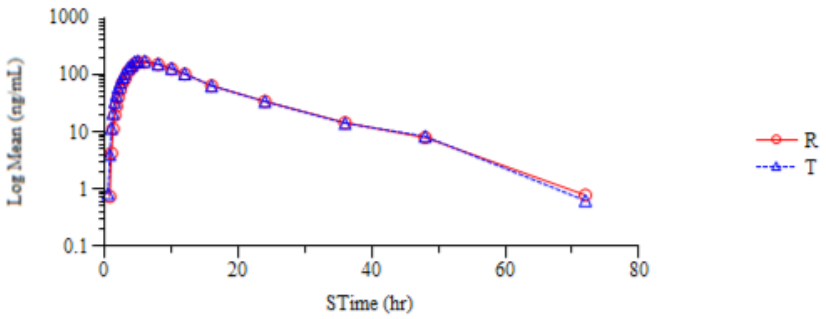
Parameter	Least square Geometric Means		T/R Ratio (%)	90% Confidence Intervals		Power (%)	Intra subject CV (%)
	Test (T)	Reference (R)		Lower (%)	Upper (%)		
C_{max} (ng/mL)	167.0553	157.1632	106.29	98.28	114.96	99.8	22.6
AUC_{0-t} (hr*ng/mL)	2431.5448	2327.2243	104.48	97.10	112.42	99.9	21.1
AUC_{0-inf}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

P-values derived from the analyses of variance (ANOVA) for the assessment of the main effects treatment, period, and sequence are given in the following table.

Main effects	Ln(C_{max})	Ln(AUC_{0-t})	Ln(AUC_{0-inf})
Sequence	0.5053	0.9054	0.9167
Period (group)	0.8463	0.8855	0.9126
Treatment	0.1974	0.3198	0.3313

The linear and the semi-log plot for mean plasma concentrations versus time for all subjects are given in the figures below.





Conclusion

Estimates for the test compared to the reference product were consistently slightly higher, but confidence intervals were small for all comparisons. The size of the extrapolated area was consistently < 20% in all subjects in the study.

Trientine t_{max} was shorter for test versus the reference product (median, range: 1.25 hr, 0.17 – 4.00; 2.00 hr, 0.50 – 4.50), but comparable between test and reference product for the metabolites N1-acetyl triethylenetetramine (MAT; 5.00 hr, 3.00 – 6.00; 5.00 hr, 3.50 – 6.00) and N1,N10-diacetyltriethylenetetramine (DAT; 6.00 hr, 3.50 – 10.00; 6.00 hr, 3.50 – 10.00). Since rapid release is not considered clinically relevant, the difference in t_{max} for trientine is acceptable.

In conclusion, the provided pharmacokinetic study indicates bioequivalence between the test product Trientine Waymade 200 mg hard capsule and the reference product Trientine dihydrochloride capsules 300 mg by Univar Solutions BV.

Pharmacodynamics bioequivalence study P-62420

Although the application is based on showing bioequivalence by the provided pharmacokinetic data, study 62420 included to monitor relevant factors associated with the pharmacodynamic action of trientine as secondary objectives while recognising that some of the parameters are less likely to be influenced by a single dose of trientine and that there might be relatively high inter-subject variability. The following laboratory tests data and descriptive statistics were provided:

- eGFR (glomerular filtration rate) via spot urine and blood creatinine,
- zinc, copper, iron, ferritin, soluble transferrin receptor parameters, and ceruloplasmin using biological matrix blood, and
- copper using biological matrix urine.

Overall, the collected pharmacodynamic data showed comparable longitudinal changes between the test and reference groups. Tests directly related to copper metabolism showed similar patterns between test and reference. There were no notable differences observed for eGFR evaluations using blood creatinine and urine spot creatinine levels.

III.3.1 Additional data

Dissolution

According to the Applicant “The composition of Waymade’s Trientine Dihydrochloride Capsules is very similar to Univar’s reference product with only minor differences in excipients,” and “The in vitro biodissolution profile has been shown to be similar between Waymade’s Trientine Dihydrochloride Capsules is very similar to Univar’s reference product.”. The following data are given in the dossier concerning in vitro dissolution data.

Dissolution testing Site		Study Report Location <vol/page, link> *Refer 3.2.P.2.2.1.5.2* In-vitro dissolution study profile in Module 3, section 3.2.P.2 Pharmaceutical Development
Dissolution Conditions	Apparatus	USP Type-II (paddle)
	RPM	50
	Medium	Purified water
	Volume	500 ML
	Temperature	37 ± 0.5 °C
	Surfactant	--

Dissolution Medium		Collection Times (minutes or hours)					f2*
		5	10	15	30	45	
Strength 200 mg # of units 12 # Batch no: **641903I** Trientine 200mg hard capsules	pH=1.2	99.1	99.4	99.5	99.4	100.6	
	pH=4.5	98.8	100.1	99.9	100.3	100.5	
	pH=6.8	98.1	98.6	98.7	99.4	100.4	
	QC medium (Purified water)	97.2	98.8	99.3	99.4	99.1	
Strength 200 mg # of units 12 # Batch no; **7346601,** Cufence 200mg hard capsule	pH = 1.2	-	20.6	30.5	48.4	59.9	
	pH= 4.5	-	9.7	18.1	37.8	50.9	
	pH= 6.8	-	10.7	17.6	43.3	54.7	
	QC medium Purified water)	-	6.0	17.7	36.6	50.2	

f2 not calculated as > 85% of drug is dissolved within 15 minutes for both test and reference product in all medium.

The provided dissolution data are not in line with the Applicant's initial statement that the composition of both the test and the reference product are very similar and that the in vitro biodissolution profile has been shown to be similar between both products. However, an adequate update of section 2.7.1 of the dossier has been provided reflecting on differences in composition of the test and reference product and discussing the observed differences in dissolution profile.

During the MHRA scientific advice the Applicant was informed that although according to the CHMP guideline on the investigation of bioequivalence, bioequivalence demonstrated in vivo prevails the comparative in vitro dissolution profiles of the biobatches, possible reasons for the discrepancy observed between the in vitro and in vivo results should be addressed and justified.

Safety data

According to the Applicant, in study 62420 both treatments were well tolerated, with no significant side effects and no relevant differences in safety profile observed between both products. A total of three (3) adverse events (2 itching all over the body; 1 back pain) were reported by 3 subjects during the study. Out of these, 1 adverse event (itching all over the body) each was reported by subject S5 and subject S36 and 1 adverse event of back pain was reported by subject S18 during period-II. These adverse events were considered unlikely to be related to the study drug and were moderate in nature. All events resolved and did not result in subject discontinuation. The events are further summarised in the following tables.

Subject Number	Study Drug (Test/ Reference)	Adverse Event			Relationship to study drug	Severity	Management	Onset		Resolved	
		AE Description	Preferred Term	System Organ Class				Date	Time (hr)	Date	Time (hr)
S5	Test	Itching all over body	Pruritus generalized	Skin and subcutaneous tissue disorders	Unlikely	Moderate	Continued in the study	30/08/2020	09:05	30/08/2020	14:21
S18	Test	Back pain	Pain	General disorders and administration site conditions	Unlikely	Moderate	Continued in the study	28/08/2020	17:15	28/08/2020	23:25
S36	Tesst	Itching all the over body	Pruritus generalized	Skin and subcutaneous tissue disorders	Unlikely	Moderate	Continued in the study	31/08/2020	18:10	31/08/2020	22:24

Coding according to MedDRA 22.1
AE = Adverse event

Subject Number	Study Drug	Event	Medication given	Interaction with Study drug Pharmacokinetics	Medication given		Resolved	
					Date	Time (hr)	Date	Time (hr)
S5	Test	Itching all over body	Tab Okaset (Cetrizine Hydrochloride 10 mg)	No	30/08/2020	09;25	30/08/2020	14:21
S18	Test	Back pain	Tab Voveran 50 mg (Diclofenac sodium 50 mg)	No	28/08/2020	17:24	28/08/2020	23:25
			Injection Dynapar AQ (Diclofenac sodium 75 mg/mL)	No		19:20		
S36	Test	Itching all over the body	Injection Avil (Pheniramine Maleate 45.50 mg/ 2mL)	No	31/08/2020	18:38	31/08/2020	22:24

There were no deaths or serious adverse events reported in the study and no abnormal laboratory values have been reported.

In conclusion the provided safety data do not indicate any new or unexpected safety findings, but assessment is limited by the small study size with only one exposition to the test and the reference product each. Safety assessment is thus primarily based on the data available for the reference product.

Summary Pharmacovigilance system

The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's / Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS/Rapporteur considers the Summary acceptable.

Risk Management Plan

The MAA has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to the medicinal product(s) applied for authorisation.

Safety specification

According to the Applicant the safety specification is in full accordance with the current safety specification agreed and published for a similar product/similar products which is acceptable.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the Applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the Applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan is considered acceptable.

After approval 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 RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:
- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

Common renewal date

The proposed common renewal date is 5 years after the end of the procedure.

IV BENEFIT RISK ASSESSMENT

The benefit / risk ration is considered positive.

V LIST OF QUESTIONS as proposed by RMS

V.1 Quality aspects

Major Objections

None

Other concerns

None

V.2 Non-clinical aspects

Major objections

None

Other concerns

None

V.3 Clinical aspects

Major objections

None

Other concerns

None

VI RECOMMENDED CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

VI.1 Legal Status

Product on restricted medical prescription.

VI.2 Proposed list of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

N/A

VI.3 Proposed list of conditions pursuant to Article 21a or specific obligations pursuant to article 22 of Directive 2001/83/EC

N/A

VI.4 Module I – Application related comments (including product name)

Product name

The proposed product name for procedure DE/H/6991/001/DC (in annex 5.19) “Trientin Waymade 200 mg Hartkapseln” can be accepted.

VI.5 Summary of Product Characteristics (SmPC)

The SmPC is essentially in line with that of the originator.

VI.6 Package Leaflet (PL)

VI.6.1 Package Leaflet

The PL is essentially in line with that of the originator.

VI.6.2 Assessment of User Testing

Although the Applicant had stated that a readability test would be performed during clock stop the Applicant has submitted a user testing bridging proposal instead. The provided bridging is considered acceptable (see assessment in the 'QRD Guidance and Checklist for the Review of User Testing Results' below).

VI.7 Labelling

VII APPENDIX

QRD GUIDANCE AND CHECKLIST FOR THE REVIEW OF USER TESTING RESULTS

PRODUCT INFORMATION

Name of the medicinal product:	Trientine Waymade 200 mg hard capsules
Name and address of the Applicant:	Waymade B.V. Herikerbergweg 88 1101CM Amsterdam Netherlands
Name of company which has performed the user testing:	Waymade B.V. Netherlands
Type of Marketing Authorisation Application:	Article 10(1) generic application
Active substance:	Trientine dihydrochloride
Pharmaco-therapeutic group (ATC Code):	Other alimentary tract and metabolism, various alimentary tract and metabolism products (A16AX12)
Therapeutic indication(s):	Trientine Waymade capsules are 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

- Full user testing report provided ☐ yes ☒ no

- Bridging report provided ☒ yes ☐ no

(In case of bridging report, multiple bridging is, in principle, not acceptable. However, a maximum of 3 bridging procedures could be accepted for one product: e.g. first bridging to address the scientific content, a second one to address the device and a last one to address the layout of the PL).

- Grounds for bridging based on a sound justification:
  - ☒ extensions for the same route of administration
  - ☒ reference to test on same class of medicinal product
  - ☒ reference to test with same safety issues
  - ☒ other: reference to test with common design, layout and style of writing

Is the justification for bridging acceptable? ☒ yes ☐ no

Assessor's comment

The Applicant has provided a bridging report instead of a full user testing. As regards the content including key safety messages reference is made to PIL of the centrally authorised product Cufence 200 mg hard capsules (EMEA/H/C/004111, authorised in the EU since 25 July 2019). This is considered acceptable.

As regards design and layout reference is made to the PIL of Doxycycline 50mg and 100mg Capsules (PL 06464/3108 – 0001, authorised in the UK since 21 April 2020); the report on successful full user testing for this product by Cambridge Regulatory Services Ltd, Fenstanton UK, has been provided (dated 10 January 2018). Critical aspects for bridging like font type, text size, heading/subheading formatting, leaflet dimensions, design,

layout, colour, style of writing and layout of critical safety sections for both ‘parent’ and ‘daughter’ PILs are comparable. Real size mock-ups of ‘parent’ and ‘daughter’ leaflets have also been provided.

In summary the provided bridging to the content of the centrally authorised product Cufence 200 mg hard capsules (EMEA/H/C/004111) and the design and layout of the user tested ‘daughter’ PIL to the provided PIL of Trientine Waymade 200 mg hard capsules are considered acceptable.