Decentralised Procedure

RMS Day 70 Preliminary 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
Date of this report:	09.09.2021
Deadline for comments (day 100):	09.10.2021 (new)

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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	Waymade PLC, Josselin Road, Burnt Mills Industrial Estate, Basildon, Essex, SS13 1QF, United Kingdom Waymade PLC, Sovereign House, Miles Gray Road, Basildon, Essex SS14 3FR, United Kingdom Drehm Pharma GmbH Hietzinger Hauptstraße 37/2, Wien, 1130 Austria
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 Waymade PLC, Josselin Road, Burnt Mills Industrial Estate, Basildon, Esse United Kingdom 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. DSG Biotec GmbH Institut für Pharma-Analytik Kirchstr. 10 83229 Aschau, Germany QC Testing: Chemical/Physical

	SYNLAB Analytics & Services Germany GmbH Hauptstraße 105 04416 Markkleeberg, Germany QC Testing: 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** Tel: Email: [redacted]
Names of the assessors:	**Quality**: **Name:** [redacted] Email: [redacted] **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) Tel: Email:	[redacted]

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 not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of questions (Section V).

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). However, the outcome of this inspection has not been identified in the dossier and should be provided (OC).

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. Some questions regarding the impurity profile are raised.

The drug substance is controlled by an in-house specification. The specification includes description, solubility, Identification (IR), 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.
However, an issue concerning impurity specification should be resolved.

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 one batch of increased batch size, to date 3 months data are available. The proposed retest period of 48 months under the storage conditions "Preserve under an inert gas in tight light resistant container and store at 2°C to 8°C temperature" should be supported by further results.

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. Clarification is requested concerning quality references of the ink.

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. However, the Applicant is requested to further address and justify possible reasons for the discrepancy in the dissolution profiles.

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, but a few issues should be clarified. 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 12 months of a still ongoing long-term stability study (5°C ±3ºC) are available, meeting the specifications. However, the proposed shelf-life of 2 years when stored at 2-8°C in the proposed container closure system should be justified by further results of the ongoing long term stability study.

Conclusion:

Several issues concerning the drug substance and the drug product should be resolved. One major concern is raised because no evaluation of the risk of a contamination of the finished product with nitrosamines is provided.

The drug product could be approvable provided that satisfactory responses are given to the preliminary list of questions.

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.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is presently not fully adequate for the following reason: In the nonclinical overview regarding impurities of the medicinal product under review it is stated “All the observed elemental (metal) impurities level is meeting the 30% limit (ICH Q3D) oral limit, no further control required”. On possible impurities other than elemental (metal) impurities no information can be found. The Applicant is asked to report on and assess any possible impurities other than elemental (metal) impurities in the medicinal product under review and to state whether they are in line with the respective European guidelines. Such information should be amended to the Nonclinical overview (Module 2.4). (**Other concern**)

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 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 h 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

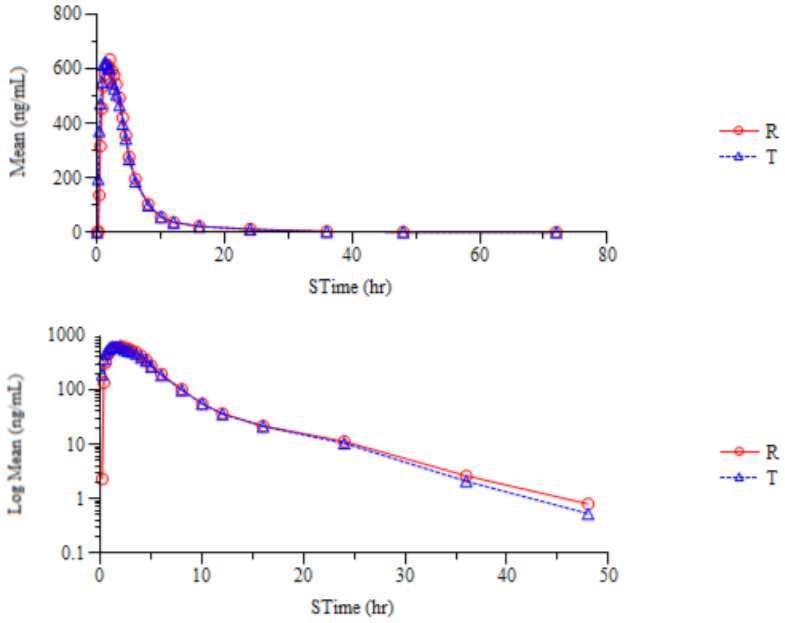
*t_{max} is represented as median (range)

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

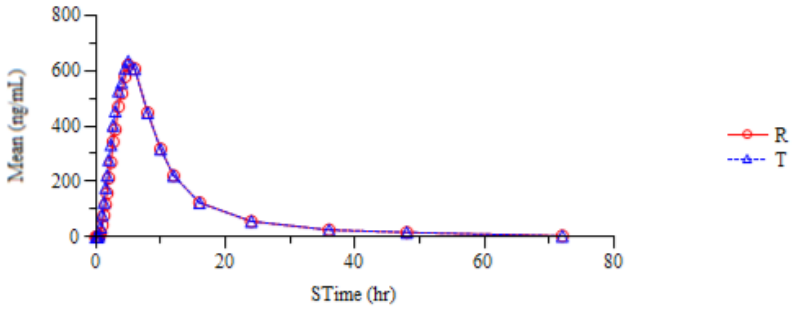
*t_{max} is represented as median (range)

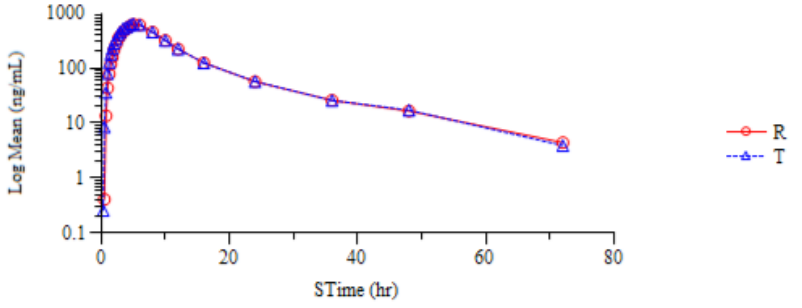
Parameter	Least square Geometric Means		T/R Ratio (%)	90% Confidence Intervals		Power (%)	Intra subject CV (%)
	Test (T)	Reference (R)		Lower (%)	Upper (%)		
C_{max} (ng/mL)	634.1766	607.2029	104.44	97.02	112.44	99.9	21.3
AUC_{0-t} (hr*ng/mL)	6597.8877	6303.8912	104.66	97.40	112.47	100.0	20.7
AUC_{0-inf}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

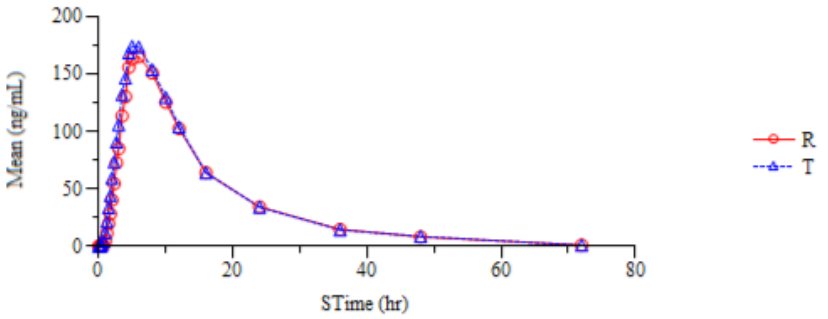
*t_{max} is represented as median (range)

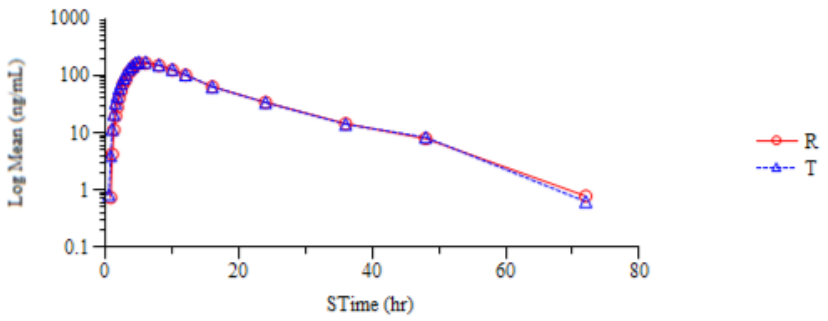
Parameter	Least square Geometric Means		T/R Ratio (%)	90% Confidence Intervals		Power (%)	Intra subject CV (%)
	Test (T)	Reference (R)		Lower (%)	Upper (%)		
C_{max} (ng/mL)	167.0553	157.1632	106.29	98.28	114.96	99.8	22.6
AUC_{0-t} (hr*ng/mL)	2431.5448	2327.2243	104.48	97.10	112.42	99.9	21.1
AUC_{0-inf} (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, but some issues need to be addressed before a final conclusion.

Pharmacodynamics bioequivalence study P-62420

Although the application is based on showing bioequivalence by the provided pharmacokinetic data, according to the investigational plan of study 62420, secondary objectives were to monitor relevant factors associated with the pharmacodynamic action of trientine to allow for a more comprehensive analysis of the test and reference products. In the study protocol however, these issues appear to be reported as safety measurements. In the clinical overview, it is stated that as endorsed by MHRA, the Applicant has collected additional plasma and urine parameters to support further the bioequivalence data. Laboratory tests to monitor factors associated with the PD action of trientine were:

- 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.

According to a short statement in the clinical overview, the results for these parameters were analysed using descriptive statistics, they showed similar longitudinal changes between the test and reference groups, and the pattern of changes was consistent with that reported for these attributes in the published literature. Results appear not to be contained in ECTD 2.7 and in the study report, only some additional tables in section 14 have been identified without analysis or discussion. The Applicant is requested to provide an adequate presentation and discussion of the pharmacodynamic results obtained in study 62420 (OC).

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 follwing 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.

These provided dissolution data are not in line with the Applicant's 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. No explanation for the significant differences in the dissolution profiles between the test and the reference product has been identified and the Applicant is requested to justify the statement or to correct the provided clinical summary. See also relevant question concerning Module III.

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. The Applicant needs to provide such a discussion and justification (OC).

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

Proposed common renewal date 5 years after the end of the procedure.

IV BENEFIT RISK ASSESSMENT

Somme issues need to be clarified before a conclusion on the benefit / risk ratio can be made from the clinical point of view.

From a quality perspective, a positive benefit risk assessment can be stated provided that satisfactory responses are given to the preliminary list of questions.

V LIST OF QUESTIONS as proposed by RMS

V.1 Quality aspects

<u>Major Objections</u>

Drug Substance

None

Drug Product

1. Evaluation on the risk for presence of nitrosamines in the API has been provided by the ASM only. In addition, the MAH / Applicant should carry out a risk evaluation/risk assessment of manufacturing processes of API and of the drug product for the presence of N-nitrosamines as part of the marketing authorisation application (MAAs) – see documents “European

Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) No 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020)" and "Q&A for the implementation of the Article 5(3) referral (EMA/409815/2020 Rev.4)".

Other concerns

Drug Substance

3.2.S.2.2

2. In the description of the synthesis, information on the yield is missing and should be provided for larger and for smaller batch size for each stage of the synthesis.

3. In the reaction scheme of Stage-I, Triethylenetetramine, the use of purified water and sodium hydroxide should be added, in line with the described synthesis.

4. It should be clarified if in Stage III Trientine Dihydrochloride, step 6, the reaction mass is filtered through a cartridge filter with 0.2µm. The detailed description and the flow diagram should be updated accordingly in section 3.2.S.2.2. The used filter (pore size, filter material) should be described in section 3.2.S.2.3.

5. The quantity and quality of the water used in the synthesis should be stated in section 3.2.S.2.2 for all stages.

6. Any reprocessing steps should be described and justified.

3.2.S.2.3

7. A discussion on the possible impurities of the starting materials 1,2-dichloroethane and Ethylenediamine and their fate in the subsequent processing should be provided.

8. According to section 3.2.S.2.3, two qualities of methanol (methanol and methanol (LR grade)) is used in the synthesis. It should be indicated in detail in section 3.2.S.2.2, in which steps of the synthesis, methanol and in which steps methanol (LR grade) is used. The reason for the two qualities and the differences in quality should be explained. Furthermore, it should be clarified if methanol / methanol (LR grade) is used in Stages II & III only as stated in section 3.2.S.2.2 or in Stages I, II & III, as stated in section 3.2.S.2.3.

9. Information on quality of the water used in the synthesis of Trientine dihydrochloride is totally missing and must be provided for each stage of the synthesis along with representative Certificates of Analysis. Sections 3.2.S.2.2. and 3.2.S.2.3 should be updated accordingly. The quality of the water should be in accordance with the 'Guideline on the quality of water for pharmaceutical use' (EMA/CHMP/CVMP/QWP/496873/2018)

3.2.S.2.4

10. The purity of the isolated intermediate Triethylenetetramine is 75.0% only according to the specification of this intermediate. For one unidentified impurity at about RRT 1.2, NMT 20.0% and for any unspecified impurities NMT 3.0% are specified. A detailed discussion on the formation of possible impurities in manufacture of Triethylenetetramine should be provided. Especially, the formation of chlorinated moieties should be addressed. Information on purging and fate of the impurities of Triethylenetetramine in the subsequent processing based on appropriate data should be provided. Especially, it should be confirmed that chlorinated moieties are not present in the final API Trientine dihydrochloride.

3.2.S.3.1

11. Trientine dihydrochloride is known to exhibit polymorphism. To support that always the same polymorphic form is manufactured, additional XRPD data of batches with larger/increased batch size should be provided.

3.2.S.3.2

12. Justification should be provided for the specified limit for the residual solvent diisopropyl ether. Furthermore, the specified limit of NMT 1100ppm should be reduced as all results for residual diisopropylether were below the quantitation limit of 28ppm.

13. In stages II and III of the synthesis, methanol / methanol (LR grade) is used. According to the specifications, benzene is limited in methanol to 50ppm, while the amount of benzene in methanol (LR grade) is unknown as no limit for benzene is set in the specification of this solvent. Because of the possible contamination of methanol with benzene, a limit of not more than 2ppm for residual benzene based on a validated analytical method should be included in the specification of the final API Trientine dihydrochloride.

3.2.S.4

14. The footnote of drug substance specification of the DPM "@ Assay by GC and Assay by Titrimetry both shall be performed during release. In case of any discrepancy in analysis result, Pharmacopoeial method shall be considered" should also be added to the drug substance specification of the ASM.

15. As in two commercial size batches from 2020, the results for TAMC were 200 cfu/g (batch [redacted] batch size 89,300kg) or 250 cfu/g (batch [redacted] 91.63 kg), microbial quality should be tested at each batch. The footnote on frequency of # Microbial Enumeration Tests should be updated accordingly in the drug substance specifications of the ASM and the DPM.

16. In the drug substance specification, reference should be made to Ph. Eur. methods, where applicable.

17. The specified limit for Ethylenediamine of NMT 0.10% is above the qualification threshold of ICH Q3A. In line with ICH Q3A, ethylenediamine should be qualified at a 0.10% level or the limit for Ethylenediamine in the drug substance should be reduced to "not more than 0.05%".

3.2.S.5

18. Information on the preparation of the in-house Trientine dihydrochloride working standard should be provided.

19. According to the certificates of analysis, the Trientine dihydrochloride working standard WS-DS133-16/004 and WSDS 13317/002 have expired. A Certificate of analysis of the current reference standard Trientine dihydrochloride should be provided.

20. The impurity reference standards Diethylenetriamine standard, 1-(2-aminoethyl) piperazine standard, Tris (2-aminoethyl) amine standard, Ethylenediamine standard, and Piperazine standard are outdated, as they were manufactured in 2013 – 2015. Certificates of analysis of the current impurity reference standards, used for control of impurities and for control of assay of Trientine dihydrochloride should be presented.

3.2.S.6

21. For the white coloured opaque High-Density Polyethylene (HM-HDPE) bag used as Primary packing component, a certification on compliance with EU Regulation 10/2011 and with Ph. Eur. 3.1.3 should be provided by the supplier.

3.2.S.7

22. The stability data of the ongoing long term stability studies available by now should be provided.

23. Only one batch of the stability batches relates to current full production scale batches, as the batch size was increased. The available stability data of three current full production scale batches (batches with larger batch size) kept for long term stability studies should be provided, together with a commitment to continue the studies through the proposed re-test period.

24. It should be demonstrated that the polymorphic form is stable over the proposed retest period by XRPD data of stored batches.

25. Results of a photostability study according to ICH Q1B should be provided.

Drug Product

3.2.P.1

26. The quantity of the active moiety Trientine equivalent to Trientine Dihydrochloride should be clearly stated in the composition table in section 3.2.P.1.

27. The type of stearic acid should be stated in sections 3.2.P.1 and in the excipient´s specification in section 3.2.P.4.1. This should be in line with the excipient used in the validation batches. From the CoA provided in section 3.2.P.4, stearic acid (50) is used.

28. For the ingredients of the Black Ink, also reference should be made to the Ph. Eur where applicable, in line with the declaration of the supplier.

29. The name of the proposed drug product is “Trientine 200mg hard capsules”, while on the capsules, it is printed “Trientine 300mg”. According to the SPC, “the recommended doses are expressed as mg of Trientine base (i.e. not in mg of the trientine dihydrochloride salt)”. To avoid misleading of the user, “Trientine 200mg” should be printed on the capsules. All relevant sections of the dossier should be updated accordingly."

30. According to the information in section 3.2.P.7, the closure of the bottle is a white polypropylene screw cap with induction heat seal liner. Section 3.2.P.1 should be updated accordingly.

3.2.P.2

31. In the dissolution profiles of the test bio-batch (batch [redacted] and the reference bio-batch Cufence 200 mg hard capsule (batch# [redacted] the reference batch showed considerably lower dissolution in all media. Although for these batches a BE study was conducted, in accordance with the ‘Guideline on the Investigation of bioequivalence’ the Applicant is requested to address and justify possible reasons for the discrepancy. In the evaluation, not only the change in manufacture of the reference product should be addressed but also further possible reasons, like the differences in the excipients between test and reference product.

3.2.P.3.1

32. For the finished product manufacturer Apothecon Pharmaceuticals Pvt. Ltd, the GMP Certificate issued by the MHRA (based on an inspection at 03/12/2019) is restricted to the manufacture and primary packaging of tablets and hard shell capsules in Block B. The information on the manufacturer of the drug product should be updated accordingly with the statement that manufacture and primary packaging of the Trientine 200mg hard capsules is performed in Block B only.

33. The batch release site and batch control testing sites, located in the United Kingdom, should also be removed from section 3.2.P.3.1.

34. The name of the EEA Control testing site in Module 3 (DSG Biotec Umwelt und Pharma-Analytik GmbH) is not the same as stated in Module 1, eaf section 2.5.1.2 and Annexes 5.6, 5.8, 5.9 (DSG Biotec GmbH Institut für Pharma-Analytik). Module 3.2.P.3.1 should be corrected accordingly.

3.2.P.3.3

35. Due to the hygroscopicity of Trientine dihydrochloride, relative Humidity NMT 45 % and temperature NMT 25 °C was kept in manufacture of the validation batches. These conditions should also be included in section 3.2.P.3.3.

3.2.P.5

36. Specificity of the analytical method for assay (UV/VIS) with respect to impurities / degradants should be demonstrated by appropriate data.

37. For the demonstration of suitability of identification of the drug substance in the drug product by IR, representative IR spectra of drug product and reference standard should be provided.

38. Control of microbiological quality of the drug product at release should be performed on every batch, as in the validation batches, the results for TAMC were up to 200 cfu/g and TYMC was up to 40 cfu/g

3.2.P.6

39. Certificates of analysis for the current reference standard Trientine dihydrochloride and for the current impurity standards used for control of the drug product should be provided.

3.2.P.7

40. According to the information from the supplier of the closure, exechon, and the supplier of the liner, Tekniplex, the closure is a white polypropylene screw cap with induction heat seal liner. This should be clearly indicated in section 3.2.P.1, 3.2.P.7, section 2.2.3.1 of the Application Form and the SPC and PIL.

41. For the HDPE bag used during hold time of lubricated blend and filled capsules, a certification on compliance with EU Regulation 10/2011 should be provided. The HDPE should comply with Ph. Eur. 3.1.3.

3.2.P.8

42. Stability data of the ongoing long term stability studies (5°C ±3ºC) at T18 and T24 should be provided to justify the proposed shelf-life of 2 years.

43. In-use stability data of at least one batch after 24 months storage should be provided. The test design should be in accordance with the "Note for Guidance on In-use Stability Testing of Human Medicinal Products, CPMP/QWP/2934/99".

44. Results of a photostability study of the drug product performed according to ICH Q1B should be provided.

Module 1

45. The type of stearic acid should be stated in section 2.6.1 of the Application Form. This should be in line with the excipient used in the validation batches. From the CoA provided in section 3.2.P.4, stearic acid (50) is used.

46. In section, 2.6.1 of the Application Form, the qualitative and quantitative composition of Black Ink should be stated. For the ingredients, also reference should be made to the Ph. Eur where applicable, in line with the declaration of the supplier. Black iron oxide should meet the requirements of (EU) 231/2012 (E172).

47. According to the information in Module 3, section 3.2.P.7, the closure of the bottle is a white polypropylene screw cap with induction heat seal liner. Section 2.2.3.1 of the Application Form should be updated accordingly.

48. For the finished product manufacturer Apothecon Pharmaceuticals Pvt. Ltd, the GMP Certificate issued by the MHRA (based on an inspection at 03/12/2019) is restricted to the manufacture and primary packaging of tablets and hard shell capsules in Block B. The information on the manufacturer of the drug product should be updated accordingly in section 2.5.2 of the Application Form with the statement that manufacture and primary packaging of the Trientine 200mg hard capsules is performed in Block B only.

SmPC and PL:

49. According to the information in Module 3, section 3.2.P.7, the bottle is closed with a white polypropylene screw cap with induction heat seal liner. Section 6.5 of the SPC and section 6 of the PIL. should be updated accordingly.

V.2 Non clinical aspects

Major objections
None

Other concerns

Toxicology

The Applicant is asked to report on and assess any possible impurities other than elemental (metal) impurities in the medicinal product under review and to state whether they are in line with the respective European guidelines. Such information should be amended to the Nonclinical overview (Module 2.4).

V.3 Clinical aspects

Major objections

None

Other concerns

1. The Applicant should provide information on the outcome of the MHRA inspection indicated in module 2.7.1.

2. The Applicant is requested to provide an adequate presentation and discussion of the pharmacodynamic results obtained in study 62420.

3. The provided dissolution data are not in line with the Applicant's 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.

   No explanation for the significant differences in the dissolution profiles between the test and the reference product has been identified and the Applicant is requested to justify the statement or to correct the provided clinical summary. Although according to the relevant CHMP guideline, 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. The Applicant needs to provide such a discussion and justification.

VI RECOMMENDED CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

VI.1 Legal Status

Product on prescription

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

None

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) can be accepted given that the German word Trientin (instead of Trientin**e**) is used.
Therefore, please update the name in annex 5.19 to "Trientin Waymade 200 mg Hartkapseln".

VI.5 Summary of Product Characteristics (SmPC)

Clinical and non-clinical: The SmPC is essentially in line with that of the originator.

Quality:
According to the information in Module 3, section 3.2.P.7, the bottle is closed with a white polypropylene screw cap with induction heat seal liner. Section 6.5 of the SPC should be updated accordingly.

VI.6 Package Leaflet (PL)

VI.6.1 Package Leaflet

Clinical and non-clinical: The PL is essentially in line with that of the originator.

Quality:
According to the information in Module 3, section 3.2.P.7, the bottle is closed with a white polypropylene screw cap with induction heat seal liner. Section 6 of the PIL should be updated accordingly.

VI.6.2 Assessment of User Testing

The applicant has stated that the readability test will be performed during clock stop. The RMS agrees with this.

VI.7 Labelling