Trientine: comparison of formulations available in the UK (November 2020)

Information provided for the BASL Wilson Disease Special Interest Group Meeting, 20th November 2020 by Professor Aftab Ala (with minor editing by RP)

Brand Name	**Cuprior 150 mg film-coated tablets**	**Cufence 200 mg hard capsules**	**Trientine dihydrochloride 300 mg capsules**	**Trientine dihydrochloride Tillomed 250 mg capsules, hard**
Indication	For the treatment of Wilson's Disease in patients intolerant of D-Penicillamine therapy, in adults, adolescents and children aged 5 years or older.[1,2,3,4]			
Market Authorisation Holder	Orphalan UK Ltd / formerly GMP Orphan UK Ltd	Univar Solutions	Univar Solutions	Tillomed Laboratories Limited
Active ingredient	Trientine tetrahydrochloride	Trientine dihydrochloride	Trientine dihydrochloride	Trientine dihydrochloride
Trientine salt content	300 mg	300 mg	300 mg	250 mg
Trientine base content	150 mg	200 mg	200 mg	167 mg
Country of manufacture	Germany	UK	UK	India
Size and description of formulation	Tablet length 16.0 mm, width 8 mm with a score line on each side. The tablet can be divided into equal doses	Capsule length 21.7 mm, diameter 7.65 mm. White hard capsule.	Capsule length 21.7 mm, diameter 7.65 mm. White hard capsule.	Capsule length between 18.9 mm and 19.7 mm. Brown opaque hard gelatine capsule.
Dosage form and packaging	Film coated tablets in blister pack, 72 tablets, 8 per blister	Amber glass bottle with a polypropylene cap and induction heat seal liner with a sachet of dried silica gel as desiccant. Pack size: 1 bottle of 100 hard capsules.	100 capsules in an amber glass bottle with a polypropylene cap with induction heat seal liner, also containing a sachet of dried silica gel as desiccant.	White opaque HDPE bottle with a PP child-resistant closure. Pack size: 100 capsules.
Storage	This medicinal product does not require any special storage conditions.	Two versions of Cufence are available. One does not require any special storage conditions unopened. After opening the bottle, store in a refrigerator (2 °C – 8 °C). Do not freeze.	Store in a refrigerator (2 °C – 8 °C). Do not freeze. Store in the original container and retain the silica gel sachet in the bottle in order to protect from moisture.	This medicinal product does not require any special temperature storage conditions. Keep the bottle tightly closed in order to protect from moisture.

		Keep the bottle tightly closed in order to protect from moisture. The second product requires refrigeration at all times.		
Regulatory information and Bioequivalence information	Cuprior has been approved as a hybrid product through centralised procedure by regulatory authorities using Univar trientine 300 mg capsules as reference product (EMA) on 05 September 2017.[5] Bioequivalence has been investigated in the TRIUMPH study[6] against Univar trientine and according to Cuprior EPAR Cuprior has higher bioavailability than Univar trientine so a conversion factor of 0.6 has been used to adjust the dose from Univar trientine to Cuprior, therefore the recommended daily dose is less	Approved as similar by centralised procedure by regulatory authorities using Univar trientine 300 mg capsules as reference product (EMA) on 25 July 2019.[7] Variation approved on 30 January 2020 for formulation change and change to storage conditions.[8, 9] Bioequivalence was investigated in the study TR-003 PK comparing "fast" dissolution formulation (Cufence) against "slow" dissolution formulation (Univar trientine 300 mg capsules).[10] Bioequivalence could not be claimed but the differences were not considered to be of clinical relevance by Univar Solutions	Approved through national procedure by MHRA (then MCA) in 1985 in UK only. No PAR identified	Tillomed trientine has been approved as a hybrid product through centralised procedure by regulatory authorities using Univar trientine 300 mg capsules as reference product (EMA) on 17 January 2020.[11] Bioequivalence has been investigated in a study against Univar trientine 300 mg capsules and according to the Tillomed EPAR Tillomed trientine has higher bioavailability than Univar trientine and so is used at lower doses
Dose equivalence	0.6 of Univar trientine 300 mg capsule dose as per Cuprior EPAR	Same as Univar trientine 300 mg capsule dose	Reference product	Dose according to licenced dose range but specific equivalence information not provided in EPAR
Licensed Dose	Adults: 450-975 mg (3-6.5 tablets) per day in 2-4 divided doses Children: The dose is usually between 225 mg and 600 mg per day (1½ to 4 film-coated tablets) in 2 to 4 divided doses.	Adults: 800-1,600 mg (4-8 capsules) per day in 2-4 divided doses Children: The dose should be adjusted according to clinical response; 400 – 1,000 mg (2-5 capsules) have been used at initiation of therapy	Adults: 1,200-2,400 mg (4-8 capsules) per day in 2-4 divided doses Children: The dose should be adjusted according to clinical response. 0.6-1.5 grams have been used at initiation of therapy.	Adults: 1,000-2,000 mg (4-8 capsules) per day in 2-4 divided doses Children: The recommended initial dose of trientine dihydrochloride capsule is usually between 500-1250 mg (2-5 capsules). The maintenance dose is titrated according to clinical response and serum copper level.
Interchangeability guidance	See below		See below	
Post marketing experience	Prescribed to more than 500 patients throughout Europe, 5 patients UK, 12 patients Ireland	Starting to be used in some EU countries after gaining centralised approval in 2019.	Marketed in UK since 1985, 80-90 patients UK. Prescribed unlicensed in Europe.	No clinical experience or market data available to date as only authorised in 2020

	Market dominant in Germany, France, Ireland, Italy, Sweden, Norway, Netherlands. Available but not dominant in UK, Spain and Portugal	Market dominant in Greece and Denmark. Also available in Germany and Portugal	Market dominant in UK. No longer present in most European countries as being gradually replaced by Cufence	
Clinical program	CHELATE Phase 3 clinical ongoing[12]. Last patient week 36 completed. Last patient week 60 completed Jan 2021, last patient week 108 completed December 2021	Post authorisation PK and efficacy study to be conducted as part of marketing authorisation commitment. PK study due Q4 2022, efficacy study due Q4 2025		
NHS England	Added to NHS England Trientine in Wilson's Disease Clinical Commissioning Guideline[13]	Assumed to be included in NHS England Trientine in Wilson's disease Clinical Commissioning Guideline	Included in NHS England Trientine in Wilson's disease Clinical Commissioning Guideline	Assumed to be included in NHS England Trientine in Wilson's disease Clinical Commissioning Guideline
NHS Scotland	Accepted for use within NHS Scotland in the treatment of Wilson's Disease[14] and preferred trientine formulation for NHS Scotland[15]			
Ireland	Only prescribable trientine and the only reimbursed option following appraisal by HPRA, HSE and CPU			
Customer Service	Homecare arrangement, free of charge: Drug home delivery service Home phlebotomy service and delivery to lab. Home delivery of and collection of 24 hour urine sample to lab. service.	Homecare arrangement free of charge : Drug home delivery service in some locations	Homecare arrangement free of charge : Drug home delivery service in some locations	Not known

Suggested interchangeability between Cuprior 150 mg tablets and trientine dihydrochloride 300 mg capsules: guidance only

Below are calculations for guidance only adopted from the practice of the French Reference Centre for Rare Diseases[16] if the treating physician decided to convert the patient from trientine dihydrochloride 300 mg capsules (200 mg base) to Cuprior tablets (150 mg base) or vice versa.

The Cuprior Summary of Product Characteristics (SmPC) Section 4.4 states: "When switching a patient from another formulation of trientine, caution is advised because doses expressed in trientine base may not be equivalent".

A pharmacokinetic study was performed comparing Cuprior tablet single dose 600 mg base (4 tablets), to trientine capsule single dose 600 mg base (3 capsules). The study demonstrated that Cuprior tablet (150 mg base) has higher bioavailability than trientine capsule (200 mg base) and so a lower oral dose is required to achieve the same trientine base exposure. **Based on systemic trientine exposure following oral dosing, the conversion between oral doses of Trientine dihydrochloride capsules 300 mg (200 mg base) and Cuprior is 0.64.**[5]

Once in the intestine, the pharmacokinetics of the dissolved trientine base will be the same irrespective of the administration of the dihydrochloride or the tetrahydrochloride salt. Therefore, relative bioavailability of trientine is determined by aqueous solubility/dissolution of the formulated salt.

Suggested interchangeability between Cufence 200 mg capsules and Cuprior 150 mg tablets (guidance only)

Cufence (trientine dihydrochloride capsules; 200 mg free base)		**Cuprior (trientine tetrahydrochloride tablets; 150 mg free base)**	
Total daily capsules (200 mg trientine base per capsule)	Total daily oral dose (as mg of trientine base)	Total daily oral dose (as mg of trientine base)	**Total daily whole and half tablets**
1	200	150	**1**
2	400	225	**1.5**
3	600	375	**2.5**
4	800	450	**3**
5	1000	600	**4**
6	1200	750	**5**
7	1400	900	**6**
8	1600	975*	**6.5 ***

*Maximal dose per Cuprior Summary of Product Characteristics; last updated September 2020

References

1. Cuprior 150 mg film-coated tablets Summary of Product Characteristics (last updated September 2020). Available at www.medicines.org.uk/emc
2. Cufence 200 mg capsules Summary of Product Characteristics (last updated March 2020). Available at www.medicines.org.uk/emc
3. Univar trientine dihydrochloride 300 mg capsule Summary of Product Characteristics (last updated November 2019)
4. Tillomed trientine dihydrochloride 250 mg capsules Summary of Product Characteristics (last updated January 2020). Available at www.medicines.org.uk/emc
5. Cuprior European Public Assessment Report, https://www.ema.europa.eu/en/documents/assessment-report/cuprior-epar-public-assessment-report_en.pdf
6. Comparative pharmacokinetic profile for two distinct trientine salt formulations used for treatment of Wilson Disease, Weiss KH, Morley T, Thompson C. Journal of Hepatology, August 2020, Volume 73 Suppl. 1, p S546. Presented as poster.
7. Cufence European Public Assessment Report https://www.ema.europa.eu/en/documents/assessment-report/cufence-epar-public-assessment-report_en.pdf
8. Cufence procedural steps taken and scientific information after the authorisationhttps://www.ema.europa.eu/en/documents/procedural-steps-after/cufence-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf
9. Haute Autorité de Santé Transparency Committee Opinion, Cufence 200 mg hard capsules https://www.has-sante.fr/upload/docs/evamed/CT-18086_CUFENCE_PIC_INS_Avisdef_CT18086.pdf, p 24
10. A study to determine the potential effects of dissolution rate and food on the pharmacokinetics of trientine dihydrochloride following single oral administrations in healthy subjects, Dogterom P, Gerrits M, Abd-Elaziz K, van Scheppingen D, Kruse C. Hepatology, October 2019, Volume 70 Number 1 (Suppl) p1174A. Presented as poster.
11. Trientine Tillomed European Public Assessment Report https://mri.cts-mrp.eu/human/downloads/NO_H_0305_001_PAR.pdf
12. Trientine tetrahydrochloride (TETA 4HCL) for the treatment of Wilson's Disease https://clinicaltrials.gov/ct2/show/NCT03539952?term=trientine&draw=2&rank=10
13. Clinical Commissioning Policy: Trientine for Wilson's Disease (all ages) NHS England Reference: 170094P https://www.england.nhs.uk/publication/trientine-for-wilson-disease-all-ages/
14. SMC advice on new medicines: Trientine tetrahydrochloride film-coated tablets (Cuprior) Product Update SMC2222. https://www.scottishmedicines.org.uk/medicines-advice/trientine-tetrahydrochloride-cuprior-abb-smc2222/
15. Personal communication NHS Scotland
16. Communique-du-CRMRW-et-Cuprior-03-Nov-2019. https://www.crmrwilson.com/wp-content/uploads/2019/12/Communique%CC%81-du-CRMRW-et-Cuprior-03-nov-2019.pdf