6 June 2019
EMA/342173/2019
Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Cufence (Trientine dihydrochloride)
Treatment of Wilson's disease
EU/3/03/172 (EMA/OD/043/03)
Sponsor: Univar BV

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Table of contents

2. Product and administrative information

Product	
Active substance	Trientine dihydrochloride
International Non-Proprietary Name	Trientine dihydrochloride
Orphan condition	Treatment of Wilson's disease
Pharmaceutical form	Capsule
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	A16AX12
Sponsor's details:	Univar BV Schouwburgplein 30, 3012 CL Rotterdam, The Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Univar Ltd
COMP opinion date	10 September 2003
EC decision date	24 October 2003
EC registration number	EU/3/03/172
Post-designation procedural history	
Transfer of sponsorship	Transfer from Univar Ltd to Univar BV – EC decision of 31 July 2013
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	Milena Stain, Constantinos Markopoulos
Applicant	Univar BV
Application submission date	8 February 2018
Procedure start date	1 March 2018
Procedure number	EMA/H/C/004111
Invented name	Trientine dihydrochloride
Therapeutic indication	Treatment of Wilson's disease in patients intolerant to D-penicillamine therapy, in adults, adolescents and children aged 5 years or older. Further information on Cufence can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/cufence
CHMP opinion date	29 May 2019
COMP review of orphan medicinal product designation procedural history	
COMP Rapporteurs	A. Lorence/ D. Duarte
Sponsor's report submission date	5 March 2019
COMP discussion and adoption of list of questions	21-23 May 2019
Sponsor's removal request	3 June 2019
Removal from the Register	6 June 2019

3. Grounds for the COMP opinion (at the designation stage)

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2003 was based on the following grounds:

- Wilson's disease (hereinafter referred to as "the condition") was estimated to be affecting approximately 0.6 in 10,000 persons in the Community, at the time the application was made;
- the condition is chronically debilitating due to due to neurological disability, progressive hepatic impairment and eventually fatal course, in the absence of treatment;
- although satisfactory methods of treatment of the condition have been authorised in the Community, justifications have been provided that trientine dihydrochloride may be of significant benefit to those affected by the condition.

4. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Wilson's disease (WD) is an inherited autosomal recessive disorder associated with a defect in copper metabolism that is caused by a mutation in the ATP7B gene. The defect in the ATP7B gene results in malfunction of the protein, the accumulation of copper in the liver, accumulation of excess copper in the circulation and deposition of copper in other organs. WD presents with hepatic and neurological manifestations, and many patients present with both.

The approved therapeutic indication "Cufence is indicated for the treatment of Wilson's disease in patients intolerant to D-Penicillamine therapy, in adults and children aged 5 years or older" falls within the scope of the designated orphan indication "treatment of Wilson's disease".

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat the condition has been justified.

Chronically debilitating and/or life-threatening nature

The condition has been presented to the COMP to remain life-threatening and chronically debilitating.

The initial presenting symptom may be hepatic, neurologic or psychiatric. WD is universally fatal if not treated. If treatment is begun early enough, symptomatic recovery is usually complete, and a life of normal length and quality can be expected. All patients with WD require treatment for life. Inadequate treatment or disruption of drug therapy may result in life-threatening complications or irreversible organ damage. Fulminant hepatic failure may occur if chelation therapy is inadvertently discontinued. In these patients, the prognosis is extremely poor, which may result in catastrophic hepatic decompensation and death in about 75% within 2.5 years, and sometimes as quickly as within 3 months.

Patients with advanced liver failure benefit from liver transplantation (which also involves its own substantial risks of mortality and morbidity). In some patients the outcome would be fatal without liver transplantation and subsequent treatment.

There have been no changes in the chronically debilitating or life-threatening nature of WD since the orphan designation of trientine dihydrochloride. The COMP concluded that condition remains chronically debilitating and can be life-threatening due to the toxic effects of copper, first accumulating in the liver and subsequently in the brain. The liver disease can present with symptoms ranging from mildly elevated transaminases to acute liver failure or liver cirrhosis. Around 5% of all patients are diagnosed only when they develop fulminant acute liver failure, sometimes fatal.

Number of people affected or at risk

At the time of designation the prevalence was agreed to be approximately 0.6 per 10,000. For this review the prevalence has been estimated to be 0.65 per 10,000.

In the scientific literature WD is described to have an an estimated incidence of < 30 per million or 1 in 30,000 prevalence, with a gene frequency of 0.56% and a carrier frequency of 1 in 90. No systematic literature search has been conducted. A detailed table with selected epidemiological literature has been presented (table 1). It remains unclear how valid and/or representative those figures are. Nevertheless, there are no reports to suggest an increase in prevalence since designation. The COMP accepted the figure of 0.6 per 10,000 for this review.

Table 1. Population-based prevalence data in Europe

Poujois et al, 2016	France	1.5:100000	French national health insurance records
Coffey et al, 2013	UK	1:7026	Population molecular screening
Garcia-Villarreal, 2000 et al (via Mak & Lam, 2008)	Spain	1:2600 (3.85:10000)	Hospital records
Gea et al, 2013	Andorra	2:80000*	Observational study of pharmacy database from the national hospital
Loudianos et al, 1999	Sardinia	1.4:10000	Population molecular screening
Reilly et al, 1993	Republic of Ireland	3.6 per million	Medical records. Prevalence calculated per census from ’71, ’79, ’81 & ’86.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are currently four medicinal products authorised in the EU for the treatment of WD:

- D-Penicillamine: a chelator treatment for the urinary excretion of copper is nationally authorised in various EU member states.

- Trientine dihydrochloride (UK): a chelator therapy authorised for the patients that are intolerant to penicillin. It is authorised in the UK for patients intolerant to penicillamine.
- Trientine tetrahydrochloride (Cuprior) is authorised centrally and is indicated for the treatment of Wilson's disease in adults, adolescents and children ≥ 5 years intolerant to D-penicillamine therapy.
- Zinc: is currently centrally authorised with a therapeutic indication for Treatment of Wilson's disease.

There is a current consensus European EASL clinical practice guideline for the treatment of WD (J Hepatol. 2012 Mar;56(3):671-85). It describes additional pharmaceutical treatments and antioxidants for adjunctive treatment. Liver transplantation is frequently necessary for patients presenting with acute liver failure or decompensated cirrhosis.

Significant benefit

In line with the therapeutic indication, significant benefit for Cufence needs to be demonstrated in WD patients intolerant to D-Penicillamine therapy, in adults and children aged 5 years or older. Taking into consideration the therapeutic indication of currently authorised medicinal products, it was considered that significant benefit needs to be demonstrated over Cuprior (trientine tetrahydrochloride) and trientine dihydrochoride, which is authorised in the UK. Zinc is also used in patients intolerant to D-Penicillamin. Nevertheless, zinc is not a de-coppering agent and used for maintenance treatment in clinically stable WD patients with copper below toxic levels. The COMP noted that there was no need to demonstrate significant benefit over zinc due to the different clinical positioning of zinc in the consensus treatment algorithm.

Trientine dihydrochloride (UK marketing authorisation):

Significant benefit is claimed on the basis of a major contribution to patient care due to the assumption that a central marketing authorisation would allow for treatment of WD patients, who are currently unable to access trientine hydrochloride UK. Further evidence is required to support the proposed assumption, i.e. evidence demonstrating that (a) trientine dihydrochloride UK is not available to patients, (b) the unavailability of trientine dihydrochloride UK leads to patient harm, and (c) Cufence can overcome the documented patient harm.

Cuprior (trientine tetrahydrochloride):

Cufence contains the same active as Cuprior but in a different salt form. Significant benefit over Cuprior is claimed on a major contribution to patient care. It is argued that Cufence provides WD patients, who are adequately managed with trientine dihydrochloride, with the possibility to continue their treatment with Cufence on their established dose without switching to Cuprior, which is an alternative salt and formulation that is associated with dose corrections. Indeed, the SmPC of Cuprior states that "when switching a patient from another formulation trientine, caution is advised because doses expressed in trientine base may not be equivalent." Nevertheless, the impact of dose corrections to patient care is not clear. Evidence needs to be provided (a) to outline documented difficulties in switching between trientine dihydrochloride (Cufence and UK authorisaiton) and trientine tetrahydrochloride (Cuprior), and (b) to demonstrate that Cufence can overcome the documented difficulties.

In conclusion, significant benefit of Cufence over trientine dihydrochloride UK and Cuprior is argued on the basis of major contribution to patient care. Currently both claims remain unsubstantiated.

Following the receipt of the list of issues, Cufence (trientine dihydrochloride) was withdrawn from the Community Register of designated orphan medicinal products on 6 June 2019 on request of the sponsor.

5. COMP list of issues

The applicant is requested to provide evidence in support of the claims for significant benefit.

Regarding the claims for significant benefit over Cuprior, please provide data to confirm the hypothetical difficulties of patients switching between trientine dihydrochloride UK and Cuprior. Moreover, evidence needs to be submitted to demonstrate that Cufence can overcome the documented difficulties.

Regarding the claims for significant benefit over trientine (national UK authorisation), please provide data to demonstrate that patients are faced with substantial problems in the access to trientine UK. Moreover, please provide evidence that demonstrate patient harm associated with a documented lack of access to trientine when taking into consideration the marketing authorisation of Cuprior.