EU Risk Management Plan for Cufence (trientine dihydrochloride)

RMP version to be assessed as part of this application:

RMP Version number: 5.0

Data lock point for this RMP: 05 September 2022

Date of final sign off: 16 August 2024

Rationale for submitting an updated RMP:

Updated RMP due to fulfilment of the post-authorisation measure PK/PD sub-study for study UNV-TR-004 (Efficacy and safety of trientine dihydrochloride in Wilson's disease patients).

Summary of significant changes in this RMP:

PK/PD sub-study Due Dates are removed from Table Part IV.1 and Annex II D of the Cufence® 200 mg and 100 mg SmPC.

Details of the currently approved RMP:

Version number: 4.0

Approved with procedure: EMEA/H/C/004111/IB/0018

Date of approval (opinion date): 17 April 2024

QPPV name: Ulrike Müller

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Trientine dihydrochloride
Pharmacotherapeutic group(s) (ATC Code)	A16AX12
Marketing Authorisation Holder	Univar Solutions B.V. Schouwburgplein 30-34 3012 CL Rotterdam The Netherlands
Medicinal products to which this RMP refers	Trientine dihydrochloride capsules 300 milligram (mg), equivalent to 200 mg trientine. Trientine dihydrochloride capsules 150 milligram (mg), equivalent to 100 mg trientine.
Invented name(s) in the European Economic Area (EEA)	Cufence
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical Class: Trientine dihydrochloride (N,N'-bis (2-aminoethyl)-1,2-ethanediamine dihydrochloride) (trientine) is a white to pale yellow crystalline hygroscopic powder that is freely soluble in water, soluble in methanol, slightly soluble in ethanol, and insoluble in chloroform and ether. The empirical formula is C6H18N4 · 2HCL with a molecular weight of 219.2.
	Summary of mode of action: Trientine is a chelating compound for removal of excess copper (Cu) from the body. Trientine forms a highly stable 1:1 chelation complex with loosely bound serum Cu. The resulting Cu(II)-complex is then excreted in urine. There is an initial profound cupriuresis in previously untreated patients, but the degree of cupriuresis appears to decrease with increasing duration of treatment. The continued improvement in patients treated with trientine suggests that it adequately controls Cu balance by other modes of action than increasing cupriuresis including by blocking intestinal Cu absorption and increasing faecal excretion.
	Important information about its composition:

	Cufence 200 mg hard capsules contain 300 mg trientine dihydrochloride, equivalent to 200 mg trientine base. Cufence 100 mg hard capsules contain 150 mg trientine dihydrochloride, equivalent to 100 mg trientine base.
Hyperlink to the Product Information	Cufence proposed Product Information
Indication(s) in the EEA	Current (if applicable): Cufence is indicated for the treatment of Wilson's disease in patients intolerant to D-Penicillamine therapy, in adults, adolescents and children aged 5 years or older.
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current (if applicable): 800 – 1,600 mg daily in 2 to 4 divided doses at least one hour before meals or two hours after meals, and at least one hour apart from any other medicinal product, food or milk.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): Hard capsules, 200 mg and Hard capsules, 100 mg
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication

Wilson's disease is an autosomal, recessively inherited genetic disorder of copper metabolism caused by mutations of the Wilson's disease protein (copper-transporting P-type adenosine triphosphate [ATP7B]) gene). The ATP7B protein is a member of the P-type cat-ion transport ATPase family and comes to expression in numerous cell types. It is most abundant in the liver and brain and has an essential role in copper homeostasis. In hepatocytes, the ATP7B protein has two known functions. The transport of intracellular copper to the trans-Golgi network, where the copper is bound to apoceruloplasmin to form ceruloplasmin, which is subsequently released into the bloodstream and it has an essential role in the transport of intracellular copper for excretion into the bile. In Wilson's disease, the ATP7B protein loses (part of) its function, which leads to copper build up in hepatocytes and other cell types (Polishchuk, R.S. 2018).

Wilson's disease is characterized by decreased copper excretion and copper build-up in predominantly the liver and brain. In the liver, severity of the disease may range from mild abnormalities of serum aminotransferases to acute liver failure. A high cellular copper content is toxic and induces cell death. This leads to the release of hepatocyte-stored copper into the bloodstream, which subsequently affects the brain and other tissues.

Incidence & prevalence:

As techniques in molecular genetics have developed, attempts have been made to better characterise and describe the underlying ATP7B gene mutations in patients with Wilson's disease from different populations. At present direct sequence analysis is a relatively accurate and standard method in identifying mutations in the ATP7B gene, which has resulted in the identification of approximately 760 unique ATP7B mutations as reported in the Human Gene Mutation Database (Lo et al., 2017). Of these, the most common mutations include H1069Q in Europe and North America, Arg778Lue in South Korea, Japan and China, 2007del7 in Iceland and Met646Arg in Spain (Rodriguez-Castro et al., 2015). A genotype-phenotype correlation for different mutations is unclear, despite research (Bandmann et al., 2015).

The estimated prevalence of Wilson's disease of 30 per million is a well-known number. The heterozygous carrier frequency is estimated to be one in 90 individuals in most populations and is also stated in many scientific papers. Wilson's disease occurs worldwide in people of all ethnicities. However, several (isolated) areas, such as Sardinia, Crete and Romania have a higher prevalence, due to limited genetic diversity (Ferenci, 2018. Dedoussis et al., 2018. Rodriguez-Castro et al., 2015).

Over 600 pathogenic variants in ATP7B have been identified. A variety of mutations, single-nucleotide missense and nonsense mutations being the most common ones, can result in the ATP7B protein losing (part of its) function and thus clinical manifestation of Wilson's disease. Analysis of the ATP7B gene is needed to achieve or confirm a definitive diagnosis. It also has great value in screening family members to enable early diagnosis and treatment to prevent (irreversible) deterioration (Kirk, 2018. Vierling and Sussman, 2018)

There is a significant discrepancy between the number of individuals predicted on the basis of genetic studies to be affected with Wilson's disease and those clinically diagnosed. In France, a recent nationwide population-based study using data from the national health insurance system identified 906 cases of

WD, yielding a crude prevalence of 15 cases per million (Poujois et al., 2017). This is even less than the previously mentioned 30 per million. However, when looking at recent genetic studies the discrepancy becomes clear. In the United Kingdom (UK), a sequencing study found a frequency of individuals predicted to be carriers of two pathogenic ATP7B mutations of 142 per million, over 4 times the previously mentioned prevalence of 30 per million. Also, this study led to a revised figure of the frequency of heterozygous mutation carriers of one in 25 individuals. A recent genetic study from France found one in 31 individuals, which corresponds to what was found in the UK. This discrepancy may be explained by the fact that Wilson's disease can be hard to diagnose due to mild or atypical features. It has been estimated that a correct diagnosis is made in only a quarter of all patients with Wilson's disease (Coffey et al., 2013; Vierling and Sussman, 2018).

Demographics of the population in the authorised indication and risk factors for the disease:

Wilson's disease is a rare autosomal, recessively inherited genetic disorder affecting adults and children aged 1-18 years. Hepatic disease and neurologic/neuropsychiatric symptoms are the main risk factors for patients with Wilson's disease.

The main existing treatment options:

First line treatment for Wilson's disease is D-Penicillamine. However, D-Penicillamine has a high historical incidence of side effects, some of which are potentially fatal. Trientine is indicated as second line treatment and is associated with fewer anticipated side effects and requires less rigorous clinical surveillance; trientine has an efficacy equivalent to D-Penicillamine for the treatment of Wilson's disease patients with hepatic symptoms. A nation-wide population-based study in France showed that 14% of WD patients was treated with Trientine (Poujois et al., 2017). More wide-spread, global access to trientine as a substitute or alternative to D-Penicillamine will be expected to promote adherence to treatment and improve the clinical outcome of patients with Wilson's disease.

Zinc salts are also used for the treatment of Wilson's disease. Zinc salts are usually not recommended for the initial therapy of symptomatic patients because of the slow onset of action, but may be used as monotherapy in asymptomatic patients or for maintenance therapy when copper levels are below toxic thresholds and patients are clinically stable. Zinc salts may be considered also in symptomatic patients in combination with a chelating agent, D-Penicillamine or trientine.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Patients with Wilson's disease usually go through a period where they have no symptoms, during which build-up of copper in the liver causes inflammation of the liver that progresses ultimately to cirrhosis and liver failure.

In addition, copper build-up in the central nervous system causes a range of neurological disorders leading to abnormalities in movement, cognition, and psychological function. Neurological symptoms usually develop in the mid-teens or twenties. However, the severity of liver and neuropsychiatric disease may vary widely and Wilson's disease can lead to a variety of problems ranging from those with no symptoms through to a severe and sudden onset of liver failure with anaemia and acute kidney failure. If left untreated, Wilson's disease is invariably a fatal condition.

Important co-morbidities:

Patients with Wilson's disease may have a variety of clinical conditions, most commonly liver disease and neuropsychiatric problems. Most patients have some degree of liver disease that occurs most commonly at between eight and 18 years of age.

References

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Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage: None

Non-clinical data describing the absorption, distribution, metabolism, excretion and pharmacokinetic drug interaction data for trientine have been described in published literature.

The marketing authorisation holder has conducted six non-clinical and bioanalytical studies with trientine. These studies and the conclusions are summarised in Table 1. No significant safety findings could be concluded from these studies.

Table 1: key safety findings from non-clinical studies

Study number	Summary	Safety conclusion
QBR114248QB04	LP-compliant validations of bioanalytical methods for trientine in rat plasma to support rat toxicokinetics and clinical PK investigations. The method was validated in rat plasma over a trientine concentration range from 20 to 2000 ng/mL.	The method was considered to be adequately validated and fit for purpose using trientine-D4 as internal standard.

		There were no findings relevant to non-clinical or clinical safety of trientine.
QBR114248QB02	LP-compliant validations of bioanalytical methods for trientine in human plasma to support rat toxicokinetics and clinical PK investigations. The method was validated in human plasma over a trientine concentration range from 20 to 2000 ng/mL.	The method was considered to be adequately validated and fit for purpose. There were no findings relevant to non-clinical or clinical safety of trientine.
APT-REP-01	Assessments of CYP450 inhibition and induction, plasma protein binding and in vitro metabolic stability	No cytotoxicity of trientine was observed.
8269052	A GLP-compliant Ames test conducted in a single strain of S.typhimurium with and without added copper	This demonstrated that trientine is a mutagen for bacterial cells. Further studies were not deemed necessary because induced copper deficiency in healthy animals would be misrepresentative in terms of the clinical use in Wilson's disease patients.
AB13652	A dose range-finding study in pregnant rats, including toxicokinetics and determination of plasma copper concentration	No evidence of teratogenicity observed at any dose level
ICN001drkls	Toxicological analysis of 5 impurities using Derek Nexus and Leadscope	Impurities BAPZ, EAPZ, TREN, AEPZ and TEPA were not considered to have mutagenic or carcinogenic potential following in silico analysis.

Part II: Module SIII - Clinical trial exposure

Cumulative subject exposure to trientine in clinical trials is only available from April 2012, when the marketing authorisation for trientine dihydrochloride capsules 300 mg was changed from the Department of Health to Univar Ltd. New significant data available at the data lock point of this RMP is presented here – when applicable.

Overall, 125 subjects have been enrolled into clinical studies with trientine initiated by the applicant: 81 patients received ongoing treatment in study UVR-TRI-002 and 20 patients received a single dose of trientine in study TR-001PK. In study TR-003 PK, 24 healthy subjects received a single dose of trientine. Age and gender information is presented in Table SIII.2 and ethnic origin data is presented in Table SIII.4. Of the 125 patients, 98 patients (78%) were aged between 18 and 65 years and 116 patients (93%) were Caucasian.

Study TR-001PK (title "A Phase 1 Pharmacokinetic Profiling Study in Patients Receiving Trientine Dihydrochloride for the Treatment of Wilson's Disease") was a prospective pharmacokinetic (PK) phase I study in patients with Wilson's disease whose current treatment was trientine dihydrochloride (300 mg capsules). Patients took their usual prescribed dose on the morning of the study visit (1 dose). Blood samples were to be taken pre-dose and at 10 time-points post-dose to investigate the pharmacokinetic profile of trientine up to 12 hours after intake of the study medication. Study results show that trientine was rapidly absorbed after oral dosing. There was no marked difference in PK parameters for trientine between adult patients (n=16) and child patients (age ≥6 years, n=4). No adverse events were reported in this study.

Study UVR-TRI-002 (title: "Multicentre, Retrospective and Prospective Study to Assess Long-Term Outcomes of Chelator-Based Treatment With Trientine in Wilson Disease Patients Withdrawn from Therapy With d-Penicillamine") was an open label study with both a retrospective and prospective part. Only patients included in the retrospective part of the study were eligible for enrolment in the prospective part. Patients did not receive any additional treatment for Wilson's disease as part of the study. In the intention-to-treat (ITT) population (n=77) of the retrospective part of study UNV-TRI-002, the mean total dose per day was 1005.7 mg (Table SIII.3). Table SIII.1 presents duration of exposure data in the ITT population. There were no significant safety findings in both parts of the study.

Study TR-003 PK (title: "A single-dose, open label, randomized, three-way cross-over study in healthy volunteers to characterize the pharmacokinetics of the 300 mg trientine capsule and to assess the effect of dissolution rate and the effect of food on the pharmacokinetics of trientine") evaluated the PK, pharmacodynamics, safety and tolerability of a single dose of 600 mg trientine dihydrochloride in 24 healthy subjects. All 24 subjects received three single doses of 600 mg; once as two 300 mg capsules with a fast dissolution profile in fasting conditions, once as two 300 mg capsules with a fast dissolution profile in fed conditions and once as two 300 mg capsules with a slow dissolution profile in fasting conditions. There was a washout of at least 7 days between consecutive administrations. There were no significant safety findings in this study.

Table SIII.1: Duration of exposure for UNV-TRI-002 – ITT population

	Trientine (N=77)
Duration of treatment with trientine (months)	
n	33
Mean (standard deviation)	73.3 (74.76)
Median (minimum, maximum)	56.7 (5, 307)
Ongoing at last available time point	65 (84.4)
Time to discontinuation for patients that withdrew trientine (months)	
n	8
Mean (standard deviation)	52.193 (27.7423)
Median	45.894
Minimum, maximum	18.43, 92.31

Abbreviations: ITT=intention to treat; N=number of patients in the treatment group analysis set; n=number of patients in the specified category with non-missing values.
Note: Duration of treatment with trientine=(Date of withdrawal/death/last contact - Date of initiation of trientine + 1)/30.44

Table SIII.2: Age group and gender for studies TR-001PK,UNV-TRI-002 – ITT population and TR-003

Age range	Number of Subjects		
	Male	**Female**	**Total**
<18	10	10	20
18-65	35	63	98
>65	2	5	7
Total	47	78	125

Table SIII.3: Dose for UNV-TRI-002 – ITT population

	Trientine (N=77)
Total dose per day at initiation of trientine (mg)	
n	71
Mean (standard deviation)	852.1 (539.01)
Median (minimum, maximum)	600.0 (300, 2100)
Total dose per day during treatment (mg)	
n	19
Mean (standard deviation)	1005.7 (425.32)
Median (minimum, maximum)	881.3 (481, 1728)

Abbreviations: ITT=intention to treat; N=number of patients in the treatment group analysis set; n=number of patients in the specified category with non-missing values.
Note: Duration of treatment with trientine=(Date of withdrawal/death/last contact - Date of initiation of trientine + 1)/30.44
Note: The described doses are expressed as mg of trientine dihydrochloride salt (i.e. not in mg of the trientine base).

Table SIII.4: Ethnic origin for studies TR-001PK, UNV-TRI-002 – ITT population and TR-003

Ethnic origin	Number of Subjects
Asian	5
Black	2
Caucasian	116
Other	2
Total	125

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Criterion

- Patients with acute liver failure and fulminant hepatic disease with liver transplantation
- Severe anaemia
- Pregnancy

Reason for exclusion: Safety, in the clinical trial context.

Is it considered to be included as missing information: Yes (for pregnancy only)

Rationale: Patients with acute liver failure or fulminant hepatic disease with liver transplantation or severe anaemia are not to be included as missing information as in the post-marketing context these

conditions are not specifically contraindicated or associated with warnings in the Summary of Product Characteristics (SmPC).

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions and less likely to detect adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: Patients with hepatic impairment	Patients with acute liver failure and fulminant hepatic disease with liver transplantation are not included in the clinical development program
Population with relevant different ethnic origin	Patients of non-caucasian ethnic origin had a lower exposure in the clinical development program compared to caucasian ethnic origin
Severe anaemia	Not included in the clinical development program

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Univar Solutions became MAH of Cufence 200 mg hard capsules (trientine dihydrochloride) in the EU in July 2019 via a centralised procedure. Previously, Univar Solutions also held a UK license for Trientine Dihydrochloride capsules 300 mg. However, in response to the EU approved Cufence – this license was withdrawn. After Brexit – the EU MA for Cufence 200 mg was 'grandfathered' in the UK via Centrally Authorised Product (CAP) Conversion; the MA was approved on 01-Jan-2021. The trade name "Cufence 200 mg hard capsules" is used for both product licences.

Based on the assumption that patients take six 300 mg capsules per day on average (recommended dose four to eight capsules daily) and that the medication is taken continuously, it can be calculated that each patient would take approximately 2,190 capsules per year. The number of patients exposed to the Univar's trientine can subsequently be calculated by multiplying the number of bottles sold by Univar by 100 to (obtain the total number of capsules) and dividing this number by 2,190 (the estimated number of capsules taken in a year by a patient).

Exposure (number of patients) = $\frac{Number\ of\ bottles\ sold\ x\ 100}{2190}$

It is challenging to calculate cumulative patient exposure because trientine is given as ongoing daily treatment and therefore a significant number of patients exposed every year are likely to be the same patients. Furthermore, the product authorised on the EU and UK licence is not only marketed in the EU and UK, it is also exported to other non-EU countries where supply is restricted to named patients only.

Given the above-mentioned variable means of supply and the assumption that many of the patients exposed will be on long term treatment the cumulative exposure figures in table SV.1 (expressed as total number of patients) are estimated.

SV.1.2 Exposure

Exposure data is available since 2001 for the now withdrawn UK license for Trientine Dihydrochloride capsules 300 mg as well as both the EU and UK license for Cufence 200 mg. Cumulatively from 2001 until September 2019, an estimated 8866 patients were exposed to Trientine Dihydrochloride capsules 300 mg, equalling almost 500 patients per annum. Supply of Cufence 200 mg hard capsules and Trientine Dihydrochloride capsules 300 mg overlapped until November 2020 and are presented as estimated overall Cufence exposure in in table SV.1. Cufence 200 mg hard capsules is only 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, and no age- or sex-specific exposure data is available.

Table SV.1: Exposure table by region (cumulative).

Product	Dose	Formulation	Region (Annual Estimated Total Patients)		
	Assumption (Data from SmPC)		EU Member States	Rest of World (incl. UK)	Total*
Cufence 200 mg hard capsules	800 – 1,600 mg (4 – 8 capsules) per day	Oral	262	121	406

*Includes free of charge Cufence distributed to both EU member states and rest of world.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

There is no expected potential for or experience with misuse of the product for illegal purposes.

No specific studies have been undertaken to investigate potential drug abuse, however the mode of action of trientine is such that these effects would not be expected.

Trientine has been approved for use in the UK and the US since 1985. This has led to a wealth of clinical experience being gained on the use of trientine in the clinical setting. There have been no reports of drug abuse associated with the long-term use of trientine in the treatment of Wilson's disease patients.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

- Nausea
- Skin rash
- Duodenitis and severe colitis
- Anaemia
- Lupus like syndrome and Lupus Nephritis
- Neurological deterioration (e.g. Dystonia and Tremor)
- Interaction with zinc
- Interaction with iron
- Interaction with calcium and magnesium antacids
- Interaction with food and drink

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

- Nausea, on initial treatment, is an adverse reaction listed in section 4.8 of the SmPC, but it is not associated to a relevant risk.
- Skin rash, which can occasionally occur, is an adverse reaction listed in section 4.8 of the SmPC, but it is not associated to a relevant risk. A cumulative search of Univar's safety database[1] (to the data lock of this RMP) for valid or invalid ICSRs of rash, identified one valid ICSR of rash. This was a non-serious event in a 39-year-old male patient with an onset of one month after the start of trientine treatment. In addition, no further ICSRs have been received in the System Organ Class "Skin and subcutaneous disorders". Therefore, it is considered that medically important skin reactions are not expected.
  [1]Univar's safety database contains all spontaneous ICSRs and all serious adverse events from Univar clinical studies.
- Duodenitis and severe colitis are adverse reactions which have been reported. However, the clinical impact of these risks on patients is considered minimal in relation to the severity of the indication treated and these risks should therefore not be classified as important.
- Anaemia is an adverse reaction which has been reported very rarely. However, the clinical impact of this risk on patients is considered minimal in relation to the severity of the indication treated and this risk should therefore not be classified as important. In the case of iron deficiency anaemia this can usually be treated easily using iron supplements.

- Interaction with zinc is likely due to chelation of zinc by trientine, thus reducing the effect of both active substances. However, the clinical impact of these risks on patients is considered minimal in relation to the severity of the indication treated and these risks should therefore not be classified as important. Also, interaction with zinc can be avoided if taken at least 2 hours before or after taking trientine.

- Interaction with iron in supplements as trientine may cause complexes if taking concurrently. However, this can be easily avoided if the iron supplements are taken at least 2 hours before or after taking trientine.

- Although there is no evidence of reduced efficacy of trientine with the concomitant use of calcium and magnesium antacids as a precaution it is recommended that these products are taken at last 2 hours before or after taking trientine.

- Whilst there is no evidence that food and drink intake has an influence on efficacy of trientine, as a precaution food and drink (other than water) should be taken at least one hour before meals or two hours after meals, and at least one hour apart from any other medicinal product, food or milk to allow for maximum absorption and reduce the likelihood of the formation of complexes by metal binding in the gastrointestinal tract.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Missing information 1: Drug exposure during pregnancy

There are limited amounts of data from the use of trientine in pregnant women.

Risk-benefit impact:

At this time, published data does not indicate or confirm any possible teratogenic effects of trientine in humans. However, trientine should be used in pregnancy only after careful consideration of the benefits compared with the risks of discontinuing treatment in the individual patient.

Factors to consider include the risks associated with the stage of disease, the risk of those alternative treatments which are available and the possible effects of trientine.

If treatment with trientine is to be continued following a risk-benefit analysis, consideration should be given to reducing the dose of trientine to the lowest effective dose and monitoring compliance with the treatment regimen.

The pregnancy should be monitored in order to detect possible foetal abnormality and to assess maternal serum copper levels throughout the pregnancy. The dose of trientine used should be adjusted in order to maintain serum copper levels within the normal range.

Babies born to mothers being treated with trientine should be monitored for serum copper and ceruloplasmin levels where appropriate.

Routine pharmacovigilance will ensure that this potential risk is monitored and only if this activity indicates an increased risk in this population will additional pharmacovigilance activities be considered and employed, as appropriate.

Missing information 2: Use of drug in lactation and in neonates

It is unknown definitively whether trientine is excreted in human breast milk.

Risk-benefit impact:

It needs to be ensured that new-born babies are adequately monitored for any adverse effects if being treated with trientine or breastfeeding from mothers being treated with trientine.

Routine pharmacovigilance will ensure that this potential risk is monitored and only if this activity indicates an increased risk in this population will additional pharmacovigilance activities be considered and employed, as appropriate.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

No new safety concerns have been identified.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable.

SVII.3.2. Presentation of the missing information

Missing information: Drug exposure during pregnancy

Evidence source:

There are limited amounts of data from the use of trientine in pregnant women and at this time, published data does not indicate or confirm any possible teratogenic effects of trientine in humans.

However, trientine should be used in pregnancy only after careful consideration of the benefits compared with the risks of discontinuing treatment in the individual patient. Factors to consider include the risks associated with the stage of disease, the risk of those alternative treatments which are available and the possible effects of trientine.

If treatment with trientine is to be continued following a risk-benefit analysis, consideration should be given to reducing the dose of trientine to the lowest effective dose and monitoring compliance with the treatment regimen.

Anticipated risk/consequence of the missing information:

Women who are pregnant, think they may be pregnant or are planning to have a baby, should ask their doctor or pharmacist for advice before taking trientine.

As with all anti-copper agents overtreatment carries the risk of copper deficiency, which is especially harmful for pregnant women since copper is required for proper growth and mental development. In these patient groups, urinary copper levels should be kept a little above the upper limit of normal or in the high normal range (i.e. 40 – 50 microgram/24 h). Laboratory follow-up including haematological surveillance and lipoproteins determination should also be performed in order to detect early manifestations of copper deficiency, such as anaemia and/or leukopenia resulting from bone marrow depression, and decrease in HDL cholesterol and HDL/total cholesterol ratio.

Patients should consult their doctor if they become pregnant whilst taking trientine. The pregnancy should be monitored in order to detect possible foetal abnormality and to assess maternal serum copper levels throughout the pregnancy. The dose of trientine used should be adjusted in order to maintain serum copper levels within the normal range.

Babies born to mothers being treated with trientine should be monitored for serum copper and ceruloplasmin levels where appropriate.

Missing information: Use of drug in lactation and in neonates

Evidence source:

It is unknown definitively whether trientine is excreted in human breast milk.

Anticipated risk/consequence of the missing information:

Women who are breast-feeding should ask their doctor or pharmacist for advice before taking trientine.

Babies born to mothers being treated with trientine should be monitored for serum copper and ceruloplasmin levels where appropriate as the risk of copper deficiency is harmful for neonates since copper is required for proper growth and mental development.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

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

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Targeted pregnancy follow up forms for both ongoing and completed pregnancies are used as part of routine pharmacovigilance activities. These pregnancy forms (Template reference number PHV-TL-005) have been incorporated in Annex 4.

There is no requirement for further routine pharmacovigilance activities.

III.2 Additional pharmacovigilance activities

There is no requirement for additional pharmacovigilance activities.

III.3 Summary Table of additional Pharmacovigilance activities

There is no requirement for additional pharmacovigilance activities.

Part IV: Plans for post-authorisation efficacy studies

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due date
Efficacy studies which are conditions of the marketing authorisation				
Efficacy and safety of trientine dihydrochloride in Wilson's disease patients (UNV-TR-004) *Ongoing*	*- To assess the efficacy of treatment with trientine dihydrochloride by analyses of the course of hepatic, neurological and psychiatric disease.* *- To evaluate the pharmacokinetic (PK) – pharmacodynamic (PD) relationship of Cufence by analysis of trientine exposure and the direct pharmacodynamic (PD) effect on Cu storage and metabolism parameters.* *- To evaluate dosing and titration practices based on a response-guided approach vs conventional treatment.*	*Dose exposure response relationship*	*Final report*	*Q4 2026 (main study)*

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Drug exposure during pregnancy	Routine risk communication: *SmPC section 4.6.* *PL section 2.* Routine risk minimisation activities recommending specific clinical measures to address the risk: The pregnancy should be monitored in order to detect possible foetal abnormality and to assess maternal serum copper levels throughout the pregnancy. The dose of trientine used should be adjusted in order to maintain serum copper levels within the normal range.

	Babies born to mothers being treated with trientine should be monitored for serum copper and ceruloplasmin levels where appropriate. Other routine risk minimisation measures beyond the Product Information: None
Use of drug in lactation and in neonates	Routine risk communication: *SmPC section 4.6.* *PL section 2.* Babies born to mothers being treated with trientine should be monitored for serum copper and ceruloplasmin levels where appropriate. It is unknown definitively whether trientine is excreted in human breast milk during breastfeeding. Other routine risk minimisation measures beyond the Product Information: None

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Drug exposure during pregnancy	Routine risk minimisation measures: *SmPC section 4.6.* *PL section 2.* Additionally, the pregnancy should be monitored in order to detect possible foetal abnormality and to assess maternal serum copper levels throughout the pregnancy. The dose of trientine used should be adjusted in order to maintain	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Pregnancy Report Form A Pregnancy Report Form B Additional pharmacovigilance activities: None

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

Part VI: Summary of the risk management plan

Summary of risk management plan for Cufence (trientine)

This is a summary of the risk management plan (RMP) for Cufence. The RMP details important risks of Cufence, how these risks can be minimised and how more information will be obtained about Cufence's risks and uncertainties (missing information).

Cufence's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Cufence should be used.

This summary of the RMP for Cufence should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Cufence's RMP.

I. The medicine and what it is used for

Cufence is authorised for the treatment of Wilson's disease in patients intolerant of D-Penicillamine therapy (see SmPC for the full indication). It contains trientine as the active substance and it is given orally.

Further information about the evaluation of Cufence's benefits can be found in Cufence's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/cufence.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Cufence, together with measures to minimise such risks and the proposed studies for learning more about Cufence's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- Authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Cufence is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Cufence are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Cufence. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

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

II.B Summary of important risks

Missing information: Drug exposure during pregnancy	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.6.* *PL section 2.* Routine risk minimisation activities recommending specific clinical measures to address the risk: Additionally, the pregnancy should be monitored in order to detect possible foetal abnormality and to assess maternal serum copper levels throughout the pregnancy. The dose of trientine used should be adjusted in order to maintain serum copper levels within the normal range. Babies born to mothers being treated with trientine should be monitored for serum copper and ceruloplasmin levels where appropriate. Additional risk minimisation measures: None

Missing information: Use of drug in lactation and in neonates	
Risk minimisation measures	Routine risk minimisation measures:

	SmPC section 4.6. *PL section 2.* Additionally, babies born to mothers being treated with trientine should be monitored for serum copper and ceruloplasmin levels where appropriate. It is unknown definitively whether trientine is excreted in human breast milk during breastfeeding. Additional risk minimisation measures: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Study Short name: *Characterization of the Pharmacokinetics and Pharmacodynamics of Cufence (Trientine Dihydrochloride) in Wilson's Disease Patients.*

Purpose of the study:
- To assess the efficacy of treatment with trientine dihydrochloride by analyses of the course of hepatic, neurological and psychiatric disease.
- To evaluate the pharmacokinetic (PK) – pharmacodynamic (PD) relationship of a single dose of Cufence by analysis of trientine exposure and the direct pharmacodynamic (PD) effect on Cu storage and metabolism parameters.
- To evaluate dosing and titration practices based on a response-guided approach vs conventional treatment.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Cufence.

Part VII: Annexes

Table of contents

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

There are no studies being performed which are conditions of the marketing authorisation or a specific obligation in relation to Cufence.

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

There are no studies being performed which are conditions of the marketing authorisation or a specific obligation in relation to Cufence.

Annex 4 - Specific adverse drug reaction follow-up forms

There are no specific adverse drug reaction follow-up forms required in relation to Cufence other than a targeted pregnancy follow up form to collect pregnancy outcomes and will be used as appropriate.

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

The protocol of the post-authorisation efficacy study TR-004 was submitted post marketing authorisation.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product and therefore additional risk minimisation activities are not required.

Annex 7 - Other supporting data (including referenced material)

No other relevant supporting data is required for this medicinal product.

Annex 8 – Summary of changes to the risk management plan over time

Version	**Approval date** **Procedure**	**Change**
1.0	25/07/2019 EMEA/H/C/004111/000025/07/2019	First RMP
1.2	17/10/2022 EMEA/H/C/004111/IB/0011	Post-Authorisation Efficacy Study Current Due Dates as described in Table Part IV.1 and Annex II D of the Cufence 200 mg SmPC were changed from: *Q4 2025 (main study).* *Q4 2022 PK/PD sub-study.*

		to: *Q4 2026 (main study).* *Q4 2023 PK/PD sub-study.* <u>SV.1 Post-authorisation exposure</u> Text added in SV.1.1 to clarify the current product license status. SV.1.2 including Table SV.1 was updated with data current at the data lock point of this RMP.
2.0	14/09/2023 EMEA/H/C/004111/X/0014/G	<u>Part I: Product(s) Overview:</u> Inclusion of information concerning Cufence 100 mg hard capsules to reflect the line extension. <u>Part II: Module SIII - Clinical trial exposure</u>: Inclusion of study overview and data in tables SIII.2 and SIII.4 concerning study TR-003 PK. <u>Annex 5</u>: Link to the Post-Authorisation Efficacy Study protocol.
3.0	Not applicable EMEA/H/C/004111/IB/0018	<u>Post-Authorisation Efficacy Study</u> Current Due Dates as described in Table Part IV.1 and Annex II D of the Cufence 200 mg and 100 mg SmPC were changed from: *Q4 2026 (main study).* *Q4 2023 PK/PD sub-study.* to: *Q4 2027 (main study).* *Q4 2024 PK/PD sub-study.* Study status in Table Part IV.1 updated to *ongoing*. Personal data and commercial confidential information redacted on the cover page and in Annex 4.
4.0	17/04/2024 EMEA/H/C/004111/IB/0018	<u>Post-Authorisation Efficacy Study</u> Current Due Dates as described in Table Part IV.1 and Annex II D of the Cufence 200 mg and 100 mg SmPC were changed from: *Q4 2026 (main study).* *Q4 2023 PK/PD sub-study.* to: *Q4 2026 (main study).* *Q3 2024 PK/PD sub-study.*
5.0	At the time of approval	<u>Post-Authorisation Efficacy Study</u> PK/PD sub-study as described in Table Part IV.1 and Annex II D of the Cufence 200 mg and 100 mg SmPC

		removed due to fulfilment of this post-authorisation commitment.

	Pregnancy Report Form A

Section 1.01 *Case-ID:*		*Section 1.02 Date received by MAH (day 0):*	
For company use only			

1. Mother's characteristics before/at beginning of Pregnancy			
Initials:	Weight (kg):	Height (cm):	Date of birth/age:
Trial Number:		Centre Number:	Patient Number:

Were there any relevant maternal risk factors in the home/work environment (such as x-rays, chemical exposure, decreased pregnancy rate, etc.)?	☐ No ☐ Yes (please describe):

2. Relevant anamnesis of the mother		
Habits	Alcohol	☐ No ☐ Yes (please describe):
	Smoking	☐ No ☐ Yes (please describe):
	Recreational drugs	☐ No ☐ Yes (please describe):
Medical history (include underlying and concomitant diseases, allergies, any endocrinological problems, recent infections or diseases which needed treatment, any fertility problems or use of fertility methods)		
Is there any family history of malformations, significant obstetrical outcomes or hereditary disorders?		☐ No ☐ Yes (please describe):

Is there any relevant information from the father in relation to this pregnancy? (e.g. drug intake around conception, …)	☐ No ☐ Yes (please fill separate *Pregnancy Report Form A* for the father)

3. Previous pregnancies	
Has the mother been pregnant before?	☐ No ☐ Yes
If yes, please describe	Gravida: Para: Abortions: Number of normal outcomes: Number of abnormal * outcomes: Number of unknown outcomes:
* Please describe any abnormal outcomes (including elective abortions, miscarriages and malformations): In case of a previous abnormal pregnancy outcome, list all known medications used:	

4. Present pregnancy	
When was the last menses?	
Is the pregnancy confirmed?	☐ No ☐ Yes (by urine test strip) ☐ Yes (by health care professional)
What is the expected date of delivery?	

	Pregnancy Report Form A

Did the mother experience any medical problem during this pregnancy?	☐ No ☐ Yes (please describe):
Was an echography / ultrasound performed?	☐ No ☐ Yes (please describe):
Where any investigations performed?	☐ No ☐ Yes (please describe):
What is the clinical condition of the foetus(es)?	☐ Unknown ☐ Normal ☐ Abnormal (please describe): Congenital anomalies: ☐ No ☐ Yes Developmental delay of foetus: ☐ No ☐ Yes
What is the status of the current pregnancy?	☐ continuing ☐ spontaneous abortion (please fill form B section 2) Date of abortion: ☐ elective abortion (please fill form B section 2) Date of abortion: ☐ abortion scheduled for:

5. Medication

Which medications has the mother used since last menses date?
(Include: company drug, medical prescriptions (Rx), OTC and Vitamins)

Medicinal product	Dosage form	Route of administration	Daily dose	Therapy start date	Therapy end date	Indication for use	Exposure time in gestational weeks
Trade name: Batch no.: Active substance:							
Trade name: Batch no.: Active substance:							
Trade name: Batch no.: Active substance:							
Trade name: Batch no.: Active substance:							

6. Details of reporter

Name		☐ physician
Address or stamp		☐ pharmacist ☐ other healthcare professionals
Telephone		☐ patient/relative
E-mail		☐ lawyer

	Pregnancy Report Form A

Permission to contact for further information
I hereby agree to be contacted for additional questions: ☐ Yes ☐ No

Date	**Signature**

	Pregnancy Report Form B

Part B: Please fill after pregnancy

Section 1.03 *Case-ID:*		*Section 1.04 Date received by MAH (day 0):*	
For company use only			

1. Mother's characteristics			
Initials:	Weight (kg):	Height (cm):	Date of birth/age:
Trial Number:		Centre Number:	Patient Number:
Did the mother experience any medical problems since the last report?	☐ No ☐ Yes (please describe):		

2. Outcome of pregnancy	
Interrupted pregnancy	
What is the final status of the pregnancy?	☐ spontaneous abortion Date of abortion: Gestational age (weeks): ☐ elective abortion Date of abortion: Gestational age (weeks): ☐ Intrauterine death (≥20 gestational wks) Date of abortion: Gestational age (weeks):
Please specify suspected cause:	
Please describe the developmental status of the foetus (incl. malformations):	
Uninterrupted pregnancy	
Delivery date:	Gestational age (weeks):
What was the method of delivery?	☐ Spontaneous ☐ Caesarean section ☐ Vacuum extraction ☐ Forceps ☐ Induced ☐ Other, please specify:

2. Characteristics of the baby	
General appearance	☐ mature ☐ premature ☐ postmature Sex: ☐ male ☐ female Weight (g): Length (cm): Head circumference (cm):
Apgar score	1 min: 5 min: 10 min:
Placenta normal?	☐ Yes ☐ No (please describe):
Clinical condition of the baby	☐ Healthy baby ☐ Developmental delay * ☐ Congenital abnormality * (please describe): ☐ Neonatal problem/adverse events* (please describe): ☐ Neonatal death * ☐ Stillbirth * Date of death:
* Please describe the probable cause for the abnormal outcome:	

	Pregnancy Report Form B

Was the baby's hospitalisation prolonged?	☐ No ☐ Yes (please describe):
Did the baby receive any special treatment?	☐ No ☐ Yes (please describe):

5. Medication

Which **medications** has the mother used since first menses **until day of delivery**?
(Include: Rx, OTC and Vitamins; but exclude medication used during labour and delivery)

	Medicinal product	Dosage form	Route of administration	Daily dose	Therapy start date	Therapy end date	Indication for use	Exposure time from / to gestational weeks
1								
2								
3								
4								
5								

Please append extra sheet if needed

Did the mother receive any **medication during labour and delivery**? (including anaesthesia)

	Medicinal product	Dosage form	Route of administration	Daily dose	Therapy start date	Therapy end date	Indication for use
1							
2							
3							
4							
5							

Please append extra sheet if needed

Was any relationship suspected between the abnormal pregnancy outcome and the use of the company drug?	☐ No ☐ Yes (please describe): Causality assessment between abnormal pregnancy outcome and company drug: ☐ certain ☐ probable ☐ possible ☐ unlikely ☐ unassessable
Was any relationship suspected between the abnormal pregnancy outcome and the use of concomitant medications?	☐ No ☐ Yes (please describe):

6. Details of reporter

Name		☐ physician
Address or stamp		☐ pharmacist ☐ other healthcare professionals
Telephone		☐ patient/relative
E-mail		☐ lawyer

	Pregnancy Report Form B

Permission to contact for further information
I hereby agree to be contacted for additional questions: ☐ Yes ☐ No

Date	**Signature**