21 April 2017
EMA/308946/2017

CHMP assessment report

Cuprior

International non-proprietary name: trientine tetrahydrochloride

Procedure No. EMEA/H/C/004005/0000

Note

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

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Administrative information

Name of the medicinal product:	Cuprior
Applicant:	gmp-orphan SA Pépinière Paris Santé Cochin 27-29 rue du Faubourg Saint-Jacques 75014 Paris FRANCE
Active substance:	Trientine tetrahydrochloride
International Nonproprietary Name:	trientine
Pharmaco-therapeutic group (ATC Code):	OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS, Various alimentary tract and metabolism products (A16AX)
Therapeutic indication(s):	Cuprior is indicated for the treatment of Wilson's disease in adults, adolescents and children ≥ 5 years intolerant to D-penicillamine therapy.
Pharmaceutical form(s):	Tablet
Strength(s):	150 mg
Route(s) of administration:	Oral use
Packaging:	blister (OPA/alu/PVC/alu)
Package size(s):	72 tablets

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List of abbreviations

Abbreviation	Meaning
AE	Adverse event
ANOVA	Analysis of variance
apt	Activated partial thromboplastin time
AUC0-t	Area under the plasma concentration-time curve from time zero to the last quantifiable time point
AUC0-∞	Area under the plasma concentration versus time curve from time zero to infinity
BMI	Body mass index
Cmax	Maximum observed plasma concentration
CRA	Clinical Research Associate
CRF	Case Report Form
DAT	N1, N10-diacetyltriethylenetetramine
DSC	Differential Scanning Calorimetry
EC	European Commission
EMA	European Medicines Agency
EU	European Union
FT-IR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
GCP	Good Clinical Practice
GMR	Geometric mean ratio
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INR	International Normalised Ratio
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LDPE	Low density polyethylene
MAA	Marketing Authorization Application
MAT	N1-acetyltriethylenetetramine

MedDRA Medical Dictionary for Regulatory Activities

MS Mass Spectrometry

NMR Nuclear Magnetic Resonance

PD Pharmacodynamic(s)

PK Pharmacokinetic(s)

Ph. Eur. European Pharmacopoeia

PT Prothrombin time

QWP Quality Working Party

RH Relative Humidity

SAE Serious adverse event

SD Standard deviation

SmPC Summary of Product Characteristics

SOC System Organ Class

SOP Standard Operating Procedures

t1/2 Terminal elimination half-life

TEAE Treatment-emergent adverse event

TETA Trientine

TETA 2HCL Trientine dihydrochloride

TETA 4HCL Trientine tetrahydrochloride

TGA Thermo-Gravimetric Analysis

tmax Time of maximum observed plasma concentration

TSE Transmissible Spongiform Encephalopathy

UV Ultraviolet

WD Wilson's disease

XR(P)D X-Ray (Powder) Diffraction

λz Rate of elimination for the terminal phase of the time-by concentration curve

1. Background information on the procedure

1.1. Submission of the dossier

The applicant gmp-orphan SA submitted on 7 December 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Cuprior, through the centralised procedure under Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 May 2015.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication Cuprior is indicated for the treatment of Wilson's disease in patients intolerant of D-Penicillamine therapy.

Cuprior was designated as an orphan medicinal product EU/3/15/1471 on 19 March 2015. Cuprior was designated as an orphan medicinal product in the following indication: Treatment of Wilson's disease. The ground of the ODD at the time of designation was the lack of availability of the Reference Medicinal Product in the EU, resulting in an unmet medical need for the patients in the community.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Cuprior as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designation.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, a comparative PK study with the reference medicinal product Trientine Dihydrochloride 300 mg capsule, a second supportive PK study (that did not include the reference medicinal product), and appropriate non-clinical data

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Trientine Dihydrochloride 300 mg capsule, hard
- Marketing authorisation holder: Univar BV
- Date of authorisation: (08-08-1985)
- Marketing authorisation granted by:
  - Member State (EEA) : United Kingdom
  - National procedure (PL 41626/0001)

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Trientine Dihydrochloride 300 mg capsule, hard

- Marketing authorisation holder: Univar BV
- Date of authorisation: (08-08-1985)
- Marketing authorisation granted by:
  - Member State (EEA) : United Kingdom
  - National procedure (PL 41626/0001)

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Trientine Dihydrochloride 300 mg capsule, hard
- Marketing authorisation holder: Univar BV
- Date of authorisation: (08-08-1985)
- Marketing authorisation granted by:
  - Member State (EEA) : United Kingdom
  - National procedure (PL 41626/0001)
- Bioavailability study number(s): 2015-002199-25

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: David Lyons Co-Rapporteur: Milena Stain

- The application was received by the EMA on 7 December 2015.
- The procedure started on 31 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 March 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 21 March 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 31 March 2016.
- During the meeting on 28 April 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 28 April 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 11 August 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 20 September 2016.
- During the PRAC meeting on 29 September 2016, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 13 October 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 24 January 2017.
- During the CHMP meeting on 23 February 2017 the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- During a meeting of a PK Working party on 25-26 October 2016, experts were convened to address questions raised by the CHMP.
- During the meeting on 21 April 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Cuprior.

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

2.1.1.1. Disease or condition

Wilson's disease (WD) is an autosomal recessive disorder that results in pathological copper accumulation. A mutation in the ATP7B gene, located on chromosome 13, is responsible for WD. The mutations lead to a defective ATP7B protein that normally mediates the binding of copper molecules to apoceruloplasmin in hepatocytes, forming ceruloplasmin, which can then safely transport the bound copper to its intended sites. In addition, the ATP7B protein serves to transport excess copper from hepatocytes into the bile for subsequent excretion, thus permitting safe elimination of excess copper. Such copper transport systems are required as, although copper is essential for cellular function, free copper is toxic and causes cell damage.

Normal dietary consumption and absorption of copper (1 to 5 mg per day) exceeds the metabolic need of approximately 0.75 to 0.9 mg per day. Homeostasis of copper is maintained exclusively by biliary excretion; therefore if the excretory capacity is exceeded copper progressively accumulates in the liver and other tissues such as the brain, kidney, and cornea leading to the clinical manifestations of WD.

2.1.1.2. Epidemiology

Wilson disease is found worldwide, with an estimated prevalence of 1 case per 30,000 live births in most populations. More recent data from population screening by molecular sequencing in the UK suggest a potentially higher prevalence (Coffey, Brain 2013).

2.1.1.3. Clinical presentation, diagnosis and prognosis

WD presents symptomatically at any age, with the majority between 5 and 35 years (EASL 2012); asymptomatic patients are most often detected by family screening.

Symptoms at the time of the initial presentation, and those that subsequently develop are most commonly categorised as hepatic or neurologic/neuropsychiatric. Hepatic symptoms are the initial clinical manifestation in about 40-50% of WD patients. The hepatic dysfunction symptoms are highly variable, ranging from enlargement of the liver or asymptomatic biochemical abnormalities, to overt cirrhosis or acute hepatic failure (Pfeiffer 2007).

Neurologic or neuropsychiatric manifestations of WD typically present later than liver disease, most commonly in the third decade of life, but can also be present in childhood. There is a range of presenting neurologic abnormalities which are initially present in 40-50% of patients (Yarze, Martin et al. 1992). They include Parkinson-like akinetic-rigid syndrome, pseudosclerosis with tremor, ataxia, and dystonic syndrome. Neuropsychiatric abnormalities can also develop. These most commonly include personality changes and mood disturbances, particularly depression, but may also manifest as impulsiveness, disinhibition, paranoia or poor school performance.

Other manifestations of WD include an ophthalmological marker, namely the presence of Kayser–Fleischer rings, which are caused by deposition of copper in Descemets membrane of the cornea. These are present in 95% of patients with neurologic symptoms and over 50% of those without neurologic symptoms. According to

EASL clinical practice guidelines in the European Union (EU) (EASL 2012), "for routine monitoring, serum copper and ceruloplasmine, liver enzymes and international normalised ratio (INR), functional parameters, complete blood count and urine analysis as well as physical and neurological examinations should be performed regularly, at least twice annually (Grade II-2, B, 1, AASLD Class I, Level C)".

Untreated WD is universally fatal. Prognosis for survival depends on the severity of liver and neurological disease, and, of upmost importance, compliance with drug treatment (Ala, Walker et al. 2007).

2.1.1.4. Management

Treatment of WD aims to control free serum copper levels within acceptable limits. Dietary control of copper intake is not sufficient in most patients, and pharmacological treatments are therefore needed. It is generally accepted that the most effective treatments are copper chelators which bind with copper and promote copper excretion from the body.

There are two currently approved types of copper chelating agents, D-penicillamine and trientine. According to EASL clinical practice guidelines in EU (EASL 2012), "Initial treatment of symptomatic patients with WD should include a chelating agent (D-penicillamine or trientine). Trientine may be better tolerated (Grade II-1, B, 1, AASLD Class I, Level B)". Due to its better efficacy, D-penicillamine is the first line treatment for patients with WD.

However, about 20 to 30% of the WD patients using D-penicillamine will experience adverse reactions (Merle, Schaefer et al. 2007; EASL 2012; D-Penicillamine SmPC 2014) in the first 1-3 weeks of the treatment, which often result in discontinuation of treatment. Long-term use of D-penicillamine carries further risks of side effects.

The trientine salt TETA 2HCl was introduced in 1969 as a copper chelator alternative to D-penicillamine (Walshe 1969). Trientine may have a dual mechanism of action for decreasing copper levels by also reducing copper absorption from the gut (Ala, Walker et al. 2007; EASL 2012). TETA 2HCl is registered in the UK and US and mostly used for treatment of WD in patients intolerant to D-penicillamine (Schilsky 2001; Ferenci 2004; Ala, Walker et al. 2007).

Zinc salts are also used for the treatment of WD. 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.

Pharmacological therapy remains the primary treatment in WD, although its efficaciousness may diminish in more advanced disease states. If patients are already presenting with decompensated cirrhosis, they may be treated intensively with chelators, however if patients are unresponsive to this approach a liver transplant would be required. For patients who develop acute liver failure, liver transplantation is the only option for survival, with survival rates reported up to 59- 76% at 5-10 years (Medici, Mirante et al. 2005), with poorer outcomes observed in those patients with neuropsychiatric symptoms. The use of liver transplantation has also been reported to be used in patients with severe neurological disease (Schumacher, Platz et al. 1997), however its use as a primary treatment is not recommended (Roberts and Schilsky 2008).

2.1.2. About the product

Cuprior contains the active substance trientine tetrahydrochloride (TETA 4HCl) and is presented as 150 mg scored tablets (150 mg trientine base). The application is a hybrid referring to the reference product Univar's trientine dihydrochloride (TETA 2HCl) 300 mg capsules (200 mg trientine base). TETA 4HCl and TETA 2HCl share the same active moiety (trientine) and the same mechanism of action.

The therapeutic indication of Cuprior proposed by the applicant was that of the reference product "Treatment of Wilson's Disease in patients intolerant to D-penicillamine". Univar's TETA 2HCl capsules have been approved in the United Kingdom for the treatment of WD in patients intolerant of D-penicillamine therapy since 1985.

The dosing regimen proposed by the applicant was 3-7 tablets of Cuprior, administered 2 to 4 times a day in adults and 2-4 tablets administered 2 to 4 times a day in children. The product is titrated to target according to clinical response and serum copper levels.

The therapeutic indication approved by the CHMP is:

"Cuprior is indicated for the treatment of Wilson's disease in adults, adolescents and children ≥ 5 years intolerant to D-penicillamine therapy."

The dosing regimen approved by the CHMP is:

The starting dose would usually correspond to the lowest dose in the range and the dose should subsequently be adapted according to the patient's clinical response.

The recommended dose is between 450 mg and 975 mg (3 to 6½ tablets) per day in 2 to 4 divided doses.

Paediatric population

The starting dose in paediatrics is lower than for adults and depends on age and body weight.

Children ≥ 5 years

The dose is usually between 225 mg and 600 mg per day (1½ to 4 tablets) in 2 to 4 divided doses.

Children aged < 5 years

The safety and efficacy of trientine in children aged < 5 years have not been established.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as tablets containing trientine tetrahydrochloride equivalent to 150 mg trientine as active substance.

Other ingredients are: mannitol, colloidal anhydrous silica, glycerol dibehenate.

The tablet can be divided into equal doses.

The product is available in OPA/Alu/PVC-Alu blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of the active substance is triethylenetetramine tetrahydrochloride corresponding to the molecular formula $C_6H_{22}N_4Cl_4$. It has a relative molecular mass of 292.08 g/mol and the following structure:

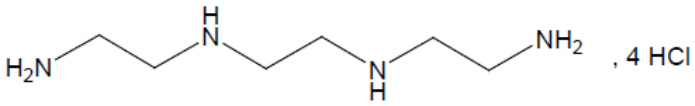


Figure 1 – Structure of triethylenetetramine tetrahydrochloride

The structure of the active substance has been confirmed by the following methods: elemental analysis, 1H- and 13C- NMR, FT-IR, mass spectroscopy, XRPD, TGA and DSC.

The active substance is a white, not hygroscopic crystalline powder, freely soluble in water.

The active substance active substance has a non - chiral molecular structure.

Polymorphism has been observed for the active substance. Two polymorphic forms have been identified. The same polymorphic form is consistently produced by the manufacturing process. Polymorph screening experiments have shown that another crystalline can be formed but always in mixture with the expected polymorphic form and only on specific conditions which cannot be linked to the manufacturing process or storage conditions of the active substance. It has been proven that the expected polymorph form is stable over 12 months stored at long term and accelerated conditions (25°C/60%RH and 40°C/75%RH).

Trientine tetrahydrochloride is not the subject of a monograph in the Ph. Eur.

Specification

The active substance specification includes tests: appearance, identification (FT-IR), identification of chlorides (Ph. Eur.), pH (Ph. Eur.), assay (titrimetry), related substances (GC), residual solvents (GC), water content (Ph. Eur.), heavy metals (Ph. Eur.), sulphated ash (Ph. Eur.), microbiological quality (Ph. Eur.), and particle size distribution (Ph. Eur.).

The absence of control of polymorphism was considered acceptable in view of the data provided to demonstrate that the expected polymorphic form is consistently produced by the manufacturing process and is stable. It was also taken into account that the active substance is very soluble throughout the physiological pH range from pH 1.2 to 6.8 whatever its crystalline form and is absorbed in vivo in the intestinal tract in its basic form, therefore it was considered that the polymorphic form has no impact on solubility.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identification and related substances testing has been presented.

Batch analysis data for six production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data were provided for three production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for 18 months under long term conditions at 25 ºC / 60% RH and under intermediate conditions 30 ºC / 65% RH and for up to 12 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines.

The following parameters were tested: appearance, pH, loss on drying, related substances and assay.

The analytical methods used were the same as for release with the exception of the related substances method which has been redeveloped during the stability study. The specificity and stability indicating nature of the related substances method has been adequately demonstrated.

All tested parameters were within the specifications.

Stress studies were performed on the active substance (heat, humidity, heat and humidity, acid, base, light, oxidant). Results provided showed that the active substance is slightly sensitive to heat and humidity, and to oxidation.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months.

Manufacture, characterisation and process controls

The active substance trientine tetrahydrochloride is manufactured in two steps (salt formation and recrystallization) using a commercially available well defined starting material with acceptable specifications. The choice of starting material has been adequately justified. A detailed description of the manufacturing process and a flow scheme have been provided. Reprocessing is proposed for the recrystallization step and is considered acceptable.

The CHMP raised a concern related to the purging and fate of all impurities present in the starting material during the active substance manufacture. The CHMP recommended providing data by end of Q2 2017 to confirm that chlorinated moieties are not present in the active substance. The data should include an impurity tracking grid (including the steps where all impurities are formed and purged) and a list of potential genotoxic impurities.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were discussed with regards to their origin and characterised. In addition the CHMP recommended identifying an unknown impurity in the active substance.

The active substance manufacturing process development section is clearly explained, any inferences are supported by appropriate data, and the justification for moving to the final, commercial scale process is comprehensive and acceptable.

The active substance is packaged under nitrogen inside LDPE bags, the bags are placed inside an aluminium bag and a sachet of desiccant (silica gel) is inserted between the LDPE and aluminium bags. The bags are heat sealed and then placed into a high density polyethylene (HDPE) drum suitable for storage and shipping. The LDPE bags comply with Ph. Eur. 3.1.3 and the EC directive 10/2011 as amended.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is available as immediate release uncoated white to off-white scored capsule-shaped tablets (16 × 8 mm). Each tablet contains 300 mg of trientine tetrahydrochloride (TETA 4HCl) equivalent to 150 mg of trientine (TETA).

The development work started with comparative studies to the already existing finished products:

-TETA 4HCl capsules containing 150 mg of TETA 4HCl (75 mg of TETA) and spray-dried lactose given to Wilson's disease patients as compassionate use supplies

- TETA 2HCl Univar 300mg, hard capsules, approved in the United Kingdom containing TETA 2HCl equivalent to 200 mg TETA.

The objective of the formulation development was to obtain an immediate release scored tablet containing 300 mg of TETA 4HCl that is stable at room temperature and permit accurate subdivision of the tablet to provide a half-dose (150 mg) for young patients and allow flexibility for dose titration taking patient age/weight into consideration.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The compatibility of the active substance with the excipients has been assessed with binary mixtures via Micro Differential Scanning Calorimetry (DSC). A possible interaction of TETA 4HCl has been highlighted with silica colloidal anhydrous but not with mannitol and glycerol dibehenate. However, stability data obtained to date did not show any compatibility issues with the selected finished product formulation. The role, the choice of the excipients and their concentration has been satisfactorily justified.

The strategy for the formulation was to manufacture the tablets by direct compression. The choice of manufacturing process is adequately justified and exemplified, as are the decisions relating to elimination of trial formulations. The choice of final formulation was made on the basis of formulation processability and stability, which is acceptable.

The finished product is also for paediatric use: for paediatric patients from the age of 5 years. It has been confirmed that during formulation development paediatric requirements were taken into account, referencing the EMA reflection paper (formulations of choice for the paediatric population, EMEA/CHMP/PEG/194810/2005) and guideline (Pharmaceutical Development of Medicines for Paediatric Use (CPMP/805880). The applicant has provided a justification for their approach during development, which is satisfactory. Detailed discussion

regarding the acceptability of (halved-) tablet size, the number of (halved-) tablets to be taken every day and acceptability of the proposed dosage form in the paediatric population is presented in the clinical section.

The formulation used during clinical studies is the same as that intended for marketing.

The development of the dissolution method is adequately described. The discriminating power of the dissolution method was investigated and the scope of experiments performed is considered acceptable.

Dissolution profiles of TETA 4HCl capsules and TETA 2HCl Univar 300mg, hard capsules were generated in support of inclusion into clinical data for the submission. Dissolution profiles for TETA 4HCl AGEPS capsules were similar to that of Cuprior, whilst those for Univar were significantly different. Investigations into the cause of this difference were performed and were inconclusive. Consequences of these results are discussed in the clinical and non-clinical sections.

The primary packaging is OPA/Alu/PVC-Alu blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

TETA 4HCl coated tablets are made from a common direct compression procedure. The process consisted of pre-mixing including sieving, mixing, final mixing (lubrication), compression and packaging. The process is considered to be a standard manufacturing process. A detailed description of the manufacturing process and a flow scheme have been provided.

It was confirmed that there is no holding time in the manufacturing process and that any future use of holding time will be registered by way of variation.

Major steps of the manufacturing process especially final mixing and compression steps have been validated on three consecutive pilot batches by a number of studies. In view of the validation results obtained, in view of the absence of validation for some steps of the process and in view of the process changes implemented after the process validation, the CHMP recommended to validate the commercial scale manufacturing process prior to marketing taking into account the recommendations made during the MA procedure.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form: appearance of tablet, identification (TLC, GC), dissolution (Ph. Eur.), impurities (GC), uniformity of dosage units (Ph. Eur.), mean mass (Ph. Eur.), loss on drying (Ph. Eur.), subdivision of tablets (Ph. Eur.), assay (GC), microbiological quality (Ph. Eur.).

Satisfactory justifications were provided for the absence of control of the tablet dimensions and hardness of tablet in the specifications.

Comprehensive data has been provided to justify why control of polymorphic form need not be implemented. This includes clarification regarding comparative solubility data of both identified polymorphic forms

comparative dissolution testing of tablet batches made with the two polymorphic forms discussion regarding the processability of polymorphic form and a discussion regarding the PK characteristics of the active substance.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The applicant has demonstrated that the assay and related substances method is sufficiently stability indicating via forced degradation studies. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis results are provided for 4 pilot scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data were provided for 4 pilot scale batches of finished product stored for up to 12 months at 25 ºC / 60% RH and 30°C/65%RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested according to the shelf-life specifications described in the section above. The related substances method has been redeveloped and thus two methods have been used to generate related substances data.

All data meet the specification limits at all time points, in all storage conditions.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Results showed that the tablets are not light sensitive.

Based on available stability data, the proposed shelf-life of 18 months without specific storage condition as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues related to active substance impurities and finished product process validation having no impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- to provide data by end of Q2 2017 to confirm that specific impurities are not present in the active substance. The data should include an impurity tracking grid (including the steps where all impurities are formed and purged) and a list of potential genotoxic impurities.

- to identify an unknown impurity in the active substance (related substances method).

- to validate the commercial scale manufacturing process prior to marketing taking into account the recommendation made during the MA procedure.

2.3. Non-clinical aspects

2.3.1. Introduction

The sponsor has submitted a non-clinical overview of the pharmacological, pharmacokinetic and toxicological properties of trientine. The non-clinical strategy is to refer largely to data in the published literature. The sponsor conducted *in silico* evaluations of the genotoxic potential of TETA 4HCL and three main impurities using DEREK and Leadscope assays. The sponsor also conducted an Ames test with TETA 4HCL.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Table 2.1.2: Literature data on primary pharmacodynamics of TETA

Species	Study	Major findings	Reference
Rat	i.v. injections of ^{67}Cu and 40 mg/kg TETA 4HCl	• ↑amount of ^{67}Cu bound to small molecules in serum • ↓^{67}Cu in liver • ↑^{67}Cu in kidney • ↑urinary excretion of ^{67}Cu	Sarkar et al. 1977
Rat (Wistar, LEC)	Wistar rats (10 weeks) LEC rats (6 and 13 weeks) → treatment with 25 mg/kg	• cumulative 7-days TETA urinary excretion lower in LEC than in Wistar rats • absorption rates from jejunal loop	Iseki et al. 1992

	TETA 2HCl p.o. for 7 days <u>parameters investigated:</u> -urinary excretion of TETA 2HCl and Cu -hepatic Cu levels	and in vitro metabolism of liver S9 fraction approximately the same for both strains • urinary creatinine and phenolsulfonphthalein excretion lower in LEC than in Wistar rats • LEC rats (6 weeks) + TETA: ↑urinary Cu excretion, ↓hepatic Cu • LEC rats (13 weeks)+TETA: ↑urinary Cu excretion, no effects on hepatic Cu levels • non-treated LEC rats: ↑urinary Cu, ↑hepatic Cu	
Rat (LEC, WKAH*)	WKAH (control), LEC rats → treatment with TETA 2HCl p.o. from 10 weeks to 18 weeks of age <u>parameters investigated:</u> -Cu level of kidneys -COMET assay in cells of renal cortex -O_2^{-}scavenging activity -catalase activity *WKAH: Wistar King A, Hokkaido	• ↑Cu accumulation in kidneys of un-treated LEC rats from 12 to 18 weeks of age • TETA-treated LEC rats: renal Cu levels = control rat levels (WKAH) • COMET Assay in LEC rat renal cortex cells: -↑SSBs** from age 12 to 18 weeks of age -treatment of LEC rats with TETA from 10 weeks of age: levels of SSBs = control levels • O_2^{-}-scavenging activities in kidneys from LEC rats = controls; no effect of TETA • catalase activity in kidneys of LEC rats >controls, no effect of TETA	Hayashi et al. 2005

**SSBs: single-strand breaks, LEC: Long-Evans Cinnamon, O_2^{-}-:superoxide anion

The pharmacology studies sourced from published literature demonstrate proof of concept that TETA 4HCl can decrease copper levels in the liver and increase urinary excretion of copper in rats administered exogenous copper. Furthermore, in vivo models of WD in which rats accumulate copper and develop severe jaundice and fulminant hepatitis at approximately 4 months of age, were used to show the ability of TETA 2HCL to increase urinary copper excretion and reduction of hepatic copper levels. TETA 2 HCL was also shown to decrease single strand breaks associated with copper accumulation in renal cortex cells.

Secondary pharmacodynamic studies

Table 2.2: Data on secondary pharmacodynamics of TETA

Species/ Cells	**Study design**	**Major findings**	**Reference**
Cardiovascular diseases			
Zucker rats	citric acid or TETA 2HCl (20 mg/day in drinking water) from week 10 to 32 of age	• increases in end diastolic volume and pressure were prevented • improvement of ejection fraction and myocardial relaxation	Baynes et al. 2009
diabetic Wistar rats*	TETA 2HCl (20 mg/day in drinking water) for 8 weeks	• improvement of impairment of left ventricular function	Lu et al. 2013
Alzheimer disease			
APP/PS1 transgenic AD mice**	60 or 180 mg/kg/day TETA 2HCl p.o. for 3 months	• ↓advanced glycation end products • ↓Aβ deposits • ↓Cu and Zn accumulation in brain amyloid plaques • Cu, Fe, Zn levels unaltered in serum and brain	Wang et al. 2013
Anticancer			
Nude mice	1500 or 3000 ppm TETA 2HCl	• ↓growth of HuH-7 human hepatoma xenograft tumours • ↑apoptotic potential, ↓microvessel density • ↓production of IL-8	Moriguchi et al. 2002
MCF7 cells	50 or 100 µM TETA	• induction of cellular senescence phenotypes • ↑population doubling • ↑p53, ↑p21	Lixia et al. 2008
MCF7 cells	≥ 50 µM TETA 2HCl	• ↓expression of human telomerase reverse transcriptase, inhibition of telomerase • ↑antitumor activity of carboplatin,	Liu et al. 2008

	100 µM TETA 2HCl	taxol, adriamycin	
Mouse fibrosarcoma cells	10 mM TETA for 1 to 5 days	• ↑p38 MAPK activity • ↑apoptosis	Kadowaki et al. 2009
Mesothelioma bearing mice	700 µg TETA 2HCl i.p. for 2 weeks	• mesotheliomas sequestered Cu→ ↓Cu by TETA: ↓mesothelioma growth, ↓tumor vessel diameter	Crowe et al. 2013
Effects on Iron and Zinc homeostasis			
Fischer 344 rats***	cereal-based or purified diet + up to 3000 ppm TETA 2HCl p.o. (92 days)	• purified diet + 600/3000 ppm TETA: ↓Cu (plasma and liver), no effect on Fe (plasma and liver); +3000 ppm TETA: ↑Zn (plasma and liver) • cereal-based diet + 3000 ppm TETA: ↓Cu (liver)	Greenman et al. 1996
Fischer 344 rats***	0, 50, 175, 600 mg/kg/day TETA 2HCl p.o. (26 weeks)	• 600 mg/kg/day: ↓plasma Cu (males), ≥175 mg/kg/day: ↓liver Cu (males), ≥50 mg/kg/day: ↑urinary Cu (males+ females) • ≥50 mg/kg/day: ↓urinary Fe (males), ≥175 mg/kg/day: ↓plasma Fe + ↑urinary Fe (females) 600 mg/kg/day: ↑liver Fe (females) • ≥50 mg/kg/day: ↑urinary Zn (males), ≥175 mg/kg/day: ↓plasma Zn + ↑urinary Zn (females),	Yanagisawa et al. 1998

*by injection of 55 mg/kg streptozotocin; **β-Amyloid precursor protein and presenilin-1 double transgenic AD model mice, ***study also cited for repeat-dose toxicity refer to table 4.1, Aβ:Amyloid β

Secondary pharmacodynamic effects identified for trientine, were not necessarily related to the copper binding properties of the molecule. These include potential off target effects related to cardiovascular disease associated with diabetes, Alzheimer's disease, anti-cancer activity and the potential impact of trientine on divalent cations other than copper, such as iron and zinc. The possible secondary pharmacodynamic effect on iron and zinc levels is suitably addressed by wording in sections 4.4, 4.5 and 5.3 of the proposed SmPC for TETA 4HCL.

Safety pharmacology programme

Safety pharmacology studies were not required with TETA 4HCL as the active moiety is identical to that of the marketed TETA 2HCL product, for which the clinical experience to date does not indicate a cause for concern.

Furthermore, the approved therapeutic indication is similar for the reference medicinal product and Cuprior and higher bioavailability of Cuprior will be accounted for by dose adjustment.

Pharmacodynamic drug interactions

No new non-clinical safety pharmacology studies or pharmacodynamics drug interaction studies with TETA 4HCL were provided and it is accepted that they would not add value to the safety assessment for this product.

Section 4.5 of the proposed SmPC states: *"Although there is no evidence that calcium or magnesium antacids alter the efficacy of trientine, it is good practice to separate their administration".* This recommendation is in line with the reference product SmPC and as the active moiety is the same, this is acceptable.

2.3.3. Pharmacokinetics

There are limited data on the pharmacokinetics of trientine in animals and the PK section of the dossier relies on a review of animal absorption and PK data obtained with 14C-labelled trientine 2HCL (Lu, Poppitt et al. 2010), together with a small number of older publications including a distribution study of 14C-labeled TETA 4HCL in rats (Gibbs and Walshe 1985) and two excretion studies in rats by the same group (Kobayashi, Tanabe et al. 1997; Kobayashi, Fujisaki et al. 1999).

These data indicate a moderate rate of absorption in rat, rabbit and dog with low oral bioavailability due to first pass metabolism and evidence of an interaction with food, which is reflected in sections 4.2 and 4.5 of the proposed SmPC, indicating that Cuprior must be taken on empty stomach as food may impede its absorption. Nonclinical autoradiography studies indicate that trientine distribution is higher in the liver and kidney than plasma concentrations, with the highest concentration occurring at 1hr post-dose. Placental transfer of trientine has not been investigated. However, the low molecular weight suggests that exposure of the embryo can be expected. As studies in animals have shown reproductive toxicity, which was probably a result of trientine-induced copper deficiency (see section chapter on reproductive toxicity below) Cuprior should only be used in pregnancy after careful consideration of the benefits compared with the risks of treatment in the individual patient. This is appropriately reflected in the SmPC.

The non-clinical metabolism data suggest that the low oral bioavailability of trientine is due to rapid metabolism after absorption from the gastrointestinal tract, leading to the formation of acetylated metabolites. Trientine resembles spermidine in structure and SSAT2 was identified as the main acetylator of trientine in vitro. Section 5.2 of the SmPC identifies two major acetylated metabolites of trientine, N(1)-acetyltriethylenetetramine (MAT) and N(1),N(10)-diacetyltriethylenetetramine (DAT). MAT is thought to contribute to the overall copper chelating activity of trientine but the extent of this contribution of is unknown. Rat, rabbit and dog studies suggest plasma elimination half-lives of between 0.5 and 3 hours. Trientine appears to be excreted in rat urine mainly in the form of its acetylated metabolites (MAT and DAT) with highly variable (5 – 79%) overall recovery of the dose found in rat urine.

In vivo and in vitro investigations into the mechanism of renal excretion of trientine indicated a specific, active excretion system for trientine. Trientine is not recognised by the H+/organic cation transporter, but a Na+/spermine antiporter on the renal brush-border membrane contributes to the secretion of trientine in the renal proximal tubule, but does not recognise the trientine-copper complex. The effect of drug interactions on urinary excretion of trientine in rat kidney was investigated. Drugs, such as diuretics, that change the concentration of sodium ions in proximal tubules were reported to increase trientine excretion but not trientine-copper complex excretion. It is not established if a similar transporter is involved in the urinary

excretion of trientine in humans but the copper excess that occurs in WD patients favours the formation of trientine-copper complexes that are not a substrate for the Na+/spermine antiporter.

Animal data on milk transfer of trientine are not available and only very limited information exists for humans. This is appropriately addressed in the SmPC.

2.3.4. Toxicology

The toxicology package consists of bibliographical references together with in silico genotoxicity analysis and a GLP-compliant in vitro Ames test on the genotoxicity performed by the applicant. The majority of the literature references consist of studies conducted with TETA 2HCL with the assumption that TETA 4HCL will display an efficacy and safety profile in WD patients similar to TETA 2HCL as the active moiety is identical.

Table 4.1: Overview of single and repeat-dose toxicity studies with TETA 2HCl

Species	Study	Major findings	Reference
Single dose toxicity studies			
Rat	oral administration	LD_{50} >2000 mg/kg TETA	OECD 1998
Rabbit	dermal application	LD_{50} =550-805 mg/kg TETA	OECD 1998
Repeat dose toxicity studies			
B6C3F1 mice	0, 120, 600, 3000 ppm TETA 2HCl (drinking water) +cereal based or purified diet +Cu-deficient diet (18-20 animals/sex/dose) for 92 days	purified diet: ↓bw, ↓kidney weight (♂3000 ppm), ↑inflammation of lung interstitium, ↑liver periportal fatty infiltration (♂♀3000 ppm), hemapoietic cell proliferation in the spleen (♂3000 ppm)→**NOAEL= 600 ppm (92/99 mg/kg/day ♂/♀)**, no effects on Cu, Fe, Zn levels cereal based diet: ↓liver Cu (♂♀ 3000 ppm) Cu-deficient diet: no effects	Greenman et al. 1996
Fischer 344 rats	0, 120, 600, 3000 ppm TETA 2HCl (drinking water) +cereal based or purified diet +Cu-deficient diet	Cu-deficient diet: ↓bw gain (♂♀), ↑adrenal gland and heart weights (♂♀), ↑liver weight (♀), ↑kidney and testis weights (♂), anaemia (♂), liver peri-portal cytomegaly, pancreatic atrophy and necrosis, spleen hemapoietic cell proliferation (♂♀), ↑heart weight, ↓↓Cu plasma/liver (♂♀), ↓Fe plasma (♂♀) purified diet: ↓plasma Cu (>120 ppm ♂♀), ↓liver Cu (>120 ppm ♂, 3000 ppm ♀), ↑uterine dilatation (≥120 ppm)	Greenman et al. 1996

	(18-20 animals/sex/dose) for 92 days	cereal based diet ↓Cu liver →**NOAEL= 3000 ppm (270-276/323-352 mg/kg/day ♂/♀)**	
Fischer 344 rats	0, 100, 350, 1200 TETA 2HCl mg/kg/day p.o. 4/8 weeks (5 animals/sex/dose)	4/8 weeks: 2 deaths (♂ 1200 mg/kg/day), ↓bw gain, ↓food consumption, clinical signs (♂ 1200 mg/kg/day), ↑electrolyte output, ↓plasma alkaline phosphatase (≥100 mg/kg/day ♂♀), ↑lung weights, bronchiolar epithelium hypertrophy, broncho-alveolar pneumonia (♂♀ 1200 mg/kg/day), inflammation stomach (♂♀≥350 mg/kg/day)	Yanagisawa et al. 1998
Fischer 344 rats	0, 50, 175, 600 TETA 2HCl mg/kg/day p.o. 26 weeks (12 animals/sex/dose) reversibility (12 animals/sex at 0 and 1200 mg/kg/day)	1 death (♂175 mg/kg/day), 3 deaths (♂ 600 mg/kg/day), ↓bw gain (♂♀ 600 mg/kg/day), ↑electrolyte output, ↓plasma alkaline phosphatase (♂♀≥175 mg/kg/day), irreversible focal chronic interstitial pneumonitis (♂≥50, ♀ ≥175 mg/kg/day), ↓plasma Cu (♂600 mg/kg/day), ↓liver Cu (♂♀≥175 mg/kg/day), ↑urinary Cu (♂♀≥50 mg/kg/day) **NOAEL♀=50 mg/kg/day; no NOAEL for ♂**	Yanagisawa et al. 1998

Single dose toxicity

Single dose toxicity is based on an OECD-SIDS initial assessment report that considered trientine of low acute toxicity after oral administration (LD50 rat > 2000 mg/kg) and moderate toxicity after dermal application (LD50 rabbit 550-805 mg/kg). Exposure to saturated vapour was tolerated but exposure to aerosols leads to reversible irritations of the mucous membranes in the respiratory tract and trientine is considered harmful in contact with skin.

Repeat dose toxicity

Repeat-dose toxicity testing is based on two references that examine the toxicity associated with sub-chronic and chronic daily trientine administration in rodents and repeat-dose toxicity studies performed in dogs with TETA 2HCl, published by Maemura et al. 1998. Data from a 92-day drinking water administration study indicate that rats but not mice are susceptible to symptoms of copper deficiency when fed a copper-deficient diet, but TETA 2HCL reduced plasma copper levels at 600ppm and 3000ppm without inducing symptoms of copper deficiency in rats fed a diet containing nutritionally adequate levels of copper. A treatment-related increased frequency of uterine dilatation occurred in female rats at 3000 ppm TETA 2HCL but this was not considered of major toxicological significance and the rat NOAEL was considered to be 3000ppm, corresponding to an oral intake of approximately 270-276 mg/kg/day in males and 323-352 mg/kg/day in females. Treatment–related toxicity occurred in mice exposed to TETA 2HCl in drinking water at 3000ppm TETA 2HCL. Symptoms included increased frequencies of inflammation of the lung interstitium and liver periportal fatty infiltration in both sexes, with hematopoietic cell proliferation in the spleen, reduced kidney and body weights and renal cytoplasmic

vacuolization in males only. The mouse NOAEL was considered 600ppm, corresponding to an oral intake of approximately 92 mg/kg/day in males and 99 mg/kg/day in females.

Treatment-related toxicity and mortality were reported after daily oral administration of up to 1200mg/kg/day TETA 2HCL in a sub-chronic (4-8week) study in rats, with decreased body weight gain and food consumption between 5 and 8 weeks of treatment and two deaths in males with signs of pneumonia at 8 weeks of treatment at this dose. Increased electrolyte output, reported between week 4 and 8 for males treated with ≥ 100mg/kg/day and females receiving ≥ 350mg/kg/day, was thought to be related to the hydrochloride nature of TETA 2HCL and low plasma alkaline phosphatase activities were reported in animals receiving 350 or 1200 mg/kg/day of TETA 2HCL but were not considered clinically relevant. Post-mortem findings at 1200 mg/kg/day included high lung weights, bronchiolar epithelium hypertrophy and broncho-alveolar pneumonia, with submucosal acute inflammation within the glandular region of the stomach recorded for males given ≥ 350 mg/kg/day and for females given ≥ 100 mg/kg/day.

Treatment-related toxicity and mortality were also reported following chronic (26weeks) daily oral administration of up to 600mg/kg/day in rats, with treatment-related lung changes and one death in a male receiving 175 mg/kg/day and three deaths in males receiving 600 mg/kg/day, although the sub-chronic stomach findings were not replicated in this study. Post-mortem histopathology revealed dose-related incidence and severity of focal chronic interstitial pneumonitis accompanied by fibrosis of the alveolar walls in females given ≥ 175 mg/kg/day or males given ≥ 50 mg/kg/day. Microscopic examination indicated a persistent inflammatory reaction or persistent toxic effect on alveolar cells. Given trientine has irritating properties, it was considered likely that the lung findings were the result of a cytotoxic effect of trientine upon accumulation into bronchiolar epithelial cells and alveolar pneumocytes. The findings were not reversible. Reversible findings included: decrease body weight gain at 600 mg/kg/day; blood chemistry and urinalysis changes similar to those indicated in the 4- or 8-week study at dose levels ≥ 175 mg/kg/day. The rat NOAEL was considered 50 mg/kg/day for females but a NOAEL was not establish for males (≤ 50 mg/kg/day).

Subacute (4 week) and chronic (26 week) oral toxicity studies were also performed with TETA 2HCL in Beagle dogs, including toxicokinetic analysis. In the 4 week study, treatment related observations were essentially limited to animals of the high dose group receiving 300 mg/kg/day. Observations included clinical signs during the last week of treatment (hypoactivity, abnormal gait, ataxia and body tremor), a depressed extensor postural thrust reaction in some animals at the end of treatment, and occasional or multiple dark areas in the lungs at necropsy correlating with interstitial pneumonia. All findings except interstitial pneumonia showed evidence of reversibility at the end of the post-dose period. The NOAEL was established at 125 mg/kg/day. Toxicokinetic analysis revealed moderately rapid absorption (Tmax 0.9-1.3 hours) and an increase in exposure with an increase in dose. $T_{1/2}$ was somewhat longer after repeated dosing (2.6-3.8 hours) than on day 1 (1.5-1.9 hours) but no significant accumulation of trientine occurred.

In the 26 week study, three animals of the high dose 200 mg/kg/day group were sacrificed prematurely and treatment was stopped after 10 weeks treatment following the onset of severe clinical signs (marked hypoactivity, body tremors, abnormal gait, weak limbs, hunched posture and prominent carpal joints). The ante mortem neurological examination generally indicated depressed postural and flexor withdrawal reactions. These observations were rapidly reversible. Abnormal "stiff legged" gait and hypoactivity were evident from week 23 of treatment in some animals given 100 mg/kg/day. A depressed extensor postural thrust reaction and/or slightly exaggerated patellar reaction were incidentally observed at this dose level. No noteworthy macroscopic or microscopic findings were recorded in muscles or nerves. However, the observed symptoms showed similarity to those reported in enzootic ataxia (“swayback”) in lambs which is induced by copper deficiency (Bennetts and Chapman 1937). Likewise (acquired) copper deficiency has been implicated in cases of ataxic myelopathy in

humans (Jaiser and Winston 2010). In the 26-week study in dogs, all treated groups displayed low copper and zinc concentrations in the liver and high urinary copper and zinc concentrations. Copper levels were also reduced in kidney and in plasma. Changes in copper levels were much more pronounced than changes in zinc levels, and the observed clinical symptoms were attributed to the pharmacological activity of TETA 2HCl.

Clinical pathology changes observed were either minimal or also occurred in control animals and were therefore considered of no toxicological importance. Interstitial pneumonia, also observed in rats and mice, was seen in most animals including controls. The NOAEL of TETA 2HCL in this 26-week study was concluded to be 50 mg/kg/day, associated with an AUC of 47.9 µg.hr/mL in males and 97.4 µg.hr/mL in females in week 13. The safety margins compared with the pharmacokinetic values obtained in healthy volunteers (TRIUMPH PK study) with TETA 2HCL and TETA 4HCL were 5 and 4 respectively in males, 30 and 17 respectively in females.

Toxicokinetic analysis revealed a Tmax of 0.9-1.9 hours and an increase in exposure was found with an increase in dose. No significant accumulation was noted in females in week 26 compared to week 13, however exposure in males was markedly lower in week 26 than in week 13. The reduced exposure was attributed to animals being fed immediately after dosing on the sampling day in week 26, in contrast to the sampling day in week 13 where the time difference between dosing and feeding was at least 10 min (interaction with food).

Genotoxicity

A GLP-compliant Ames test conducted by the applicant indicated that TETA 4HCL is mutagenic in vitro. A similar finding was reported with TETA 2HCL (Heinz & Schroder 1981). Conversely, in vivo genotoxicity data from the literature reported that single intraperitoneal dose of up to 600 mg/kg trientine in a mouse micronucleus study in peripheral erythrocytes indicated no clastogenic activity (Leung, 1994). A second reference also reported that trientine was negative in vivo in a mouse bone marrow micronucleus assay, with oral administration of up to 6000 mg/kg and intraperitoneal administration of up to 250mg/kg (Heinz and Schroder 1981). The genotoxic effects in vitro are most likely secondary to Cu/Zn depletion and can therefore be considered as non-relevant for the clinical situation.

In silico, assessments of the three main impurities- with DEREK and Leadscope prediction assays revealed no structural alert and it is therefore concluded that these impurities are of no mutagenic concern.

Carcinogenicity

No oral carcinogenicity study was conducted for trientine nor are any bibliographical studies reported. It is reported that life-time dermal application in mice did not induce skin tumours and trientine was shown to reduce DNA damage associated with copper accumulation in renal cortex cells in rats. Given the broad clinical use of TETA 2HCL which is authorised in the UK for the treatment of WD in patients intolerant to D-penicillamine since 1985 and the clinical experience with TETA 4HCL from the compassionate use program in France from the mid 1970's to 2008, the lack of oral carcinogenicity studies can be accepted.

Reproduction toxicity

The reproductive and developmental toxicity assessment is based on two articles from the published literature, together with the OECD SIDS for TETA assessment report. An article by Walshe, 1982 states that there is no evidence of teratogenicity in animals treated with trientine, but does not support this with any data. Conversely, Keen, Cohen et al., 1982 report dose-dependent embryotoxicity (increased frequency of resorptions) and teratogenicity (increased frequency of abnormal foetuses), with the teratogenicity occurring at therapeutic concentrations in rats. However, these effects may be the results of trientine-induced copper deficiency and

possible zinc toxicity, as maternal plasma and foetal liver copper concentrations were low compared to control rats and maternal kidney and foetal liver zinc levels increased in a dose-related manner. In follow-up experiments copper supplementation reduced the teratogenicity of trientine, supporting the role of copper-deficiency in the trientine-induced teratogenicity. The need for careful monitoring of maternal serum copper levels throughout pregnancy and the potential need for dose adjustments has been identified in the SmPC (section 4.6). On this basis, the reproductive and developmental toxicity risks associated with trientine-induced alterations of copper concentrations can be accepted.

Toxicokinetic data

Please refer to above chapter on repeat dose toxicity.

Local tolerance

The local tolerance assessment for trientine is based on the nonclinical in vivo bibliographic data reporting treatment-related toxicities associated with trientine, in agreement with in silico data predicting that trientine would display sensitising properties. The repeat-dose toxicity assessment data showed increased frequencies of inflammation of the lung interstitium occurring in mice exposed to TETA 2HCl at 3000ppm in drinking water. In rats, daily oral sub-chronic (4-8 week) administration of TETA 2HCL at 1200mg/kg/day induced submucosal acute inflammation of the stomach, bronchiolar epithelium hypertrophy and broncho-alveolar pneumonia and two males died with signs of pneumonia. While, chronic (26 weeks) daily oral administration in rats resulted in chronic interstitial pneumonitis of the lung with fibrosis of alveolar walls at ≥175mg/kg/day in females and ≥ 50mg/kg/day in males, including mortality in four males (1 death at 175mg/kg/day and 3 deaths at 600mg/kg/day). Furthermore, inflammatory lesions and erosions of the skin were reported when trientine was dermally applied to guinea pigs at a dose of 4mg/animal and strong dermal irritation was also noted in pregnant rabbits given dose levels up to 125 mg/kg TETA. However, the observations in lung are thought to be the result of a persistent cytotoxic effect of trientine upon accumulation into bronchiolar epithelial cells and alveolar pneumocytes. The longstanding use of trientine in the clinic does not indicate a cause for concern related to local tolerance, this supersedes the need for further nonclinical local tolerance studies.

2.3.5. Ecotoxicity / environmental risk assessment

For the phase I ERA, calculated estimates of log Kow = -1.4 and -2.65 are reported for TETA 4HCL. Log Kow should be determined experimentally; a calculated value is generally not accepted. However, trientine is reportedly completely miscible in water, has 4 ionisable groups and would therefore not be expected to have a log Kow >4.5 within environmental pH range. Hence, the sponsor deemed PBT screening is not required and this reasoning is accepted.

The predicted environmental concentration for trientine in surface water (PECsw) was calculated with a refined Fpen. This Fpen refinement is based on a prevalence of Wilson's disease of 0.6 in 10,000 for which a worst case estimate of 1/3 will be intolerant to D-penicillamine (refined Fpen = 0.000018). This is acceptable as orphan status has been granted for TETA 4HCL (EU/3/15/1471). The worst case PECsw (0.00945µg/L) is below the action limit of 0.01 µg/L and TETA 4HCL is considered unlikely to represent a risk to the environment following its prescribed use in patients.

Table 1 Summary of main study results

Substance (INN/Invented Name): Trientine tetrahydrochloride / Cuprior			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Calculated	-1.4, -2.65	Potential PBT No
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.00945	µg/L	> 0.01 threshold No
Other concerns (e.g. chemical class)			(Y/N)

2.3.6. Discussion on non-clinical aspects

The primary pharmacodynamic studies are bibliographic. They establish proof of concept of the copper depleting properties of trientine. TETA 4HCL is shown to increase urinary excretion of copper and reduce liver copper concentration in rats administered exogenous copper, while TETA 2HCL is shown to have similar effects in a rat model of WD. Secondary pharmacodynamics, also by bibliographic reference, identified off target effects of trientine including decreasing single strand breaks associated with copper accumulation in renal cortex cells of rats. Off target effects on other divalent cations such as iron and zinc were identified, the potential effect on iron and zinc levels is addressed in section 4.4, 4.5 and 5.3 of the SmPC, indicating that iron absorption may be decreased by trientine treatment and iron supplementation may be necessary.

Safety pharmacology studies were not performed for this hybrid application with TETA 4HCL as the active moiety is identical to that of the marketed TETA 2HCL product, for which the clinical experience to date does not indicate a cause for concern. The justification for the absence of safety pharmacology studies is acceptable and the pharmacology section is considered adequate.

The pharmacokinetic studies are also bibliographic and consist mainly of rat studies, although limited data from rabbits and dogs are also reported. The rat studies indicate that TETA 2HCL and TETA 4HCL have comparable dispositions in the rat, including low oral bioavailability due to first pass metabolism, which is lower again in a fed state. This evidence of an interaction with food is reflected in sections 4.2 and 4.5 of the proposed SmPC, indicating that Cuprior must be taken on empty stomach as food may impede its absorption. SSAT2 was identified as the main acetylator of trientine in vitro and section 5.2 of the identifies two major acetylated metabolites of trientine, N(1)-acetyltriethylenetetramine (MAT) and N(1),N(10)-diacetyltriethylenetetramine (DAT). MAT may also contribute to the overall clinical activity of Cuprior, however the extent of MAT to the overall effect of Cuprior on copper is not determined.

The toxicology package consists mainly of bibliographic studies performed with TETA 2HCL. Trientine was considered to have low acute toxicity after oral administration and moderate toxicity after dermal application, based on LD50 data from rats and rabbits respectively, and trientine is considered harmful in contact with skin. Irritating and sensitising properties of Trientine shown in animals are reflected in the SmPC. Treatment-related toxicity in the stomach (sub-mucosal acute inflammation; sub-chronic study only) and the lungs (focal chronic interstitial pneumonitis accompanied by fibrosis of the alveolar walls) with associated mortality were reported from repeat-dose toxicity testing in rodents. These findings were attributed to the irritant properties of trientine and have not been confirmed in clinical use in WD patients. Duodenitis and colitis have been reported in humans and are mentioned as adverse reaction in the SmPC but there are no indications of lung lesions or adverse

respiratory effects under the clinical conditions of use. Increased electrolyte output was reported in the sub-chronic toxicity study with TETA 2HCL, thought to be related to the hydrochloride nature of TETA 2HCL, and low plasma alkaline phosphatase activities were also reported.

Repeat-dose toxicity of TETA was discussed by referring to studies in mice, rats and dogs. Toxicokinetic data were concomitantly obtained in the repeat-dose toxicity studies in the dog (Maemura et al. 1998). An exposure assessment versus human exposure based on AUC compared to PK from healthy human volunteers revealed exposure rations of 5 and 4 in males and 30 and 17 in females, for TETA 2HCL and TETA 4 HCL respectively.

TETA was clearly positive in the Ames test and other (non-GLP) *in vitro* assays but showed negative results in *in vivo* mouse bone marrow MN studies. The genotoxic effects *in vitro* are most likely secondary to Cu/Zn depletion and can therefore be considered as non-relevant for the clinical situation. No long- or short term studies on carcinogenicity with oral application of TETA are available. Clinical experience with TETA 2HCl in WD patients does so far not indicate a carcinogenic risk for TETA. Therefore, it can be agreed that carcinogenicity studies are not needed for TETA 4HCl. Impurities identified for TETA 4HCl have been sufficiently qualified through DEREK and LEADSCOPE analysis.
Trientine has shown embryotoxicity and teratogenicity in pregnant rats, with the teratogenicity occurring at therapeutic concentrations. These effects are thought to result from trientine-induced copper deficiency and possible zinc toxicity, as maternal plasma and foetal liver copper concentrations were low compared to control rats and maternal kidney and foetal liver zinc levels increased in a dose-related manner. The role of copper deficiency in the treatment-related teratogenicity finding is supported by follow-up experiments in which copper supplementation reduced the teratogenicity of trientine. The need for careful monitoring of maternal serum copper levels throughout pregnancy and the potential need for dose adjustments has been identified in the SmPC (section 4.6). On this basis, the reproductive and developmental toxicity risks associated with trientine-induced alterations of copper concentrations can be accepted.

The treatment of children is not supported by juvenile toxicity studies. However, dose adjustment will be performed for different age groups to support the safe use in the paediatric population.

In agreement with the in silico prediction that trientine would display sensitizing properties, in vivo data from dermal application of trientine indicated treatment-related inflammatory lesions and erosions of the skin in guinea pigs and strong dermal irritation in pregnant rabbits. Furthermore, persistent cytotoxic effects of trientine in the lungs were observed during the repeat-dose toxicity testing. However, the longstanding use of trientine in the clinic does not indicate a cause for concern related to local tolerance and this supersedes the need for further nonclinical local tolerance studies.

TETA 4HCL PECsurfacewater value is below the action limit of 0.01 µg/L and it is not a PBT substance as log Kow does not exceed 4.5. Hence, no environmental effects are likely and a Phase II Tier A environmental fate and effects programme is not required. TETA 4HCL is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The majority of the literature references consist of studies conducted with TETA 2HCL which was considered acceptable by the CHMP as the active moiety of TETA 4HCL is identical. Overall the bibliographic primary pharmacodynamics studies provided adequate evidence to establish proof of concept of the copper depleting properties of Cuprior.

The toxicology package consists of bibliographical references together with in silico genotoxicity analysis and a GLP-compliant in vitro Ames test on the genotoxicity performed by the applicant. TETA was clearly positive in the Ames test and other (non-GLP) *in vitro* assays but showed negative results in *in vivo* mouse bone marrow MN studies. The genotoxic effects *in vitro* were most likely secondary to Cu/Zn depletion and can therefore be considered as non-relevant for the clinical situation. No long- or short term studies on carcinogenicity with oral application of TETA are available. Clinical experience with TETA 2HCl in WD patients does so far not indicate a carcinogenic risk for TETA. Therefore, it can be agreed that carcinogenicity studies are not needed for TETA 4HCl. In silico, assessments of the three main impurities with DEREK and Leadscope prediction assays revealed no structural alert and it is therefore concluded that these impurities are of no mutagenic concern.

Safety pharmacology studies were not performed for this hybrid application with TETA 4HCL as the active moiety is identical to that of the marketed TETA 2HCL product, for which the clinical experience to date does not indicate a concern. The justification for the absence of safety pharmacology studies is acceptable and the pharmacology section is considered adequate.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for Cuprior 150 mg tablets containing trientine tetrahydrochloride equivalent to 150 mg trientine. To support the marketing authorisation application the applicant conducted two comparative PK studies with cross-over design. The TRIUMPH study providing the pivotal evidence was performed against the reference medicinal product under fasting conditions. The second comparative PK study (TRIUMPH-2) was performed against a product not authorised in the EU and provides only supportive pharmacological information on the product under assessment. In addition the application is supplemented by a retrospective, single centre, long-term cohort survey comparing efficacy and safety of TETA 4HCl and TETA 2HCl ("Lariboisière study").

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

GCP

The TRIUMPH studies were performed in accordance with GCP as claimed by the applicant. In the Lariboisière study, patient treatment (as compassionate use) and assessment was in accordance with clinical practice for the management of WD. GCP standards could not be applied due to the retrospective nature of the survey.

There were no clinical trials submitted conducted outside the community.

Clinical studies

Table 1. Tabular overview of clinical studies

Study	Description
TRIUMPH	Two way cross over study of the single dose pharmacokinetics of trientine tetrahydrochloride and the EU reference trientine dihydrochloride (Univar, approved in UK) each equivalent to 600 mg trientine base, completed by 23 healthy volunteers.
TRIUMPH-2	Four-way crossover study. Twenty-eight healthy volunteers received single doses of US reference product; Valeant's TETA 2HCl as 3 capsules and 5 capsules (167 mg trientine base per capsule), total 500 mg and 833 mg. The test product was Cuprior administered as single doses of 3 tablets and 5 tablets (150 mg trientine base per tablet) total 450 mg and 750 mg.
Lariboisière survey	A commissioned review of the use of monotherapy of trientine tetrahydrochloride and trientine dihydrochloride in a single centre in Paris comprising 43 patients receiving one or both treatments.

2.4.2. Pharmacokinetics

TRIUMPH study

Study title: A phase 1, single center, randomized, interventional, single dose, open-label, crossover study in adult healthy male and female subjects to evaluate the pharmacokinetics and the safety, tolerability of two different oral formulations.

Type of Study	Study Identifier Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
PK, safety, tolerability	TRIUMPH 5.3.3.1	To evaluate the PK parameters of both oral trientine salts (TETA 4HCl and TETA 2HCl) in adult healthy volunteers in order to define the TETA 4HCl dose providing a PK profile similar to TETA 2HCl reference product. To compare the safety and tolerability of both trientine salts in adult healthy volunteers.	Phase 1, single centre, randomised, interventional, single dose, open-label, cross-over study	TETA 4HCl 300 mg tablets developed by gmp-orphan, containing 150 mg TETA base Single-dose of 4 tablets, i.e. 1200 mg TETA 4HCl (i.e. 600 mg of TETA base) oral Comparative drug: TETA 2HCl 300 mg capsules from Univar® containing 200 mg TETA base Single dose of 3 capsules, i.e. 900 mg TETA 2HCl (i.e. 600 mg of TETA base) oral	26	Healthy subjects	Single dose

Methods

Study design

This was a single center, randomised, interventional, single dose, open-label, cross-over study with 3 days wash-out period between two treatments to evaluate the PK, safety, and tolerability, of both oral formulations in adult healthy male and female subjects.

Subjects were admitted to the clinic on Day 0 (day prior to dosing) and were requested to stay in the clinic for 3 days post-dose (Day 1 to Day 4), up to the last PK sampling time..

A single dose of 600 mg of trientine base was administered of either test or reference product (see next section).

Treatments were orally administered in a randomised order on Day 1, at time 0 (morning).

Blood samples for PK determination were taken at various time points: Pre-dose (0.0), 0.5, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 30, 36, 42, 48 and 72 h after dosing.

Safety assessments were performed during this period.

After a wash-out period of 3 days (at home), subjects returned to the clinic the evening before dosing (Day 7) and were treated with the other formulation at time 0 on Day 8. Subjects were followed-up and assessed over the subsequent three days (Day 8 to Day 11) as described for the first treatment period. A final follow-up visit at the clinic took place at Day 15 (± 1 day).

Test and reference products

Treatment A: 900 mg trientine dihydrochloride (TETA 2HCl, MAH Univar BV), 3 capsules of 300 mg, each containing 200 mg of trientine base, administered orally (total of 600 mg trientine base administered).

Treatment B: 1200 mg trientine tetrahydrochloride (TETA 4HCl, gmp-orphan), 4 tablets of 300 mg, each containing 150 mg of trientine base, administered orally (total of 600 mg trientine base administered).

Population(s) studied

Twenty-six healthy volunteers were randomised to receive equal amounts (600mg) of TETA base, either as TETA 2HCl (the EU reference product) or TETA 4HCl (Cuprior). Twenty-four subjects received TETA 2HCl and twenty-five received Cuprior. Twenty-three subjects completed the study per protocol and received both treatments.

Fourteen subjects were male and twelve were female. At screening subjects' mean (s.d.) age was 24.5 (5.6) years all were Caucasian, none was a current tobacco smoker, mean (s.d.) BMI was 22.93 (2.09) kg/m^2 with a range of 19.2 to 26.9 kg/m^2.

No subjects were excluded from analysis due to protocol deviations. There were no major protocol deviations and it is unlikely that other deviations affected the interpretation of the study results. There was no concomitant medication reported during the study.

Analytical methods

All analytes were measured using a validated high performance liquid chromatographic tandem mass spectrometric (LC-MS/MS) method. The analytical method used was validated in accordance with EMA Guideline on Bioanalytical Method Validation. The analytes were trientine (TETA), N1 acetyltriethylenetetramine (MAT) and N1,N10-diacetyl triethylenetetramine (DAT).

Pharmacokinetic variables

Pharmacokinetic parameters:

- Plasma concentrations of the parent entity (trientine base, TETA) and the two major metabolites (N1-acetyltriethylenetetramine, i.e. MAT; and N1, N10-diacetyltriethylenetetramine, i.e. DAT) at the selected time points.
- AUC0-t, AUC0-∞, t1/2, λz, Cmax, and Tmax.

The PK variables (Cmax, Tmax, AUC0-t, AUC0-∞, t½, and λz after single dose) of trientine and its two major metabolites were summarised using descriptive statistics including arithmetic mean, standard deviation, median, minimum/maximum, coefficient for the between-subject variation. For comparability of the two products the geometric mean, ratio of geometric means, confidence intervals (CI) including their logarithmic transformation together with the coefficient of variation for the within-subject variability were summarized.

Statistical methods

Statistical analysis of pharmacokinetic data was planned to be performed using SAS® version 9.3 or higher.

Results

Table 2. Pharmacokinetic parameters for trientine base (TETA), metabolites N1 acetyltriethylenetetramine (MAT) and N1-N10-diacetyltriethylenetetramine (DAT) following administration of the reference formulation (900 mg TETA 2HCl, equivalent to 600 mg base) and test formulation (1200 mg TETA 4HCl, equivalent to 600 mg base)

Parameter	**Test n =23 TETA 4HCL**	**Reference n = 23 TETA 2HCL**
	Arithmetic Mean ± SD (%CV)	Arithmetic Mean ± SD (%CV)
Trientine (TETA)		
Cmax, ng/mL	2340 ± 1170 (50.0)	1490 ± 864 (58.1)
Tmax, h	2.00 (0.50-4.00)	3.00 (1.25-6.02)
AUC0-t, h·ng/mL	10100 ± 5740 (57.0)	6600 ± 3870 (58.6)
AUC0-inf, h·ng/mL	10200 ± 5810 (56.7)	6790 ± 3950 (58.1)
λz, 1/h	0.0590 ± 0.0952 (161.3)	0.0558 ± 0.0681 (122.1)
t½, h	19.9 ± 8.70 (43.7)	23.2 ± 20.8 (89.9)
N1-acetyltriethylenetetramine (MAT)		

Cmax, ng/mL	1820 ± 694 (38.1)	1640 ± 604 (36.8)
Tmax, h	5.00 (3.00-12.00)	6.00 (3.00-12.02)
AUC0-t, h·ng/mL	17900 ± 5270 (29.5)	15200 ± 3940 (25.9)
AUC0-inf, h·ng/mL	18800 ± 5400 (28.7)	15900 ± 3990 (25.1)
λz, 1/h	0.0292 ± 0.00686 (23.5)	0.0300 ± 0.00493 (16.4)
t½, h	25.5 ± 8.44 (33.1)	23.7 ± 3.97 (16.7)
N1, N10-diacetyltriethylenetetramine (DAT)		
Cmax, ng/mL	499 ± 511 (102.3)	412 ± 404 (98.0)
Tmax, h	6.00 (4.00-12.00)	6.00 (4.00-8.02)
AUC0-t, h·ng/mL	5290 ± 3710 (70.0)	4490 ± 2830 (63.0)
AUC0-inf, h·ng/mL	5590 ± 3880 (69.4)	4700 ± 2860 (60.9)
λz, 1/h	0.0367 ± 0.0161 (43.7)	0.0339 ± 0.0102 (30.0)
t½, h	22.4 ± 9.82 (43.9)	21.9 ± 5.44 (24.9)

Table 3. Statistical Comparisons of Pharmacokinetic Parameters for Trientine (TETA), after Administration of Trientine Dihydrochloride (TETA 2HCl) and Trientine Tetrahydrochloride (TETA 4HCl) in Healthy Male and Female Subjects.

Parameters[ψ]	Least Square Geometric Mean		Least Square Geometric Mean Ratio (%) (Test / Reference)	90% Confidence Interval of the Ratio	Within Subject %CV*
	Test (TETA 4HCl)	Reference (TETA 2HCl)			
Trientine (TETA) (N=23)					
C_{max}, ng/mL	2030	1210	167.58	(142.12, 197.59)	33.2
AUC_{0-t}, h·ng/mL	8220	5230	157.11	(134.90, 182.98)	30.6
AUC_{0-inf}, h·ng/mL	8380	5380	155.57	(133.99, 180.63)	30.0
T_{max}, h[ξ]	1.80	2.74	-0.94	(-1.29, -0.60)	24.6
$t_{½}$, h	16.7	16.9	98.69	(81.17, 119.99)	39.8

Following oral administration at a single dose of 600 mg trientine base in healthy male and female subjects TETA was rapidly absorbed with median Tmax values of 2.00 hours and 3.00 hours for the test product (TETA 4HCl tablets) and reference product (TETA 2HCl capsules), respectively.

The rate (Cmax) and extent (AUC0-inf) of TETA absorption for TETA 4HCl were greater (~68% and ~56% increase in Cmax and AUC0-inf, respectively) than those after administration of the reference product. The terminal elimination rate (λz) and terminal half-life (t1/2) for TETA were similar between the test and reference products.

The terminal elimination half-life (t½β, arithmetic mean ± SD) calculated in the TRIUMPH study was 19.9 ± 8.70h for TETA 4HCl and 23.2 ± 20.8h for TETA 2HCl, with wide variability between subjects. Most published studies have reported shorter t1/2 values for trientine e.g. Cho et al. showed half-lives of 5-14 hours, increasing with dose.

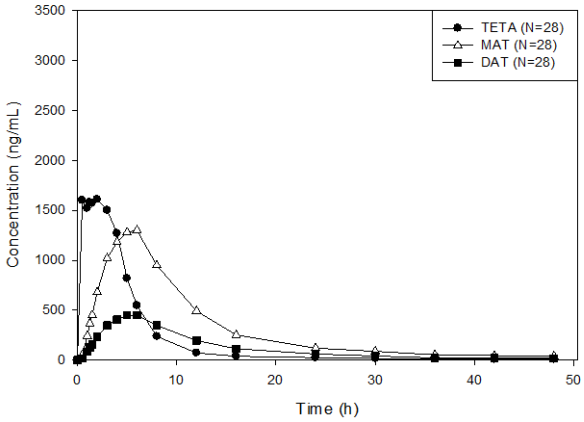
TRIUMPH-2 study

A second PK study performed to meet US registration requirements was submitted in form of a summary. Since TRIUMPH-2 was conducted versus the US FDA approved trientine product Syprine the data are only supportive, but informative for the characterisation of the PK behaviour of Cuprior (linear PK).

The TRIUMPH-2 study provides data on Cuprior for 2 oral doses (450 mg and 750 mg) of trientine base (ratio of high to low dose: 1.67). The mean plasma concentration over time for trientine and its two major metabolites (MAT and DAT) at the lower and higher oral doses of Cuprior are illustrated below:

Figure 1: Arithmetic Mean Plasma Concentrations of Trientine (TETA), N1-acetyltriethylenetetramine (MAT) and N1, N10-diacetyltriethylenetetramine (DAT) After Administration of Two Dose Levels of Cuprior in TRIUMPH-2 (N=28)

a) Low dose (



b) High dose (

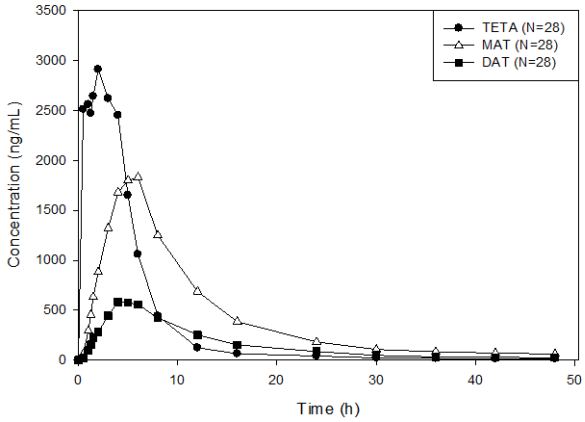


Table 1: Summary Statistics for Trientine (TETA) Exposure, After Administration of Two Dose Levels of Cuprior in TRIUMPH-2 (N=28)

Parameter	TETA 4HCl lower dose (450 mg base) Arithmetic mean ± SD	TETA 4HCl higher dose (750 mg base) Arithmetic mean ± SD	Ratio of arithmetic mean (high:low dose)
C_{max}, ng/mL	2030 ± 981	3430 ± 1480	1.69
AUC_{0-t}, h·ng/mL	9470 ± 4700	16900 ± 9360	1.78
AUC_{0-inf}, h·ng/mL	9750 ± 4910	17200 ± 9470	1.76

Additional data

Dissolution profile

The dissolution of Cuprior TETA 4HCl tablets was compared with that of

Univar's TETA 2HCl capsules that was used as a reference product for TETA 4HCl tablets in the TRIUMPH pharmacokinetic (PK) study. Dissolution was tested at pH 1.2; pH 4.0 and pH 6.8.

Dissolution tests showed that the dissolution rate for the EU reference capsules was about eight times slower than that for the tablets. In addition, while the active substance is completely released from the capsules by 120 minutes, the capsules were not completely dissolved at the end of the dissolution test (240 min), as a shell still remains. The same behaviour has been noticed in two different batches of Univar capsules.

Dose proportionality

Literature References
In an earlier study by Tanabe et al (1996) using a local Japanese TETA 2HCl formulation, the combination of trientine + metabolites levels appeared consistent with dose proportionality, which was not clearly shown for the unchanged or metabolised trientine alone.

The study by Cho et al. (2009) showed consistent single/multiple-dose PK and dose-proportional and serum concentration-proportional effects on enhancing copper excretion using a TETA 2HCl development formulation. Analysis of the AUC and Cmax confirmed their linear relationship with oral doses of 200 to 3600 mg/d.

TETA 2HCL had consistent single/multiple-dose pharmacokinetics and dose-proportional and serum concentration-proportional effects on enhancing copper excretion in healthy subjects.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Additional expert consultation

At day 180 of the procedure a major objection precluded a recommendation of marketing authorisation pertaining to the bridge to the reference product, Univar´s TETA 2HCL.

Therefore the CHMP decided to consult the Pharmacokinetic Working Party (PKWP). Questions to the PKWP as well as their advice are outlined below.

PKWP response to questions

Note on the PK bridge: The pharmacokinetic questions relates to a PK bridge to extrapolate both efficacy and safety. However, if intestinal luminal chelation and thus inhibition of copper absorption contributes to a significant part of the efficacy, PK will not be sufficient to extrapolate efficacy, in particular between two products with apparently very different dissolution characteristics. In that case, it seems appropriate to obtain PD data in healthy volunteers or patients supporting similar intestinal effect on orally administered copper. Available literature from Siegemund R. et al. (1991) demonstrated that TETA 2HCl (1.2 g/day) was able to chelate copper in the intestinal tract, reducing copper absorption into the body.

Value of knowing the exact correction factor: As this drug is individually titrated and has variable

pharmacokinetics, recommending monitoring is advisable also in the switch situation.

The impact to inter-formulation differences is to some extent reduced by the monitoring and titration as long as the monitoring can provide fast enough support to avoid safety and efficacy problems. However, the correction factor also affects the starting dose. If the corrected starting dose is not adequate, this may not be completely solved by titration.

1. **In order to account for the difference in bioavailability between Cuprior and the reference product in the TRIUMPH study the company proposes an adjustment factor to support a posology matching the exposure of Cuprior (TETA 4HCL) with the reference product (Univar´s TETA 2HCL). The PKWP is asked to comment on the robustness of the adjustment factor approach, across the entire dose range.**

PKWP response

The in vitro dissolution rate of TETA 4HCL tablets (test) is markedly faster than of Univar TETA 2HCL capsules (reference). However, a capsule with TETA 2HCL and TETA 4HCL showed similar, and quite fast dissolution. Thus, the difference in dissolution rate appeared to be more related to the formulation and not to the different salt *per se*.

The exposure of TETA comparing geometric means is approximately 56% higher after administration of the test product when comparing a 600 mg dose (as trientine base). This difference appears to reside from a higher fraction absorbed from the test product. The applicant proposes 0.6 to be used as correction factor for the dose recommendations.

However, the submitted study is not sufficient as support of the 0.6 correction factor. Bioequivalence should be confirmed comparing the test and reference product, using the corrected dose of the test product

Which dose-level to study depends on whether the pharmacokinetics is linear or not. There is data supporting linearity of a 2HCL containing product (Cho et al 2009). It is unknown to us whether the studied product is the same as the reference (i.e. has similar dissolution rate as the reference product), but based on the Clinical Overview, a product called Protemix's TETA 2HCl formulation is used. Thus, the data supporting linear pharmacokinetics may not be relevant for the reference or the test product. In a situation where linearity has not been demonstrated, investigating the lowest and highest dose is suitable.

To take the absence of linearity information into account, we propose that the bioequivalence study is performed at the lowest starting dose. As the doses relevant for the correction factor, i.e. 150 mg base for the test and 250 mg base for the reference, cannot be compared due to the absence of a 250 mg strength for the reference product, the existing strengths should be used i.e. 150 mg (as base; one 150 mg tablet) for the test and 200 mg (as base; one 300 mg capsule) for the reference. The results obtained should then be adjusted in order to estimate the results that would have been obtained if a dose of 250 mg base of the reference product had been administered. This can be done if pharmacokinetics is linear by adding an adjustment factor to the point estimate of this bioequivalence study in log scale instead of correcting all individual values of the pharmacokinetic endpoints. This adjustment factor is the logarithm of the ratio between the actually administered dose of the reference (200 mg base) and the reference dose that should have been administered if the correct strength had existed (250 mg), i.e. ln (250/200). Once the point estimate is corrected, the 90% CI is calculated based on that corrected point estimate and back-converted to the original scale as usual.

If BE is shown in the new study the correction factor is considered adequately supported over the full dose range.

2. **Please comment on the comparability of the products in terms of food effect. Taking into account the SmPC recommendation to take Cuprior (as well as the RMP) without food do you consider the absence of comparative data with respect to the impact of food intake acceptable?**

PKWP response

Cuprior should be taken on an empty stomach, 30 minutes to one hour before meals. According to the Applicant's Clinical Overview this permits maximum absorption and reduces the likelihood of inactivation of the drug by metal binding in the gastrointestinal tract. The pharmacokinetic comparison (TRIUMPH study) was performed under fasting conditions. The in vivo absorption of TETA 4HCL tablets is faster than for the 2HCL reference product (2.7 vs 1.8 hrs). It is possible that there is still some inactivation from a meal taken 30 minutes after drug administration.

The food effect on a 2HCL formulation on the systemic exposure was only investigated in one subject. It is also unknown to us whether the formulation studied was the reference product. The effect observed was modest (unchanged AUC, reduced Cmax (from 3.8 to 1.5 mg/L), delayed Tmax (from 2 to 4 h) and prolonged t1/2 (from 4 to 8 h). However, one subject is not considered sufficient to base any conclusion on regarding the food-effect. There are data in rats showing a 90% reduction in bioavailability when drug substance dissolved in water was administered with food (Sakuma et al 2007).

Complex binding with metal ions may also limit absorption when administered with food (see SmPC). This may lead to marked inter-administration variability. The effect of a faster absorption and dissolution on the direction and magnitude of such an interaction administering the drug in accordance with the SPC is difficult to foresee.

In conclusion, it is unknown whether the test product, after applying the proposed correction factor, will be bioequivalent to the reference product when taken as proposed in the SmPC, which means 30-60 minutes before a meal. Therefore, it is considered necessary to conduct a bioequivalence study between the test product with the proposed correction factor and the reference product, 30 minutes before a high fat meal. A high fat meal is recommended as a high-fat meal and the fasting condition then covers the two extremes of meal composition. Therefore, bioequivalence using the corrected dose for the test product needs to be shown also after intake of a high-fat meal 30 minutes after drug administration. Preferably the food should be representative for the daily diet with respect to interacting metal ions.

If bioequivalence is shown under fasting conditions at a low dose, this, together with the available data on 600 mg base, also gives some indications that the pharmacokinetics is linear. If so, any dose level (still using the corrected dose for the test product) can be used when investigating the bioequivalence between the test and reference taken 30 minutes before a high-fat meal.

If bioequivalence is not shown when the products are administered 30 minutes before a meal, and the applicant liked to change the food intake recommendations in the SPC, further pharmacokinetic data is needed to support the recommendation.

3. **In view of the provided data on comparative bioavailability (TRIUMPH study) but also with reference to the overall PK data package, does the WP see a need to generate additional PK data in patients?**

PKWP response

To our knowledge, there are no clear reasons to believe that product differences in absorption of TETA are different in patients than in healthy volunteers. Thus, PK data in healthy volunteers would be sufficient.

2.4.5. Discussion on clinical pharmacology

The aim of the TRIUMPH study was to compare the plasma profiles and pharmacokinetic parameters of trientine and its main metabolites, following the administration of TETA 2HCl and TETA 4HCl formulations, i.e. to establish a dose relationship or a 'conversion factor'.

The study provides information to support an adequate strength for TETA 4HCl. Rate and extent of TETA absorption after 600mg of TETA base from TETA 4HCl/Cuprior were greater by approximately 68% and 56%, for Cmax and AUC0-inf, respectively, than from the reference TETA 2HCL formulation. The TRIUMPH-2 results support linear and dose proportional kinetics of Cuprior across the evaluated dose range. The recommended dose for clinical use is between 450 mg and 975 mg (3 to 6½ tablets) per day, divided in 2 to 4 doses. The maximal single daily dose is consequently about 525mg (3.5 tablets); this is within what was tested in TRIUMPH and TRIUMPH-2. Dose linearity/ proportionality within the relevant dose range is therefore considered to be sufficiently demonstrated.

Based on the comparative PK results the geometric mean ratios of test and reference formulations were used to find an adjustment factor suggesting a dose range for TETA 4HCl achieving similar exposure as under TETA 2HCl. Applying the proposed adjustment factor of 0.6, 1 mg of Univar's trientine base equates to 0.6 mg of Cuprior's trientine base. The minimum and maximum daily dose of the originator product is 800-1600 mg trientine base per day. The proposed dose range of Cuprior is 450mg-1050mg whereas the exact range to be in accordance with the Univar recommendations would be 480 mg – 960 mg applying the adjustment factor of 0.6. Taking into account also the confidence intervals for the calculation of the adjustment factor (and thus considering the possible extremes) a slight reduction of the maximum daily dose appeared appropriate.

The recommended adult dose of Univar's TETA 2HCl capsules is 1200-2400 mg/day (4-8 capsules), corresponding to 800-1600 mg of trientine base which is divided into 2-4 doses (Univar SmPC). Accordingly the recommended dose for Cuprior is between 450 mg and 975 mg of trientine base (3 to 6½ tablets) per day in 2 to 4 divided doses.

As trientine is titrated to target and Cuprior is actually not intended as first line treatment for initial treatment of WD (only for those intolerant to penicillamine) a possible overestimation of the starting dose (resulting in an underexposure, lower limit of AUC range 80.94%) is not believed to have a relevant impact on the patient's clinical status.

As a precaution, when initiating treatment with Cuprior, the lowest dose should be administered as stated in the SmPC; subsequently it should be titrated according to clinical response. For the maximum daily dose the worst case scenario (i.e. the upper limit of AUC range 109.79%) means a possible underestimation of exposure of about 10%.

The maximum tolerated dose in a 14 days PK/PD study in healthy adult volunteers by Cho et al. 2009, was considerably higher than what could be expected for Cuprior, namely 3600mg/d ; however, the product used in that investigation (TETA 2HCL) was not further specified. In Cho's study a dose dependent increase in adverse events was apparent. The concern that overexposure to trientine could lead to higher levels of free copper in the blood stream (by mobilisation of copper from tissues) resulting in (a deterioration of) neurological symptoms, would be applicable mainly for treatment naïve patients (who are not the target population). But this concern,

while based on physiological assumptions, seems to never have been recorded in second line treatment with trientine in clinical practice.

The applicant concluded that the difference in dissolution observed between the two products was due to the unusual nature of Univar's capsule rather than due to a difference between the capsule contents or the different salts of TETA 2HCl and TETA 4HCl. This was accepted by the CHMP however, several factors could also contribute to the observed results, such as e.g. different manufacturing processes or excipients.

Indeed the individualisation of dosing with regular monitoring of copper levels once Cuprior therapy is initiated and subsequent adjustment of dose, as necessary ensure the dosing of Cuprior is in accordance with individual patients' requirements. Such an individual 'treat to target' approach is required in the management of Wilson's disease, regardless of trientine formulation, in view of the high intra- and inter-subject variability for trientine absorption and the variability and evolution in the clinical presentation.

The presence of food reduces and delays the absorption of TETA. A study following oral administration of 1500 mg TETA 2HCl in a healthy volunteer showed that food reduced Cmax (from 3.8 to 1.5 mg/L), delayed Tmax (from 2 to 4 h) and prolonged t1/2 (from 4 to 8 h).

The food effect of Cuprior as compared with the reference product has not been studied and in view of the PK characteristics of Cuprior and the reference product a difference in food effect cannot be excluded. For the reference product, the food effect is believed to play a role also in clinical practice, considering the rather slow absorption of active moiety from the gut (T_{max} 3 hours) and the relatively conservative PI recommendations. Intake of Univar's trientine within 30 min to 1h before food could result in a limited absorption and limited systemic exposure compared to Cuprior, where dissolution and absorption occur more quickly (T_{max} 2 hours). Although the difference might even be enhanced by the "stricter" food recommendation proposed for Cuprior compared to the reference product, on the other hand this would lead to a more predictable and consistent systemic exposure.

Trientine is titrated to target and individual variations are expected to be high and may have a larger impact on the systemic level of the drug. Therefore small differences in food effect between products are not being considered of clinical relevance. Relevant uncertainties such as the lack of a food effect study are appropriately outlined in 4.5 of the SmPC.

No PD or PK drug interaction studies were identified in the literature. However, trientine has been shown to chelate iron and zinc in vitro (Kodama, Murata et al 1997) and increase zinc excretion in the urine of patients (Lu, Chan et al 2007), therefore an interaction with iron and zinc, particularly if given at the same time, cannot be excluded. Thus co-administration (at the same time) of trientine with iron and zinc should be avoided; this is appropriately addressed in the SmPC and in accordance with the reference product. In addition, the SmPC specifies that although there is no evidence that calcium or magnesium antacids alter the efficacy of trientine it is good practice to separate their administration (i.e. antacids should be taken after meals, while trientine is taken before meals).

There are gaps in the data on special populations, e.g. WD patients with renal/hepatic impairment. The product information was amended with regard to limited information on renal impairment. Liver enzymes/liver function is monitored routinely in WD patients.

Besides its systemic action TETA can reduce copper absorption from the gastrointestinal tract (e.g. Siegemund 1991). The extent of its local effect (and possible consequences in view of the difference in PK between Cuprior and the RMP) were explored. A precise quantification of the contribution of intestinal luminal chelation to the efficacy of trientine is not possible due to limitations of the available data. It was concluded that when trientine

is taken separately from food as recommended in the product information, the contribution of intestinal luminal chelation to the efficacy of trientine is limited. Also taking into consideration that the product is titrated to target as outlined in the SmPC potential differences in in food effect/ food interaction between Cuprior and the RMP (due to Cuprior´s faster absorption) would be of small impact and no relevant difference in efficacy or safety due to the dual mechanism of action of trientine is expected.

2.4.6. Conclusions on clinical pharmacology

The applicant provided adequate pharmacological data to support the bridge to the reference product. Higher bioavailability of Cuprior in comparison to the reference product was addressed by calculating a conversion factor and dose reduction; adequate supportive data on dose linearity and applicability of the conversion factor over the whole dose range was provided. Possible differences in food effect and intestinal luminal chelation of copper are note of concern given dose titration in accordance with individual patients' requirements and with regular monitoring of copper levels as outlined in the SmPC.

2.4.7. Clinical efficacy

Alongside supporting literature this application includes data from long-term clinical experience (as compassionate use) from Lariboisière hospital (Paris) presented as a retrospective cohort survey (Lariboisière report). WD patients received TETA 4HCl and/or TETA 2HCl treatment, thus providing data from a clinical comparison of efficacy and safety between the different salts.

The Lariboisière study was a retrospective, single centre, long-term cohort survey. The study was submitted as a pivotal study but can, due to severe shortcomings as regards design, conduct and reporting only be considered supportive evidence

Type of Study	Study Identifier Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Efficacy, safety	[Trientine tetrahydrochloride-LARIB]	Evaluate the comparability of efficacy and safety of TETA 4HCl and TETA	Retrospective study evaluating WD patient data recorded between 15 June	TETA 4HCl capsules containing 150 mg of TETA 4HCl (75 mg of TETA base) manufactured and supplied	43	WD patients	A minimum of 12 months
	5.3.5.4	2HCL in terms of hepatic and neurological clinical outcome, and adverse effects or events leading to discontinuation of therapy	1970 and 01 July 2010 for patients treated with trientine as monotherapy according to standard medical practice through compassionate use, and followed at the Lariboisière hospital	locally by the Agence Générale des Equipements et Produits de Santé TETA 2HCl capsules containing 300 mg of TETA 2HCl (200 mg of TETA base) manufactured and supplied by Univar UK Oral Dosage regimen of TETA 4HCl and TETA 2HCl according to standard medical practice: - usual adult dose is 1500 mg/day TETA 2HCl, given in 2 to 3 divided doses - paediatric dose is 750 - 900 mg/day TETA 2HCl; the paediatric dose generally used is 20 mg/kg/day, given in 2 to 3 divided doses.			

Lariboisière study:

A Retrospective Survey of Clinical Experience with Trientine Tetrahydrochloride Salt and Trientine Dihydrochloride Salt as Therapy for Wilson's Disease

The product used in comparison to TETA 2HCL was a TETA 4HCL capsule formulation, different to Cuprior in pharmaceutical form, strength and composition. Dissolution tests between a TETA 4HCL formulation corresponding to the historical TETA 4HCl formulation used at the Lariboisière's site and Cuprior provided comparable dissolution rates in vitro (conducted at pH 1.2 only).

Forty-three of the overall 248 recorded patients were included in the evaluation; the selection was based on availability of sufficient information and whether patients have been treated continuously for at least 12 months with either product. Of the 43 selected patients 10 received both TETA 4HCl and TETA 2HCl in different treatment sequences (treatment sequences = application > 12 month duration), 2 patients received only TETA 4HCl and 31 patients received only TETA 2HCl.

The study objectives were the observation of hepatic and neurologic symptoms status in response to trientine in WD patients which are adequate in principle.

This study was not blinded. Lower starting- and minimal doses of TETA 4HCL and an imbalance according to phenotype representation at baseline (more patients in the TETA 4HCl group had a neurologic presentation of the disease compared to the TETA 2HCl group (n= 8/13, 62% versus 19/44, 43%, respectively), are noted.

Information on titration patterns (according to clinical response) was not available. Mean dosages used in the Lariboisière study (TETA 4HCL: 634.1+/- 250.5; TETA 2HCL 789.5+/-255.2, for TETA 4HCL were lower than for TETA 2HCL.

Table 2 Summary of efficacy for trial Lariboisière retrospective survey

Title: Lariboisière retrospective survey		
Study identifier	NA	
Design	A Retrospective Survey [from hospital records] Of Clinical Experience with Trientine Tetrahydrochloride Salt (TETA 4HCL) and Trientine Dihydrochloride Salt (TETA 2HCL) As Therapy For Wilson's Disease	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	June 15, 1970 and July 01, 2010 not applicable not applicable
Hypothesis	There was no formal hypothesis. The survey was of WD patients treated at a single centre in Paris (Hôpital Lariboisière) who had had at least 12 months monotherapy with TETA 4HCL and/or TETA 2HCL	
Treatments groups	43 of 248 WD patients at the Hôpital Lariboisière satisfied the selection criteria.	See below
	TETA 4HCL	13 treatment sequences with median duration of 138.9 months (range 22.8 to 391.4)

	TETA 2HCL		44 treatment sequences with median duration of 78.9 months (range 12.9 to 254.3)
Endpoints and definitions	Co-Primary endpoint	NA	Treating clinicians' rating of hepatic and neurological WD symptoms as improved/unchanged/worse
Database lock	The survey was conducted from February to August 2014		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Patients having monotherapy of at least 12 months trientine salt were eligible – the data are analysed by treatment sequences not by patient numbers. Patients could and did swap treatments so the number of sequences exceeds the number of patients.			
Dosage	The doses of trientine base given at initiation of each evaluable treatment sequence were variable. The mean total daily dose of TETA 4HCl was 634.1 ± 250.5 mg and the mean total daily dose of TETA 2HCl was 789.5 ± 255.2 mg.			
Descriptive statistics and estimate variability	Treatment group	TETA 4HCL	TETA 2HCL	NA
		n = 13	n = 44	
	Hepatic symptoms	Improved = 3 (23.1%) Unchanged = 10 (76.9%) Worse = 0	Improved = 13 (29.6%) Unchanged = 29 (65.9%) Worse = 2 (4.5%)	
	Neurological symptoms	Improved = 4 (30.8%) Unchanged = 9 (69.3%) Worse = 0	Improved = 12 (27.3%) Unchanged = 31 (70.5%) Worse = 1 (2.3%)	
Effect estimate per comparison	Co-Primary endpoint clinical safety	TETA 4HCL	TETA 2HCL	
		No patients were considered to have had treatment related AEs or SAEs	No patients were considered to have had treatment related AEs or SAEs	
		No patient died	Two patients died one of cancer and one by suicide.	
Analysis description	No formal comparative analysis was made.			

Symptoms

The evolution of hepatic and neurologic symptoms was assessed by specialist physicians from Lariboisière hospital. At the end of the treatment sequences (regardless of presence of hepatic and/or neurologic symptoms at the start of the sequence) hepatic symptoms were assessed as "Improved" or "Unchanged" in 100% of TETA 4HCl treatment sequences compared to 95.46% of TETA 2HCl sequences. Neurologic symptoms were assessed as "Improved" or "Unchanged" in 100% of TETA 4HCl sequences compared to 97.73% of TETA 2HCl sequences.

Kayser Fleischer Rings

The evolution of Kayser Fleischer rings was also scored as “Increase”, “Diminution”, “Disappearance”, or “Unchanged” at the end of the treatment sequence. Kayser Fleischer ring evolution was comparable across the two trientine salts. During one TETA 4HCl sequence, a slight increase of the ring was reported, without deterioration of neurological or hepatic symptoms. During one TETA 2HCl sequence the rings were unchanged. During all other treatment sequences the rings disappeared or decreased. No new rings were observed in treatment sequences where they were absent at baseline.

Biological Parameters

Routine liver function tests, and copper levels are summarised below. There were no clinically meaningful changes in other biological parameters during the trientine treatment sequences.

Liver Function Tests

Parameters related to liver function, in particular AST and ALT, tended to improve in both the TETA 4HCl and TETA 2HCl treatment sequences. There were no statistically significant differences between the TETA 4HCl and TETA 2HCl treatment sequences in hepatic function tests (transaminases, GGT) ($p > 0.05$).

Copper Levels

There were no meaningful differences for copper levels at baseline between the treatment groups. Overall serum copper levels and urine copper excretion tended to remain stable or decrease from the beginning to the end of the trientine treatment sequences in both treatment groups. This is consistent with the use of trientine to effectively manage copper levels in patients the majority of whom were taking trientine as a second or third line treatment. In subjects where data were recorded, there were no statistically significant difference between the TETA 4HCl and TETA 2HCl treatment sequences in serum copper levels or urinary copper excretion. In addition, there were no significant differences in ceruloplasmin levels ($p > 0.05$).

Table 3 Laboratory variables related to copper levels and excretion by trientine treatment

	TETA 4HCL – start	**TETA 4HCL – end**	**TETA 2HCL – start**	**TETA 2HCL - end**
Serum copper (µmol/L)				
	N = 8	N = 7	N = 22	N = 39
Mean (s.d.)	3.1 (2.1)	3.5 (2.3)	6.0 (7.1)	4.8 (5.4)
Urine copper excretion (µmol/24h)				
	N = 6	N = 4	N = 13	N = 15
Mean (s.d.)	9.4 (7.5)	3.7 (0.9)	4.4 (6.1)	4.0 (4.0)
Urine copper (µmol/L)				
	N = 6	N = 6	N = 22	N = 39
Mean (s.d)	5.5 (5.6)	3.9 (2.9)	6.4 (10.8)	5.0 (5.6)
Ceruloplasmin (g/L)				
	N = 6	N = 7	N = 21	N = 37

Mean (s.d)	0.04 (0.03)	0.07 (0.06)	0.3 (1.1)	0.1 (0.2)
Compiled from Study Report Tables 20 and 21 N = number of individuals contributing data.				

Literature data:

Literature data were provided and compared to the data from the Lariboisière study to confirm results on efficacy and safety. Five comparative studies have been identified from the literature 3 were considered of particular relevance for efficacy by the applicant (Walshe 1973; Brewer, Askari et al. 2006; Weiss, Thurik et al. 2013).

TETA 2HCL was used in most cases (exception: Suda et al. (1993) who reported beneficial effects of TETA 4HCL in the chronic treatment of two adult WD patients using TETA 4HCL.) The exact composition of the products is generally unknown; sometimes the trientine salt was not specified.

2.4.8. Clinical safety

Safety data relating to the application fall into three categories:

1) Applicant generated data from the single dose crossover PK comparability study of TETA 4HCL and TETA 2HCL in healthy volunteers.
2) Applicant commissioned review of the Lariboisière experience
3) Data from the published literature.

Patient exposure

TRIUMPH study

Twenty four subjects received a single 600 mg dose of trientine base as TETA 2HCL capsules and twenty five subjects received a single 600 mg dose of trientine base as TETA 4HCl tablets.

Lariboisière Survey

Data on the use of TETA 2HCl and TETA 4HCl from a compassionate use programme at the Lariboisière Hospital provide a safety comparison between the two salts in normal clinical practice. A retrospective survey evaluated patient data recorded between 1984 and 2010, and identified 43 patients who had received either or both trientine salts in monotherapy for periods of at least 12 months. Cumulatively data from more than 186 patient-years of TETA 4HCl treatment and 326 patient-years of TETA 2HCl treatment were collected.

The population included in the primary safety analysis contained 43 patients who received 57 trientine monotherapy treatment sequences comprised of 13 sequences of TETA 4HCl and 44 sequences of TETA 2HCl.

Published literature

The Applicant cites safety data from five comparative studies, seven non-comparative studies and seventeen case reports considered to be of relevance to the application.

Adverse events

According to historical data Trientine is generally well-tolerated and has a favourable safety profile when compared to D-penicillamine. Cutaneous reactions, iron deficiency due to unwanted chelating of iron and gastrointestinal events are the most frequently reported AEs and this is in accordance with the SmPC of the reference product. Systemic lupus erythematosus is mentioned in the US prescribing information (Syprine) and lupus was also observed in the Lariboisière study in one patient receiving TETA 2HCL. The relation to treatment is unknown and it was only reported for one patient receiving the reference product, therefore it was agreed not to include lupus erythematosus in the list of adverse events but to mention available information in section 4.4 of the SmPC. Lupus erythematosus was also listed as important potential risk in the Risk Management Plan. Worsening of neurologic symptoms was reported in several publications and this was noted in 4.4 of the SmPC. As this could be a concern especially at treatment initiation in patients with high copper loads (treatment naïve patients or soon after treatment initiation) as the large amounts of copper being released from tissues could cause severe symptoms. To balance this risk it was outlined in the posology that the starting dose would usually correspond to the lowest dose in the range and the dose should subsequently be adapted according to the patient's clinical response which was considered acceptable by the CHMP. However, a reliable estimation on nature and frequency of adverse events of TETA 4HCL (or TETA 2HCL) from the literature is not possible.

In the Lariboisière study very few safety events were reported and no event was considered related to treatment; no TEAEs were reported in the Clinical Overview, the Summary of Clinical Safety or the survey report. The main focus of the safety evaluation in this retrospective study was events leading to discontinuation of therapy. Consequently, there is no table listing adverse events for TETA 4HCL or TETA 2HCL treatment including respective dose, time of occurrence within treatment sequence (time to event from the first dose) and outcome of the event. Though it is acknowledged that trientine is generally well tolerated it seems unlikely that no event, such as iron deficiency or gastrointestinal discomfort, occurred during the 512 patient years (186 patient-years with TETA 4HCl and 326 patient-years with TETA 2HCl). The results of the survey are not considered consistent with the established safety profile of trientine for the treatment of WD. The triggers for initiation of hepatic or neurologic assessment are not known. Hepatic assessment seems to have been performed only at initiation and termination of trientine but not during treatment. There are no individual patient reports available to help clarifying these issues. Information on titration patterns for comparison of dosage patterns and the necessity of up- and down-titration of both drugs are not available. The absence of a control group has to be taken into account when interpreting safety results.

According to Suda et al. (1993) 4-hydrochloride is highly acidic and poses a problem in terms of its effect on mucous membrane of the gastrointestinal tract when being administered. However, impaired gastrointestinal tolerance of TETA 4HCL compared to TETA 2HCL could not be shown in the single dose setting in healthy volunteers (TRIUMPH), or multiple dose settings such as the Lariboisière study or any other historical source.

Serious adverse event / deaths / other significant events

<u>Lariboisière study</u>

Deaths:

There were two deaths during the trientine treatment sequences, both occurring in the TETA 2HCl group. The cause of death was salivary gland cancer in one patient and suicide in the other patient who had neurological WD for over 30 years. Neither was considered by the treating physician to be related to treatment with trientine.

Other serious or significant adverse events:

One *TETA 4HCl* treatment sequences was stopped due to re-occurrence of Kayser-Fleisher ring (without neurologic or hepatic deterioration).

In the *TETA 2HCl* group the following severe AEs (all leading to discontinuation of treatment) were recorded:

- two neurologic deteriorations associated with WD, which led to the addition of zinc therapy;
- One case each of:
    - increase of liver copper level without neurologic or hepatic deterioration, which led to the addition of zinc therapy;
    - lupus in a patient who had previous lupus after D-penicillamine use, which led to the replacement of TETA 2HCl by zinc treatment (see below for further details);
    - hepatic transplantation due to suspicion of hepatocarcinoma, which led to TETA 2HCl discontinuation.

The case of lupus was reported in a patient treated with TETA 2HCl who had previous lupus during their prior D-penicillamine treatment. This female patient was diagnosed with neurological WD and cirrhosis at the age of 22 years. She was treated with D-penicillamine for 5 years but treatment was stopped due to the development of lupus. She then received TETA 2HCl for nearly 11 years, with improvement of her neurologic symptoms. However, the lupus returned and TETA 2HCl was replaced by zinc treatment.

Summary from the Literature

In Weiss, Thurik et al. 2013, gastric complaints (nausea, gastric pain) was recorded in two patients (1.4%) and arthralgia in four patients (2.8%). In addition one patient (0.7%) each discontinued TETA 2HCl treatment due to pruritus, myalgia, nephropathy, leucopoenia, increase of ANA antibodies, erythema, lupus erythematosus and hirsutism, although in some cases these events were a recurrence of events seen with previous D-penicillamine treatment. In Mercier- Jacquier, et al 2011, trientine was discontinued in 1 of 6 patients due to sideroblatic anaemia. In the Taylor, Chen et al. 2009 paediatric study, TETA 2HCl treatment was stopped in 3 of 16 children due to allergic rash, low copper excretion and compliance problems requiring transplantation.

In Brewer, Askari et al. 2006, 3 deaths were reported among the 23 WD patients with neurologic disease in the TETA 2HCl arm, of whom 3 were patients who deteriorated neurologically while receiving TETA 2HCl therapy. No death related to trientine treatment was reported in the other published studies. In Dahlman, Hartvig et al. 1995, 3 of the 19 patients who received long-term TETA 2HCl treatment died: 2 patients from a multifocal cancer including the liver and 1 noncompliant patient from a ruptured spleen.

The published literature cited by the Applicant contains many patient deaths generally due to progression of WD and often associated with non-compliance with treatment. The details provided do not allow the evaluation of the possible contribution of treatment to patient death.

TRIUMPH study

No deaths or serious AEs were reported.

Laboratory findings

Lariboisière study

Clinical laboratory evaluations seem to have been performed only at the start of each treatment sequence and when a treatment sequence was stopped and only in some patients. This makes the interpretation of development of parameters over time difficult. Clinical laboratory evaluations, in particular ALT, AST, GGT, PR, platelets and total and conjugated bilirubin, were collected in 1-8 patients in the TETA 4HCL group. There are noticeable differences in certain laboratory parameters when comparing the TETA 4HCL and the TETA 2HCL treatment groups. Diverging development of some parameters, e.g. platelet count, conjugated bilirubin or GGT, are reported and could be interpreted as deteriorating effect of one product compared to the other. No further explanation/clarification is provided by the applicant. Baseline values of biological parameters seem balanced between the TETA 4HCL and the TETA 2HCL groups and are unlikely to have triggered the observed differences. However, only very few patients have undergone laboratory assessment and the sample size is too small to reliably conclude on any effect. Standard deviations are very large for certain parameters.

TRIUMPH study

In the TRIUMPH study there were no notable changes in laboratory parameters in either treatment group, and no patients had AEs related to laboratory tests. There seems to be no data/literature available comparing laboratory parameters of TETA 4HCL and TETA 2HCL in any population.

Summary from the literature

Laboratory results were not systematically reported in the literature, and the primary source of information on clinically significant laboratory abnormalities in the studies is those reported as AEs. Non adherence to treatment is a common cause of increased transaminase levels in patients with WD. This has been reported in several studies with trientine (Arnon, Calderon et al. 2007). Pancytopenia has rarely been reported (Roberts, Schilsy et al 2008). During the eight weeks of drug therapy of Brewer, Askari et al. 2006 study, one of the twenty-three patients (4.3%) in the TETA 2HCl arm reached criteria for anaemia and/or leukopenia. Overall, published studies did not report significant changes on laboratory parameters.

None of the sources can be considered an authoritative source of data on laboratory variables as indicators of treatment related AEs.

Safety in special populations

Literature data

Data on the safety of trientine are available from many regions worldwide, without an indication of a potential difference in safety. In addition, one study specifically reported the use of trientine in 3 Japanese patients with WD and associated neurological symptoms who were intolerant to D-penicillamine. TETA 2HCl was administered in 1 patient and TETA 4HCl in 2 patients for 7 to 9 years (then switched to TETA 2 HCl) with no AEs (Suda et al. 1993).

In general most of the studied populations in the literature (on TETA 2HCL) contained diabetic patients, paediatric patients, elderly patients, and patients with renal and hepatic impairment, and did not report any differences in safety.

Some additional publications specifically reported the use of TETA 2HCl or an unspecified trientine salt in paediatric patients with WD (Arnon, Calderon et al. 2007; Taylor, Chen et al. 2009; Kleine, Mendes et al. 2012; Lingam, Wilson et al. 1987; Santos Silva, Sarles et al. 1996), in elderly patients with WD (Ala et al. 2005), and in WD patients with nephroses following D-penicillamine therapy (Merle, Schaefer et al. 2007; Dubois, Rodgerson et al 1990; Siafakas, Jonas et al 1998). No differences in safety were seen in any subgroups.

The Applicant cites on publications pregnancy in WD patients.

Most of the literature data seems to have been collected with TETA 2HCL capsules.

Lariboisière survey

Paediatric patients were included in the Lariboisière study and are mentioned in many historical literature reports on trientine. As for the evaluation of efficacy, few specific clinical data are available for the assessment of safety of Cupior tablets or other TETA 4HCL formulations or trientine in general, also in the paediatric population. Most historical data were generated with TETA 2HCL.

Published literature

According to the available literature no difference in the safety profile of TETA 2HCL between adults and children is expected. Paediatric patients were generally treated with lower doses than adults and this is proposed also for Cuprior. Though safety reporting on trientine products seems to have been conducted poorly, the risk of not treating Wilson's disease is evident and outweighs concerns on robustness of historical data. Trientine has been used in the paediatric population for decades and there was no indication found to assume a higher risk compared to adults. Therefore the use of trientine in the paediatric population as second line treatment in patients intolerant to D-penicillamine, which has a worse safety profile than trientine, is generally supported. The reference product is approved for the treatment of children and adolescents and applicability of the safety profile also for Cuprior is accepted.

Immunological events

Information from the submitted literature is rare, the only report found were immunogenicity was investigated (Weiss 2013) indicates a good immunogenetic profile of TETA 2HCL as compared to D-penicillamine. However, no data for TETA 4HCL is available. Immunogenicity assessment was not performed in the TRIUMPH study. Trientine is not a noted allergen or an immunosuppressant so treatment related immunological effects are not expected.

Safety related to drug-drug interactions and other interactions

The proposed TETA 4HCl scored tablet should be swallowed whole with water and it is important that it is taken on an empty stomach, preferably 30 minutes to one hour before meals. This permits maximum absorption and reduces the likelihood of inactivation of the drug by metal binding in the gastrointestinal tract (AGEPS 1995).

Trientine chelates iron and has been found to reduce serum iron levels, possibly by reducing its absorption; iron deficiency is a recognised side effect of trientine treatment, hence iron supplements may be required. Since iron and trientine may inhibit absorption of each other, iron supplements should be taken only once at least two hours have elapsed from the administration of TETA 4HCl. As patients treated with trientine may develop symptoms of iron deficiency, patients (especially women) should be monitored for evidence of iron deficiency anaemia.

Trientine has also been shown to chelate zinc in vitro (Kodama, Murata et al. 1997) and to increase zinc excretion in the urine of patients (Lu, Chan et al. 2007). Therefore an interaction with zinc, particularly if given at the same time, cannot be excluded. Possible interaction with zinc is of interest as Zn is another common therapy option for patients with WD. Zinc salts decrease intestinal absorption of copper and induce cellular metallothioneins. A respective warning on possible interactions was added in the PI. Though both treatments are usually recommended as monotherapy, a combination in clinical practice might occur and combined treatment regimens are reported in the literature (Brewer 2006, Kalita 2014, Arnon 2007, Kleine 2012, Ala 2005).

In general mineral supplements should not be given together with trientine. Although there is no evidence that calcium or magnesium antacids alter the efficacy of trientine, it is good practice to separate their administration, as stated in the SmPC.

Discontinuation due to adverse events

In the Lariboisière study more discontinuations due to AEs were seen in TETA 2HCL patients compared to TETA 4HCl patients, probably because treatment sequences were longer and more patients were included. The AEs causing discontinuation were not considered related to treatment.

The literature studies on the use of TETA 2HCl in patients with WD report few discontinuation due to AEs. In Weiss, Thurik et al. 2013, gastric complaints (nausea, gastric pain) led to discontinuation in 2 patients (1.4%) and arthralgia in 4 patients (2.8%). In addition one patient (0.7%) each discontinued TETA 2HCl treatment due to pruritus, myalgia, nephropathy, leucopoenia, increase of ANA antibodies, erythema, lupus erythematosus and hirsutism, although in some cases these events were a recurrence of events seen with previous D-penicillamine treatment. In Mercier- Jacquier, et al 2011, trientine was discontinued in 1 of 6 patients due to sideroblatic anaemia. In the Taylor, Chen et al. 2009 paediatric study, TETA 2HCl treatment was discontinued in 3 of 16 children due to allergic rash, low copper excretion and compliance problems requiring transplantation.

TRIUMPH study

No discontinuation from the trial due to AEs was reported.

2.4.9. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.10. Discussion on clinical aspects

Clinical benefit is predominantly based on the PK bridging to the reference product and historical data with trientine in the TETA 2HCL form.

TETA 4HCL was administered to a cohort of patients in a retrospective survey from one French WD reference centre (the Lariboisière survey); the formulation used (TETA 4HCL capsules) was not identical to the composition of Cuprior.

13 sequences of TETA 4HCl and 44 sequences of TETA 2HCl treatment were observed. The overall amount of subjects, especially in the TETA 4HCL “alone” group, is considered small. However, patients were followed for long periods; thus, the patient year exposure is more extensive. Only two patients received exclusively TETA 4HCL, therefore, also taking into account the high inter- and intra-subject variability for trientine, specific characteristics of TETA 4HCL might not be sufficiently evaluable from this very small sample. In the open label

situation also the potential for bias exists, in particular related to operational bias (e.g. influence on trial conduct/differential follow up of patients) and biased safety/tolerability assessment on the subject's as well as on the investigator's side.

No detailed information on dose titration patterns, allocation to treatment and triggers for laboratory assessment are available. No documents describe plans for reporting and analyses of the retrospectively collected data were provided and reporting on efficacy parameters is fragmentary (evaluation was only performed at the beginning and the end of a treatment sequence). Reported biological parameters are very limited, laboratory analyses were available only for a subset of patients. The nature of concomitant medication is unknown, the diagnosis of Wilson's disease does not seem to have been done on the basis of standardised methods and estimates for efficacy and safety variables may not be representative of the entire WD patient population.

Dissolution tests between a TETA 4HCL formulation corresponding to the historical TETA 4HCl formulation used at the Lariboisière's site and Cuprior provided comparable dissolution rates in vitro (conducted at pH 1.2 only). Bioequivalence between both products has, however, not been established and differences in excipients could be relevant for in vivo performance.

No notable differences in efficacy and safety were detected when comparing TETA 4HCl and TETA 2HCl treatment sequences for changes in hepatic or neurological symptoms, biological markers such as serum and urine copper or Kayser Fleischer rings. Subgroup analyses did not show meaningful differences in first or second line treatment of trientine, by initial presenting symptom, or when assessing only initial exposure to trientine.

However, the results are to be interpreted in the view of the multiple limitations as outlined above. It should furthermore be noted that any interpretation of non-significant test results as conclusion of 'no difference' between treatments cannot be drawn in a statistical sense.

Overall the level of evidence is low and the study is considered of minor relevance due to deficiencies in trial design and as the formulation used (TETA 4HCL capsules) was not identical to the composition of Cuprior. Still, taking into consideration that no WD patient had been treated with Cuprior in the course of the clinical development it provides some additional assurance on clinical safety and efficacy for TETA-4HCL.

Trrientine in clinical practice has a well-established safety profile and the bridging to the reference product which contains the same active moiety is based on pharmacokinetic evaluation. There is an adequate amount of literature and historical data on the use of trientine in WD patients as the originator is marketed for more than 30 years. Its tolerability is widely recognised. Though the patients are often poorly documented, the exposure periods are very long. Severe TEAEs are hardly reported.

The following adverse drug reactions (ADRs) are included in the SmPC of the reference product for WD. The frequency of reporting of these events is not known and cannot be estimated from the available data: nausea on initial treatment, skin rash, duodenitis, severe colitis, anaemia. Due to the rarity of the disease an estimate of frequency of the ADRs is difficult to establish. The ability to detect ADRs (i.e. which are rare, which have a long latency, due to prolonged latency, due to cumulative effects) in the Lariboisière retrospective study has been limited as only 43 patients (TETA 4HCl=2, TETA 2HCl= 31, both=10) were exposed to trientine in the study. The data on unwanted events are not capable of being categorised as non-serious or serious in the regulatory sense.

A conclusion on the comparability of tolerability of TETA 4HCl from the Lariboisière study with data from the literature and Univar's SmPC cannot be drawn as no reasonable safety reporting was done for the Lariboisière study. The proposed SmPC Section 4.8 is based on that of the reference product, however, in depth assessment

of AE reporting in the literature lead to an update of this section for Cuprior. Pruritus, erythema and urticarial were included in the tabulated list of AEs and complemented by frequency, whenever possible.

The Lariboisière report shows no reasonable standard of safety reporting, no TEAEs were reported at all and none of the few AEs reported was considered related to treatment. No patient record files are available for in-depth assessment. Furthermore the formulation of TETA 4HCL used in this study considerably differs from the formulation of Cuprior, using different excipients and pharmaceutical form. The evidence level is considered comparable to the literature data. In the submitted literature the composition of the products used is often unknown (excipients), sometimes the trientine salt is not specified. However, TETA 2HCL seem to be the prevailing product used. However, once trientine base is in the systemic circulation, there is no rationale to expect a difference between trientine salts in the way trientine is distributed, metabolised or excreted as the absorbed parent compound and active moiety, trientine base, is identical.

The summary of the literature with regard to clinical data of Trientine together with the Lariboisière report and justification was considered by the CHMP sufficient evidence that the different salt of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product and no additional clinical studies were considered necessary. For impact of difference in formulation please refer to pharmacological part of this assessment and Benefit / Risk section further below.

2.4.11. Conclusions on clinical aspects

No new data with Cuprior in the treatment of Wilson's disease have been generated for this MAA. Overall, historical data support a good safety profile of trientine in patients with Wilson's disease. The Lariboisière study provides some supportive evidence on safety and efficacy of TETA 4HCL even though in a different formulation. Taking into consideration that both salts share the same active moiety the summary of the literature with regard to clinical data of Trientine together with the Lariboisière report was considered by the CHMP sufficient evidence that the different salt of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product and no additional clinical studies were considered necessary. The demonstration of efficacy and safety therefore relies on bridging to the established efficacy and safety of the reference product based on the two pharmacokinetic studies TRIUMPH and TRIUMPH-2. Relevant chapters of the SmPC have been updated based on literature provided to reflect up to date clinical knowledge.

2.5. Pharmacovigilance

Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Iron deficiency anaemia Copper deficiency Colitis (including severe colitis) Exacerbation of WD symptoms and signs on starting treatment
Important potential risks	Lupus erythematosus syndrome/disease Rash

Summary of safety concerns	
Missing information	Treatment in patients with renal impairment, hepatic impairment/cirrhosis Management/outcome of pregnancy Use during lactation Co-administration with other WD treatments.

Pharmacovigilance plan

Not applicable, the applicant did not propose any additional pharmacovigilance activities.

Risk minimisation measures

Safety concerns	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk		
Iron deficiency anaemia	**SmPC** **PIL** **Legal status** The prescription of this medicine is subject to prescribing restrictions; Treatment with TETA 4HCl should only be initiated by specialist physicians with experience in the management of WD. Patients receiving TETA 4HCl should remain under regular medical supervision and monitored for appropriate control of plasma copper levels per established clinical practice.	None proposed
Copper deficiency	**SmPC** **PIL** **Legal status** The prescription of this medicine is subject to prescribing restrictions; Treatment with TETA 4HCl should only be initiated by specialist physicians with experience in the management of WD. Patients receiving TETA 4HCl should remain under regular medical supervision and monitored for appropriate control of plasma copper levels per established clinical practice.	None proposed
Colitis (including severe colitis)	**SmPC** **PIL** **Legal status**	None proposed

Safety concerns	Routine risk minimisation measures	Additional risk minimisation measures
	The prescription of this medicine is subject to prescribing restrictions; Treatment with TETA 4HCl should only be initiated by specialist physicians with experience in the management of WD. Patients receiving TETA 4HCl should remain under regular medical supervision and monitored for appropriate control of plasma copper levels per established clinical practice	
Exacerbation of WD symptoms and signs on starting treatment	**SmPC** **PIL** **Legal status** The prescription of this medicine is subject to prescribing restrictions; Treatment with TETA 4HCl should only be initiated by specialist physicians with experience in the management of WD. Patients receiving TETA 4HCl should remain under regular medical supervision and monitored for appropriate control of plasma copper levels per established clinical practice.	None proposed
Important potential risks		
Lupus erythematosus syndrome/disease	**SmPC** **PIL** **Legal status** The prescription of this medicine is subject to prescribing restrictions; Treatment with TETA 4HCl should only be initiated by specialist physicians with experience in the management of WD. Patients receiving TETA 4HCl should remain under regular medical supervision and monitored for appropriate control of plasma copper levels per established clinical practice.	None proposed
Missing information		
Management/outcome of pregnancy	**SmPC** **PIL** **Legal status** The prescription of this medicine is subject to prescribing restrictions; Treatment with TETA 4HCl should only be initiated by specialist physicians with experience in the management of WD. Patients receiving TETA 4HCl should remain under regular medical supervision and monitored for appropriate control of plasma copper levels per	None proposed

Safety concerns	Routine risk minimisation measures	Additional risk minimisation measures
	established clinical practice.	
Use during lactation	**SmPC** **PIL** **Legal status** The prescription of this medicine is subject to prescribing restrictions; Treatment with TETA 4HCl should only be initiated by specialist physicians with experience in the management of WD. Patients receiving TETA 4HCl should remain under regular medical supervision and monitored for appropriate control of plasma copper levels per established clinical practice.	None proposed
Use in children aged below 5 years	**SmPC** **PIL** **Legal status** The prescription of this medicine is subject to prescribing restrictions; Treatment with TETA 4HCl should only be initiated by specialist physicians with experience in the management of WD. Patients receiving TETA 4HCl should remain under regular medical supervision and monitored for appropriate control of plasma copper levels per established clinical practice.	None proposed
Treatment in patients with renal impairment	**SmPC** **PIL** **Legal status** The prescription of this medicine is subject to prescribing restrictions; Treatment with TETA 4HCl should only be initiated by specialist physicians with experience in the management of WD. Patients receiving TETA 4HCl should remain under regular medical supervision and monitored for appropriate control of plasma copper levels per established clinical practice.	None proposed
Co-administration with other WD treatments	**SmPC** **PIL** **Legal status** The prescription of this medicine is subject to prescribing restrictions; Treatment with TETA 4HCl should only be initiated by specialist physicians with experience in the management of WD. Patients receiving TETA 4HCl should remain under regular medical supervision	None proposed

Safety concerns	Routine risk minimisation measures	Additional risk minimisation measures
	and monitored for appropriate control of plasma copper levels per established clinical practice.	

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.5 is acceptable.

Discussion on safety specification

Trientine is a well-established treatment for WD in all patient populations (Roberts and Schilsky 2008). The available information in the literature covers a broad spectrum of patients reflective of the use of trientine in the clinical setting. This includes paediatric and elderly patients, as well as patients from many geographic regions. The retrospective Lariboisière Survey included patients diagnosed with WD representative of the wider WD patient population, although the non-inclusion of patients receiving trientine with concurrent zinc therapy may have excluded patients with more severe disease. The 43 patients included in the analysis, included 11 paediatric patients, of whom three were less than 12 years old. The small number of published reports of pregnancies in patients treated with trientine indicates that trientine continues to be effective during pregnancy.

Since its first use in 1969, a number of case reports and cohort studies of WD patients treated with TETA 2HCl have been published. TETA 2HCl 300 mg capsules have been approved in the UK for the treatment of WD in patients intolerant to D-Penicillamine since 1985 and are still marketed. Therefore, there is already an extensive use of trientine for the treatment of WD and extensive exposure to the active substance. The number of patients reported to be exposed to trientine (mainly TETA 2HCl) in the literature exceeds 300 patients who were treated for WD.

Conclusions on the safety specification

Having considered the data in the safety specification the CHMP agrees that the safety concerns listed by the applicant are appropriate.

Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

2.6. Product information

2.6.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns trientine tetrahydrochloride tablets (TETA 4HCL) submitted as a hybrid to the reference product Univar's trientine dihydrochloride (TETA 2HCl) capsules indicated for the treatment of Wilson's Disease in patients intolerant to D-penicillamine. The active moiety of Cuprior, trientine, is known to reliably decrease serum copper levels in patients with Wilson's disease. Trientine been in therapeutic use for more than 30 years is recommended in published treatment guidelines mainly as a second line treatment to D-penicillamine.

To date, only one nationally registered trientine preparation (UK, Univar's TETA 2HCL, the reference product in this MAA) is available in the European community.

Cuprior contains trientine in a new formulation, a TETA 4HCL salt, stable at room temperature and therefore not requiring refrigerated storage (unlike the reference product).

Non-clinical studies and testing have been provided for this application, mostly based on published literature, and are considered sufficient. From a clinical perspective, this application contains new data on the pharmacokinetics as well as on the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

To bridge between the reference product Univar's Trientine dihydrochloride and Cuprior two phase I single dose studies TRIUMPH and TRIUMPH-2 in healthy subjects were submitted to evaluate the PK parameters. The TRIUMPH study compared Cuprior to the EU reference product and forms the pivotal basis of this application. The TRIUMPH-2 study contributed supportive evidence on the dose linearity of the product.

A third study "the Lariboisière study" was a commissioned review of the use of monotherapy of trientine tetrahydrochloride and trientine dihydrochloride in a single centre in Paris. This study is considered of minor relevance due to deficiencies in trial design and as the formulation used (TETA 4HCL capsules) was not identical to the composition of Cuprior. Still, taking into consideration that no WD patient had been treated with Cuprior in the course of the clinical development it provides some additional assurance on clinical safety and efficacy for TETA-4HCL.

TRIUMPH was a single dose (600mg trientine base), randomised, open-label, two-way cross over PK study in healthy volunteers (n=26). The study design was considered adequate to evaluate the relative bioavailability of both formulations and was in line with the respective European requirements. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The study demonstrated higher bioavailability of Cuprior than the EU reference product, Univar (TETA 2HCL). The geometric mean ratios of the trientine plasma levels for two formulations (TETA 4HCl/TETA 2HCl) were 168%, 157% and 156%, for Cmax, AUC0-t and AUC0-inf, respectively. Based on the higher bioavailability of Cuprior which appear to be due to differences in dissolution (as evaluated in vitro) the applicant proposed a dose adjustment factor assuming that approximately 60% of TETA 4HCl relative to TETA 2HCl needs to be

administered to provide the same trientine base exposure.

TRIUMPH-2 was a randomised four-way crossover study (showing bioequivalence to the US licensed Syprine). Cuprior was administered as single doses of 3 tablets and 5 tablets (150 mg trientine base per tablet) total 450 mg and 750 mg.

The single dose PK data for three different doses of Cuprior support dose linearity across the dosage range expected to be used in the treatment of Wilson's Disease supporting that a dose conversion factor between Cuprior and the EU reference can be established and applied. Also further literature was provided supporting that the intestinal absorption (Cmax and AUC) of trientine dihydrochloride and tertahydrochloride salts increase in a dose linear manner (Cho et al, 2009) and it would be unreasonable to assume that Cuprior differs in some way to other TETA 2HCL salts.

The individualisation of dosing with regular monitoring of copper levels once Cuprior therapy is initiated and subsequent adjustment of dose, as necessary, also ensure the dosing of Cuprior is in accordance with individual patients' requirements. Such an individual 'treat to target' approach is required in the management of Wilson's disease, regardless of trientine formulation, in view of the high intra- and inter-subject variability for trientine absorption and the variability and evolution in the clinical presentation.

The systemic action of trientine has been shown in many investigations, where it has proven to significantly increase urinary copper excretion. Due to this quality it is authorised and used since decades in WD. Clinical management of WD patients focusses on controlling the systemic levels of copper (in blood and excreted in the urine). Whereas a precise quantification of the contribution of intestinal luminal chelation to the efficacy of trientine is not possible the contribution of intestinal luminal chelation to the efficacy of trientine is considered limited. Also taking into consideration that the product is titrated to target as outlined in the SmPC potential differences in in food effect/ food interaction between Cuprior and the RMP (due to Cuprior´s faster absorption) would be of small impact and no further difference in efficacy or safety due to the dual mechanism of action of trientine is expected.

The food effect of Cuprior as compared with the reference product has not been studied. For the reference product, the food effect is believed to play a role in clinical practice, considering the rather slow absorption of active moiety from the gut (T_{max} 3 hours) and the relatively conservative PI recommendations. Intake of Univar's trientine within 30 min to 1h before food could result in a limited absorption and limited systemic exposure compared to Cuprior, where dissolution and absorption occur more quickly (T_{max} 2 hours). Although the difference might even be enhanced by the "stricter" food recommendation proposed for Cuprior compared to the reference product, on the other hand this would lead to a more predictable and consistent systemic exposure. However, the product is titrated to target and individual variations are expected to be high and may have a larger impact on the systemic level of the drug. Therefore small differences in food effect between products are not being considered of clinical relevance. Relevant uncertainties such as the lack of a food effect study are appropriately outlined in 4.5 of the SmPC.

Trientine may initially elevate serum copper levels, particularly during the start of treatment during the 'de-coppering phase' excess copper being released from tissues into the blood could cause or aggravate neurological or hepatic symptoms which, theoretically, might be more pronounced with the more rapidly bioavailable trientine formulation. Precautionary statements in the SmPC, when initiating treatment with Cuprior outline that the lowest dose in the dosing range should be administered and that patients receiving Cuprior should remain under regular medical supervision and be monitored for appropriate control of symptoms and copper levels in order to optimise the dose.

Furthermore the starting dose in paediatrics is lower than for adults and depends on age and body weight which is acceptable. Also, as trientine is titrated to target and Cuprior is actually not intended as first line treatment for initial de-coppering, a possible overestimation of the starting dose (resulting in an underexposure, lower limit of AUC range 80.94%) is not considered to have large relevant impact on the patient's clinical status.

Children are included into the label of the reference product however it is agreed with the applicant that the tablet formulation is not appropriate for the use in children <5 years of age (EMEA/CHMP/PEG/194810/2005) as outlined in the SmPC.

In summary the bridge to the reference product, Univar´s TETA 2HCL, relies on PK data, which show higher bioavailability of Cuprior by approx. 60%. This is addressed by dose adjustment. The proposed (reduced) dose was never tested clinically but taking into consideration that dose linearity has been shown to a sufficient extent and as clinical use is based on monitoring and titration the impact of inter-formulation differences on efficacy and safety can be considered sufficiently addressed by routine risk minimisation measures.

A positive benefit/risk ratio can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

3.1. Conclusions

The overall B/R of Cuprior is positive.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Cuprior is favourable in the following indication:

Cuprior is indicated for the treatment of Wilson's disease in adults, adolescents and children ≥ 5 years intolerant to D-penicillamine therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

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 European Medicines Agency;
- 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.