Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Trientine 167 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains trientinum 167 mg, which is equivalent to trientini dihydrochloridum 250 mg.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsules
Brown opaque hard gelatin size 1 capsule imprinted with "HP551" in black ink on the capsule body and cap, filled with white to pale yellow powder. Capsule length is between 18.9 mm and 19.7 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of Wilson's disease in patients intolerant of D-Penicillamine therapy, in adults, adolescents and children aged 5 years or older.

4.2 Posology and method of administration

Treatment should only be initiated by specialist physicians with experience in the management of Wilson's disease.

Posology
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 (see section 4.4).

Adults (including elderly):
The recommended dose is 670-1340 mg of trientine base (4-8 capsules) daily in 2 to 4 divided doses. The recommended doses are expressed as mg of the trientine base (i.e. not in mg of the trientine dihydrochloride salt) (see section 4.4).

Special populations
Elderly
No dose adjustment is required in elderly patients.

Renal impairment
There is limited information in patients with renal impairment. No specific dose adjustment is required in these patients (see section 4.4).

Hepatic impairment
There is no data available for the use of trientine in patients with impaired liver function. However, monitoring may be necessary to avoid either toxicity or inefficacy (see section 4.4).

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

Children ≥ 5 years
The weight-based dose is not established, but the initial dose generally used is 20 mg/kg/day (as trientine dihydrochloride) rounded off to the nearest capsule given in 2 to 4 divided doses. The recommended daily dose is 330-840 mg of trientine base (2-5 capsules). The maintenance dose is titrated according to clinical response and serum copper level.

Children aged < 5 years
The safety and efficacy of trientine in children aged < 5 years have not been established. No data are available.

Method of administration
For oral use.

The capsules should be swallowed with water. It is important that trientine is given on an empty stomach, at least one hour before meals or two hours after meals and at least one hour apart from any other medicinal product, food, or milk (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

When switching a patient from another formulation of trientine, caution is advised because doses expressed in trientine base may not be equivalent due to differences in bioavailability (see section 4.2).

Trientine is a chelating agent which has been found to reduce serum iron levels. Iron supplements may be necessary in case of iron deficiency anaemia and should be administered at a different time (see section 4.5).

The combination of trientine with zinc is not recommended. There are only limited data on concomitant use available and no specific dose recommendations can be made (see section 4.5).

In patients who were previously treated with D-penicillamine, lupus-like reactions have been reported during subsequent treatment with trientine, however it is not possible to determine if there is a causal relationship with trientine.

Monitoring
Patients receiving trientine should remain under regular medical supervision and be monitored for appropriate control of symptoms and copper levels in order to optimise the dose (see section 4.2).

The aim of maintenance treatment is to maintain free copper levels in the serum within acceptable limits. The most reliable index for monitoring therapy is the determination of serum free copper which is calculated using the difference between the total copper and the ceruloplasmin-bound copper (normal level of free copper in the serum is usually 100 to 150 microgram/L).

The measurement of copper excretion in the urine may be performed during therapy. Since chelation therapy leads to an increase in urinary copper levels, this may/will not give an accurate reflection of the excess copper load in the body but may be a useful measure of treatment compliance.

Worsening of clinical symptoms, including neurological deterioration, may occur at the beginning of chelation therapy due to excess of free serum copper during the initial response to treatment. Close monitoring is required to optimise the dose or to adapt treatment if necessary.

Special populations
Overtreatment carries the risk of copper deficiency. Monitoring for manifestations of overtreatment should be undertaken, particularly when copper requirements may change, such as in pregnancy (see section 4.6) and in children where appropriate control of copper levels are required to ensure proper growth and mental development.

Patients with renal and/or hepatic impairment receiving trientine should remain under regular medical supervision for appropriate control of symptoms and copper levels. Close monitoring of renal and/or liver function is also recommended in these patients (see section 4.2).

Excipients
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free.'

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Trientine has been found to reduce serum iron levels, possibly by reducing its absorption, and iron supplements may be required. Since iron and trientine may inhibit absorption of each other, iron supplements should be taken after at least two hours have elapsed from the administration of trientine.

There are insufficient data to support the concomitant use of trientine with Zinc. The combination of trientine with zinc is not recommended as interaction of zinc with trientine is likely, thereby reducing the effect of both active substances (see section 4.4).

As trientine is poorly absorbed following oral intake and the principal mechanism of action requires its systemic exposure (see section 5.1), it is important that the capsules are taken on empty stomach at least one hour before meals or 2 hours after meals and at least one hour apart from any other medicinal product, food, or milk (see section 4.2). This maximises the absorption of trientine and reduces the likelihood of the medicinal product binding to metals in the gastrointestinal tract. However, no food interaction studies have been performed and so the extent of the food effect on systemic trientine exposure is unknown.

Although there is no evidence that calcium or magnesium antacids alter the efficacy of trientine, it is good practice to separate their administration.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is a limited amount of data from the use of trientine in pregnant women.

Studies in animals have shown reproductive toxicity, which was probably a result of trientine-induced copper deficiency (see section 5.3).

Since copper is required for proper growth and mental development, dose adjustments may be required to ensure that the foetus will not become copper deficient and close monitoring of the patient is essential (see section 4.4).

The product should be used in pregnancy only after careful consideration of the benefits compared with the risks of treatment in the individual patient. Factors which need to be borne in mind include the risks associated with the disease itself, the risk of those alternative treatments which are available and the possible teratogenic effects of trientine.

The pregnancy should be closely monitored in order to detect possible foetal abnormality and to assess maternal serum copper levels throughout the pregnancy.

The dose of trientine used should be adjusted in order to maintain serum copper levels within the normal range. Babies born to mothers being treated with trientine should be monitored for serum copper and ceruloplasmin levels where appropriate.

Breast-feeding
It is unknown whether trientine is excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from trientine therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
It is unknown whether trientine has an effect on human fertility.

4.7 Effects on ability to drive and use machines

Trientine has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reaction with trientine is nausea. Serious iron deficiency anaemia and severe colitis may occur during treatment.

Tabulated list of adverse reactions
The following adverse reactions have been reported with the use of trientine for Wilson's disease.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

System organ class	Adverse reactions
Blood and lymphatic system disorders	*Uncommon: sideroblastic anemia.* *Not known:* iron deficiency anaemia.
Gastrointestinal disorders	*Common:* nausea. *Not known:* duodenitis, colitis (including severe colitis).
Skin and subcutaneous tissue disorder	*Uncommon:* skin rash, pruritus, erythema. *Not known*: urticaria.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Experience with doses higher than the recommended therapeutic dose is limited. In the event of overdose, the patient should be observed, appropriate biochemical analysis performed and symptomatic treatment given. There is no antidote for trientine.

In one reported case an overdose of 30 capsules did not produce any apparent adverse effects. In a second case, a large overdose of trientine (4000 mg trientine dihydrochloride salt; 200 tablets equivalent to 2672 mg of trientine base) resulted in self-limiting dizziness and vomiting with no further clinical sequelae or significant biochemical abnormalities.

Chronic overtreatment can lead to copper deficiency and reversible sideroblastic anaemia. Overtreatment and excess copper removal can be monitored using values of urine copper excretion and of non-ceruloplasmin bound copper. Close monitoring is required to optimise the dose or adapt treatment if necessary (see section 4.4).

A third overdose case with trientine was identified. This case refers to a large overdose of trientine (300 tablets, total dose 60000 mg of trientine dihydrochloride salt, equivalent to 40000 mg of trientine base) resulting in self-limiting dizziness during the first day and nausea and vomiting on day 2. All symptoms were self-limiting and resolved within 48 hours of the overdose. Due to the pharmacological effects of trientine, the patient had a low serum copper level and elevated urinary copper. There were mild biochemical abnormalities (slight decrease in serum zinc and phosphate, slight increase in serum creatinine) that resolved spontaneously and/or with administration of fluids.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, various alimentary tract and metabolism products, ATC code: A16AX12

Mechanism of action
Trientine is a copper-chelating agent which aids the elimination of copper from the body by forming a stable soluble complex that is readily excreted from the kidney. Trientine may also chelate copper in the intestinal tract and so inhibit copper absorption.

5.2 Pharmacokinetic properties

Absorption
Following oral administration at a single dose of 167 mg trientine base (250 mg trientine dihydrochloride salt) of Trientine in healthy subjects, trientine was rapidly absorbed with median T_{max} values of 1.25 hours. The terminal elimination rate (K_{el}) and terminal half-life ($t_{1/2}$) for trientine were 0.10 ± 0.07 h^{-1} and 11.26 ± 7.54 h. The C_{max} was 933.99 ± 345.99 ng/mL and AUC_{0-t} 3771.15 ± 1962.20 hr.ng/mL.

Food: Food intake inhibits absorption shown by reduced C_{max} and decreased area under the curve (AUC).

Distribution
The central and peripheral volumes of distribution are 393 L and 252 L, respectively, which indicates that trientine is widely distributed in the human body, where accumulation in certain tissues is likely to happen.

Biotransformation
Two major metabolites of trientine were detected in human urine, N_1-acetyltriethylenetetramine (MAT) and N_1,N_{10}-diacetyltriethylenetetramine (DAT).

Elimination
Trientine and its metabolites are rapidly excreted in the urine, although low levels of trientine could still be detected in the plasma after 20 hours. Unabsorbed trientine is eliminated through faecal excretion

Linearity/non-linearity
Plasma exposures in humans have shown a linear relationship with oral doses of trientine.

5.3 Preclinical safety data

Preclinical data obtained with trientine have shown adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use as follows:

Repeat dose toxicity
In mice administered in drinking water, trientine displayed increased frequencies of inflammation of the lung interstitium and liver periportal fatty infiltration. Hematopoietic cell proliferation was seen in the spleen of males. Kidney and body weights were reduced in males as was the incidence of renal cytoplasmic vacuolization. The NOAEL was established at approximately 92 mg/kg/day for males and 99 mg/kg/day for females. In rats administered oral trientines doses, up to 600 mg/kg/day for 26 weeks, histopathology revealed a dose-related incidence and severity of focal chronic interstitial pneumonitis accompanied by fibrosis of the alveolar wall. The microscopic changes in lung were considered indicative of a persistent inflammatory reaction or persistent toxic effect on alveolar cells. Taking into account that trientine has irritating properties, it was estimated that the observed chronic interstitial pneumonitis was explained by a cytotoxic effect of trientine upon accumulation into bronchiolar epithelial cells and alveolar pneumocytes. These findings were not reversible. The rat NOAEL was considered 50 mg/kg/day for females, a NOAEL was not established for males.

Dogs receiving oral doses of trientine up to 300 mg/kg/day, showed neurological and/or musculo-skeletal clinical symptoms (abnormal gait, ataxia, weak limbs, body tremors) in repeat-dose toxicity studies, attributed to the copper-depleting activity of trientine. The NOAEL was established at 50 mg/kg/day resulting in safety margins of about 4 in males and 17 in females, towards human therapeutic exposures.

Genotoxicity
Overall, trientine has shown positive effects in *in vitro* genotoxicity studies, including the Ames test and genotoxicity tests in mammalian cells. *In vivo*, trientine was however negative in the mouse micronucleus test.

Reproductive and developmental toxicity
When rodents were fed throughout pregnancy a diet containing trientine, the frequency of resorptions and the frequency of abnormal foetuses at term showed a dose-related increase.These effects are possibly due to trientine-induced copper and zinc deficiency.

Local tolerance
In silico data predict that trientine displays irritating and sensitising properties. Positive results for sensitisation potential in Guinea pig maximisation tests were reported.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Silica colloidal anhydrous(E551)
Stearic acid

Capsule shell
Gelatin
Sodium lauryl sulphate
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)

Printing ink containing
Shellac(E904)
Propylene glycol(E1520)
Potassium hydroxide(E525)
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

White opaque HDPE bottle with a PP child-resistant closure.
Pack size: 100 hard capsules.

Alu-Alu blister packs.
Pack size: 30, 72, 96, 100, 240 and 300 hard Capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Tillomed Pharma GmbH
Mittelstrasse 5/5a
Schonefeld
12529
Germany

8 MARKETING AUTHORISATION NUMBER

PA22720/010/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 6th May 2025

10 DATE OF REVISION OF THE TEXT