SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

TRIENTINE RAZ 250mg

2. Qualitative and quantitative composition

Each hard capsule contains 167 mg trientine, equivalent to 250 mg trientine dihydrochloride.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Capsule, hard.
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.

4. Clinical particulars

4.1 Therapeutic indications

For the treatment of Wilson's disease in patient's 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): 1.0 -2.0 grams (4-8 capsules) daily in 2 to 4 divided doses.
The recommended doses are expressed as grams or mg of the trientine dihydrochloride salt.

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 rounded off to the nearest 250 mg capsule of trientine dihydrochloride given in two – three divided doses. The recommended initial dose of trientine dihydrochloride capsule is usually between 500-1250 mg (2-5 capsules). The maintenance dose is titrated according to clinical response and serum copper level.

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 whole with water.
There is no information about chewing, opening and dispersing the capsule. It is important that trientine is given on an empty stomach, at least one hour before the meals or two hours after the 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 the doses expressed may not be equivalent due to

differences in bioavailability. Dose adjustment may be required (see section 4.2).

Trientine RAZ 250mg is a chelating agent which has been found to reduce serum iron levels. Iron supplements may be necessary in some cases. Concomitant oral iron should be administered at a different time than trientine (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.

There is no evidence that calcium and magnesium antacids alter the efficacy of trientine but it is recommended to separate their administration (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 using all available clinical data for appropriate control of clinical symptoms and copper levels in order to optimise treatment. Frequency of monitoring is recommended to be at least twice a year. More frequent monitoring is advised during the initial phase of treatment and during phases of disease progression or when dose adjustments are made as to be decided by the treating physician (see section 4.2).

The aim of maintenance treatment is to maintain free copper levels in plasma (also known as non-ceruloplasmin plasma copper) and the urinary copper excretion within the acceptable limits.

The determination of serum free copper, 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), can be a useful index for monitoring therapy.

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.

The use of appropriate copper parameter target ranges is described in clinical practice guidelines related to Wilson's disease.

Like with all anti-copper agents, overtreatment carries the risk of copper deficiency, which is especially harmful for children and pregnant women (see section 4.6) since copper is required for proper growth and mental development. Therefore, monitoring for manifestations of overtreatment should be undertaken.

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).

Worsening of neurological symptoms may occur at the beginning of chelation therapy due to excess of free serum copper during the initial response to treatment. It is possible that this effect may be more evident in patients with pre-existing neurological symptoms. It is recommended to monitor patients closely for such signs and symptoms and to consider careful titration to reach the recommended therapeutic dose and to reduce dose when necessary.

Dose adjustments in the trientine dose should be considered in case of signs of reduced efficacy such as (persistent) increase in liver enzymes, and worsening of tremor. When trientine doses are adjusted this should be done in small steps. The trientine dose may also be reduced in case of side effects of trientine, such as gastrointestinal complaints and haematological changes. Trientine doses should be reduced to a more tolerable dose and may be increased again, once side effects have been resolved.

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.

Zinc

There are insufficient data to support the concomitant use of zinc and trientine. 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.

Other anti-copper agents

No interaction studies have been performed on the concomitant administration of trientine with D-Penicillamine.

Food

Trientine is poorly absorbed following oral intake and food further inhibits trientine absorption. Specific food interaction studies have been performed with trientine in healthy subjects, showing a reduction of the extent of absorption of trientine up to 45%. Systemic exposure is critical for its principal mechanism of action, copper chelation (see section 5.1). Therefore, it is recommended that trientine is taken 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 to allow for maximum absorption and reduce the likelihood of the formation of complexes by metal binding in the gastrointestinal tract (see section 4.2).

Other products

Trientine has been found to reduce serum iron levels. Therefore, iron supplements may be necessary in some cases. Concomitant oral iron or other heavy metals should be administered at a different time than trientine to prevent the formation of complexes (see section 4.4).

Although there is no evidence that calcium and magnesium antacids alter the efficacy of trientine, it is good practice to separate their administration (see section 4.4).

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).

Trientine should be used in pregnancy only after careful consideration of the benefits compared with the risks of discontinuing treatment in the individual patient. Factors to consider include the known risks associated with untreated or undertreated Wilson’s disease, risks associated with the stage of disease, the risk of those alternative treatments which are available and the possible effects of trientine (see section 5.3).

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

The pregnancy should be 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. 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).

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 RAZ 250mg has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Nausea can commonly occur on initial treatment and occasionally skin rash can occur. Duodenitis and severe colitis have been reported. Neurological deterioration can occur at the start of the treatment.

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

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*: anaemia, aplastic anaemia, sideroblastic anaemia.
Nervous system disorders	*Uncommon*: dystonia, tremor. *Not known:* dysarthria, muscle rigidity, neurological deterioration.
Immune system disorders	*Not known*: lupus-like syndrome, lupus nephritis.
Gastrointestinal disorders	*Common:* nausea. *Not known:* duodenitis, colitis.
Skin and subcutaneous tissue disorder	*Uncommon:* rash.

Description of selected adverse reactions

There have been reports of neurological deterioration at the start of treatment in Wilson's disease patients treated with copper chelators including trientine, with symptoms of, for example, dystonia, rigidity, tremor and dysarthria (see section 4.2).

Paediatric population

Clinical trials with trientine including a limited number of children in the age range of 5 to 17 years at the start of treatment indicate that frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il.

4.9 Overdose

Occasional cases of trientine overdose have been reported. In cases up to 20g of trientine base there were no apparent adverse effects reported. A large overdose of 40 g of trientine base resulted in self-limiting dizziness and vomiting with no other clinical sequelae or significant biochemical abnormalities.

In the event of overdose the patient should be observed, appropriate biochemical analysis performed and symptomatic treatment given. There is no antidote for trientine.

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).

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-selective chelator that enhances systemic elimination of divalent copper by forming a stable complex that is readily excreted by the kidneys.

Trientine is a chelator with a polyamine-like structure and copper is chelated by forming a stable complex with the four constituent nitrogens in a planar ring. Thus, the pharmacodynamic action of trientine is dependent on its chemical property of chelating copper and not on its interaction with receptors, enzyme systems or any other biological system that might differ between species. 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 RAZ 250mg in healthy subjects, trientine was rapidly absorbed with median T_{max} values of 1.25 hours. The C_{max} was 933.99 ± 345.99 ng/mL and AUC_{0-t} 3771.15 ± 1962.20 hr.ng/mL.

Food intake inhibits absorption shown by reduced C_{max} and decreased area under the curve, AUC. Thus, trientine is to be given on empty stomach at least one hour before meals or 2 hours after meals.

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

Trientine is acetylated in two major metabolites, N1-acetyltriethylenetetramine (MAT) and N1,N10-diacetyltriethylenetetramine (DAT). Clinical data in healthy subjects indicate that the plasma exposure to the MAT metabolite is approximately 3 times that of unchanged trientine, while exposure to the DAT metabolite is slightly lower compared to trientine. The metabolites of trientine have Cu-chelating properties, however the stability of these Cu-complexes is low due to the introduction of the acetyl groups. Clinical data in healthy volunteers suggest limited contribution of chelating activity by the MAT and DAT metabolites. The extent of MAT and DAT's contribution to the overall effect of trientine on copper levels in Wilson's Disease patients remains to be determined.

Trientine is metabolised by acetylation via spermidine/spermine N-acetyltransferase and not via N-acetyltransferase 2.

Elimination

After absorption, trientine and its metabolites are rapidly excreted in the urine, either bound to copper or unbound. The unabsorbed fraction of orally administered trientine is bound to intestinal copper and eliminated through faecal excretion.

The elimination half-life of trientine is approximately 4 hours (mean t1/2 of 3.8 ± 1.3 hours measured at steady state in WD patients and 4.4 ± 4.7 hours measured after a single dose in healthy volunteers). The elimination half-lives of the two metabolites were 14.1 ± 3.7 hours for MAT and 8.5 ± 3.0 hours for DAT after a single dose administration of trientine in healthy subjects.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on a series of studies investigating cardiovascular safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to embryofoetal development.

Effects in non-clinical studies were largely consistent with induced copper deficiency in the plasma and liver of previously copper normative animals and as such could be attributed to the pharmacological action of trientine. The main toxicological findings associated with trientine, which were generally seen across all species examined, included body weight loss or lower body weight gain, altered urinary electrolytes, low plasma copper levels and various histopathological changes in the lungs (mainly interstitial pneumonitis). All effects were reversible with the exception of the lung findings; however the

dose levels where these effects were observed are far in excess of those used clinically. Moreover, there was some doubt about the relationship to trientine, as the lung findings were also observed in most of the control dogs in the 26 week study. In dogs, ataxia, tremors, abnormal gait and underactivity were observed following administration of very high levels of trientine. Some functional neurological abnormalities were also identified, particularly in severely affected animals, however no associated nerve damage was observed. Electrocardiography was also unaffected.

In pregnant animals, high dose trientine associated with significant reductions in serum copper, revealed an early effect on embryo survival and a marginally lower foetal weight. There was no evidence of embryo-foetal toxicity at lower dose levels despite dose-related reductions in serum copper. These effects were observed only at exposures sufficiently in excess of maximum human exposure to indicate little relevance to clinical use.

No fertility data are available but estrous cyclicity was unaffected and reproductive organs were not identified as target organs in general repeat dose toxicity studies.

The OECD SIDS triethylenetetramine 2002 classifies the genotoxic profile of trientine as low priority/concern. Some positive in vitro mutagenicity data were obtained but in vivo test systems showed no mutagenic activity. No long term animal carcinogenicity trials have to date been performed with trientine via the oral route, but via the dermal route, there was no increases in cancers above baseline. Moreover, there is evidence to suggest that trientine actually reduces endogenous DNA damage in a strain of rat (Long-Evans Cinnamon) considered to represent an appropriate model of Wilson's disease. This suggests a reduced carcinogenic risk for Wilson's disease patients as a result of trientine therapy.

Trientine dihydrochloride is a known irritant, especially to mucus membranes, upper respiratory tract and skin, and induces skin sensitisation in guinea pigs, mice and man (OECD SIDS triethylenetetramine 2002).

6. Pharmaceutical particulars

6.1 List of excipients

Capsule content:
Stearic acid (Kolliwax S fine)
Silica colloidal anhydrous (Aerosil 200 pharma)

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

Printing ink containing:
Shellac
Black iron oxide (E172)
Propylene glycol
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging material.

6.4 Special precautions for storage

Store below 25ºC. Keep the bottle tightly closed in order to protect from moisture.

Storage conditions after first opening (relevant for bottle package only):
Stable for 100 days after first opening when stored at temperature of 2-8ºC.
Or
Stable for 60 days after first opening when stored at temperature of 15-30ºC.

6.5 Nature and contents of container

White opaque HDPE bottle with a PP child-resistant closure in a pack size of 100 capsules, or in a blister pack of 30, 72, 96, 100, 240 or 300 capsules.
Not all pack sizes might be marketed.

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6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder and importer

RAZ PHARMACEUTICS LTD.,
31 Gesher haetz Street, Industrial Park, Emek Hefer, Israel.

8. Marketing authorisation number(s)

170-23-36784-99

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