

TRIENTINE RAZ 250 MG

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. Capsule length is between 18.9 mm and 19.7mm.

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 with water. It is important that trientine is given on an empty stomach, at least one hour before the meal or two hours after the meal 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 RAZ 250mg 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 RAZ 250mg 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 RAZ 250mg 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 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 RAZ 250mg 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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	<i>Not known:</i> iron deficiency anaemia.
Gastrointestinal disorders	<i>Common:</i> nausea. <i>Not known:</i> duodenitis, colitis (including severe colitis).
Skin and subcutaneous tissue disorder	<i>Uncommon:</i> skin rash, pruritus, erythema. <i>Not known:</i> urticaria.

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

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 (40 g; 200 tablets) 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 60 g of trientine dihydrochloride salt, equivalent to 40 g 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 RAZ 250mg 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 RAZ 250mg 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 RAZ 250mg 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 RAZ 250mg were $0.10 \pm 0.07 \text{ h}^{-1}$ and 11.26 ± 7.54 . The C_{max} was $933.99 \pm 345.99 \text{ ng/mL}$ and AUC_{0-t} $3771.15 \pm 1962.20 \text{ hr.ng/mL}$.

Food: 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

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

Elimination

Trientine RAZ 250mg 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 trientine 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:

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 25°C.

Keep the bottle tightly closed in order to protect from moisture.

Stable for 100 days after first opening when stored at temperature of 2-8°C.

or

Stable for 60 days after first opening when stored at temperature of 15-30°C.

6.5 Nature and contents of container

White opaque HDPE bottle with a PP child-resistant closure.

Pack size: 100 capsules.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

RAZ PHARMACEUTICS LTD.,

6 Hamatechet st., Kadima, Israel.

8. Manufacturer

EMCURE PHARMACEUTICALS LIMITED,

Hinjwadi, Pune, India.

8. Registration number

170-23-36784-99

Approved in September 2022 according to MOHs guidelines.

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