Summary of Product Characteristics

ZOLON ZINC TABLET (ZINC 50MG)

1. Name of the medicinal product

Zolon Zinc 50 mg hard capsules

2. Qualitative and quantitative composition

Each hard capsule contains 50 mg of zinc (corresponding to 167.84 mg of zinc acetate dihydrate).

3. Pharmaceutical form

Capsule.

Capsule with green opaque cap and body.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of Wilson's disease.

4.2 Posology and method of administration

Zinc treatment should be initiated under the supervision of a physician experienced in the treatment of Wilson's disease (see section 4.4). Zinc is a life-long therapy.

There is no difference in dose between symptomatic and presymptomatic patients.

Zinc is available in hard capsules of 25 mg or 50 mg.

• Adults:

The usual dose is 50 mg 3 times daily with a maximum dose of 50 mg 5 times daily.

• Children and adolescents:

Data are very limited in children under 6 years but since the disease is fully penetrant, prophylactic treatment should be considered as early as possible. The recommended dosage is as follows:

- from 1 to 6 years: 25 mg twice daily

- from 6 to 16 years if bodyweight under 57 kg: 25 mg three times daily

- from 16 years or if bodyweight above 57 kg: 50 mg three times daily.

• Pregnant women:

A dose of 25 mg 3 times daily is usually effective but the dose should be adjusted to copper levels (see section 4.4 and section 4.6).

In all cases, dose should be adjusted according to therapeutic monitoring (see section 4.4.).

Zinc must be taken on an empty stomach, at least 1 hour before or 2-3 hours after meals. In case of gastric intolerance, often occurring with the morning dose, this dose may be delayed to mid-morning, between breakfast and lunch. It is also possible to take Zinc with a little protein, such as meat (see section 4.5).

In children who are unable to swallow capsules, these should be opened and their content suspended in a little water (possibly sugar or syrup flavoured water).

When switching a patient on chelating treatment to Zinc for maintenance therapy, the chelating treatment should be maintained and co-administered for 2 to 3 weeks since this is the time it takes for the zinc treatment to induce maximum metallothionein induction and full blockade of copper absorption. The administration of the chelating treatment and Zinc should be separated by at least 1 hour.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use
Zinc acetate dihydrate is not recommended for the initial therapy of symptomatic patients because of its slow onset of action. Symptomatic patients must be initially treated with a chelating agent; once copper levels are below toxic thresholds and patients are clinically stable, maintenance treatment with Zinc can be considered.

Nevertheless, while awaiting zinc induced duodenal metallothionein production and consequential effective inhibition of copper absorption, zinc acetate dehydrate could be administered initially in symptomatic patients in combination with a chelating agent.

Although rare, clinical deterioration may occur at the beginning of the treatment, as has also been reported with chelating agents. Whether this is related to mobilisation of copper stores or to natural history of the disease remains unclear. A change of therapy is recommended in this situation.

Caution should be exercised when switching patients with portal hypertension from a chelating agent to Zinc, when such patients are doing well and the treatment is tolerated. Two patients of a series of 16 died from hepatic decompensation and advanced portal hypertension after being changed from penicillamine to zinc therapy.

Therapeutic monitoring

The aim of the treatment is to maintain the plasma free copper (also known as non-ceruloplasmin plasma copper) below 250 microgram/l (normal: 100-150 microgram/l) and the urinary copper excretion below 125 microgram/24 h (normal: < 50 microgram/24 h). The non-ceruloplasmin plasma copper is calculated by subtracting the ceruloplasmin-bound copper from the total plasma copper, given that each milligram of ceruloplasmin contains 3 micrograms of copper.

The urinary excretion of copper is an accurate reflection of body loading with excess copper only when patients are not on chelation therapy. Urinary copper levels are usually increased with chelation therapy such as penicillamine or trientine.

The level of hepatic copper cannot be used to manage therapy since it does not differentiate between potentially toxic free copper and metallothionein bound copper.

In treated patients, assays of urinary and/or plasma zinc may be a useful measure of treatment compliance. Values of urinary zinc above 2 mg/24 h and of plasma zinc above 1250 microgram/l generally indicate adequate compliance.

Like with all anti-copper agents overtreatment carries the risk of copper deficiency, which is especially harmful for children and pregnant women since copper is required for proper growth and mental development. In these patient groups, urinary copper levels should be kept a little above the upper limit of normal or in the high normal range (i.e. 40 – 50 microgram/24 h).

Laboratory follow-up including haematological surveillance and lipoproteins determination should also be performed in order to detect early manifestations of copper deficiency, such as anaemia and/or leukopenia resulting from bone marrow depression, and decrease in HDL cholesterol and HDL/total cholesterol ratio.

As copper deficiency may also cause myeloneuropathy, physicians should be alert to sensory and motor symptoms and signs which may potentially indicate incipient neuropathy or myelopathy in patients treated with Zinc.

The capsule shell contains sunset yellow FCF (E110), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Other anti-copper agents

Pharmacodynamic studies were conducted in Wilson's disease patients on the combination of Zinc (50 mg three times daily) with ascorbic acid (1 g once

daily), penicillamine (250 mg four times daily), and trientine (250 mg four times daily). They showed no significant overall effect on copper balance although mild interaction of zinc with chelators (penicillamine and trientine) could be detected with decreased faecal but increased urinary copper excretion as compared with zinc alone. This is probably due to some extent of complexion of zinc by the chelator, thus reducing the effect of both active substances.

When switching a patient on chelating treatment to Zinc for maintenance therapy, the chelating treatment should be maintained and co-administered for 2 to 3 weeks since this is the time it takes for the zinc treatment to induce maximum metallothionein induction and full blockade of copper absorption. The administration of the chelating treatment and Zinc should be separated by at least 1 hour.

Other medicinal products

The absorption of zinc may be reduced by iron and calcium supplements, tetracyclines and phosphorus-containing compounds, while zinc may reduce the absorption of iron, tetracyclines, fluoroquinolones.

Food

Studies of the co-administration of zinc with food performed in healthy volunteers showed that the absorption of zinc was significantly delayed by many foods (including bread, hard boiled eggs, coffee and milk). Substances in food, especially phytates and fibres, bind zinc and prevent it from entering the intestinal cells. However, protein appears to interfere the least.

4.6 Pregnancy and lactation

Pregnancy

Data on a limited number of exposed pregnancies in patients with Wilson's disease give no indication of harmful effects of zinc on embryo/foetus and mother. Five miscarriages and 2 birth defects (microcephaly and correctable heart defect) were reported in 42 pregnancies.

Animal studies conducted with different zinc salts do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

It is extremely important that pregnant Wilson's disease patients continue their therapy during pregnancy. Which treatment should be used, zinc or chelating agent should be decided by the physician. Dose adjustments to guarantee that the foetus will not become copper deficient must be done and close monitoring of the patient is mandatory (see section 4.4).

Lactation

Zinc is excreted in human breast milk and zinc-induced copper deficiency in the breast-fed baby may occur. Therefore, breast-feeding should be avoided during Zinc therapy.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects
Reported adverse reactions are listed below, by system organ class and by frequency.

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).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	**Adverse drug reactions**	
Blood and lymphatic system disorders	*uncommon:*	sideroblastic anaemia, leukopenia
Gastrointestinal disorders	*common:*	gastric irritation
Investigations	*common:*	blood amylase, lipase and alkaline phosphatase increased

Anaemia may be micro-, normo- or macrocytic and is often associated with leukopenia. Bone marrow examination usually reveals characteristic "ringed sideroblasts" (i.e. developing red blood cells containing iron-engorged paranuclear mitochondria). They may be early manifestations of copper deficiency and may recover rapidly following reduction of zinc dosage. However, they must be distinguished from haemolytic anaemia which commonly occurs where there is elevated serum free copper in uncontrolled Wilson's disease.

The most common undesirable effect is gastric irritation. This is usually worst with the first morning dose and disappears after the first days of treatment. Delaying the first dose to mid-morning or taking the dose with a little protein may usually relieve the symptoms.

4.9 Overdose
Three cases of acute oral overdose with zinc salts (sulphate or gluconate) have been reported in the literature. Death occurred in a 35 year-old woman on the fifth day after ingestion of 6 g of zinc (40 times the proposed therapeutic dose) and was attributed to renal failure and haemorrhagic pancreatitis with hyperglycaemic coma. The same dose did not produce any symptoms except for vomiting in an adolescent who was treated by whole-

bowel irrigation. Another adolescent who ingested 4 g of zinc had serum zinc level of about 50 mg/l 5 hours later and only experienced severe nausea, vomiting and dizziness.

Treatment of overdose should be with gastric lavage or induced emesis as quickly as possible to remove unabsorbed zinc. Heavy metal chelation therapy should be considered if plasma zinc levels are markedly elevated (> 10 mg/l).

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: various alimentary tract and metabolism products, ATC code: A16AX05.

Wilson's disease (hepatolenticular degeneration) is an autosomal recessive metabolic defect in hepatic excretion of copper in the bile. Copper accumulation in the liver leads to hepatocellular injury and eventual cirrhosis. When the liver capacity of storing copper is exceeded copper is released into the blood and is taken up in extra hepatic sites, such as the brain, resulting in motor disorders and psychiatric manifestations. Patients may present clinically with predominantly hepatic, neurologic, or psychiatric symptoms.

The active moiety in zinc acetate dihydrate is zinc cation, which blocks the intestinal absorption of copper from the diet and the reabsorption of endogenously secreted copper. Zinc induces the production of metallothionein in the enterocyte, a protein that binds copper thereby preventing its transfer into the blood. The bound copper is then eliminated in the stool following desquamation of the intestinal cells.

Pharmacodynamic investigations of copper metabolism in patients with Wilson's disease included determinations of net copper balance and radiolabelled copper uptake. A daily regimen of 150 mg of Zinc in three administrations was shown to be effective in significantly reducing copper absorption and inducing a negative copper balance.

5.2 Pharmacokinetic properties

Since the mechanism of action of zinc is an effect on copper uptake at the level of the intestinal cell, pharmacokinetic evaluations based on blood levels of zinc do not provide useful information on zinc bioavailability at the site of action.

Zinc is absorbed in the small intestine and its absorption kinetics suggest a tendency to saturation at increasing doses. Fractional zinc absorption is negatively correlated with zinc intake. It ranges from 30 to 60% with usual dietary intake (7-15 mg/d) and decreases to 7% with pharmacological doses of 100 mg/d.

In the blood, about 80% of absorbed zinc is distributed to erythrocytes, with most of the remainder being bound to albumin and other plasma proteins. The liver is the main storage for zinc and hepatic zinc levels are increased during maintenance therapy with zinc.

The plasma elimination half-life of zinc in healthy subjects is around 1 hour after a dose of 45 mg. The elimination of zinc results primarily from faecal excretion with relatively little from urine and sweat. The faecal excretion is in the greatest part due to the passage of unabsorbed zinc but it is also due to endogenous intestinal secretion.

5.3 Preclinical safety data

Preclinical studies have been conducted with zinc acetate and with other zinc salts. Pharmacological and toxicological data available showed large similarities between zinc salts and among animal species.

The oral LD50 is approximately 300 mg zinc/kg body weight (about 100 to 150 times the human therapeutic dose). Repeat-dose toxicity studies have established that the NOEL (No Observed Effect Level) is about 95 mg zinc/kg body weight (about 48 times the human therapeutic dose).

The weight of evidence, from *in vitro* and *in vivo* tests, suggests that zinc has no clinically relevant genotoxic activity.

Reproduction toxicology studies performed with different zinc salts showed no clinically relevant evidence of embryotoxicity, foetotoxicity or teratogenicity.

No conventional carcinogenicity study has been conducted with zinc acetate dihydrate.

6. Pharmaceutical particulars

6.1 List of excipients

Capsule content

maize starch

magnesium stearate

Capsule shell

gelatin

titanium dioxide (E171)

sunset yellow FCF (E110)

Printing ink

black iron oxide (E172)

shellac

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store below 30°C away from sunlight

6.5 Nature and contents of container
Zolon Zinc 50mg tablets are available in Alu/PVC blisters

Pack sizes: 10x10 and 1x90 Blisters packed in a paper box along with pack insert

6.6 Special precautions for disposal and other handling
No special requirements

7 . **Registrant (Marketing Authorization Holder and Manufacturing Site Address**

Zolon Healthcare Limited, Nigeria Limited located at No 11 Town planning way Ilupeju lagos

Manufacturer: Emzor Pharmaceutical Industries Limited, Flowergate Mixed Development Scheme,Km 1 Sagamu/Benin Expressway,Sagamu,Ogun State, Nigeria.

8. **Marketing Authorization Number**

A7-4802

9. **Date of First Authorization/Renewal**

First authorized March 29, 2021.

10. **Manufactured By**

Emzor Pharmaceutical Industries Limited located at Flowergate Mixed Development Scheme,Km 1 Sagamu/Benin Expressway,Sagamu,Ogun State, Nigeria.