MEDICATIONS AND AVAILABILITY

Trientine
Available as:

- Syprine® (Trientine Hydrochloride), 250mg capsules. Merck & Co. Inc. Whitehouse Station, NJ 08889 U.S.A.
- Trientine dihydrochloride, 300 mg capsules. Univar Ltd., U.K.

D-Penicillamine
Available as:

- Cuprimine® (Penicillamine), 125mg or 250 mg capsules. Merck & Co. Inc. Whitehouse Station, NJ 08889 U.S.A.

Zinc
Available as:

- Galzin™ (zinc acetate), 25mg or 50mg capsules. Gate Pharmaceuticals, Div. of TEVA Pharmaceuticals USA. Sellersville, PA. 18960
- Wilzin (zinc acetate dihydrate), 25mg or 50mg capsules. Orphan Europe SARL, France

Members of the WDA Medical Advisory Committee recommend, that when available and practical, the preferred drugs are prescription medications whose effectiveness, purity, bioavailability, consistency from pill to pill, and authenticity has been assessed and is regulated. Zinc acetate is the only form of zinc salt approved by the United States FDA for use in the treatment of Wilson's Disease. Other countries report favorable results with the use of zinc suphate and other zinc salts.

"The Wilson's Disease Association funds research and facilitates and promotes the identification, education, treatment, and support of patients and other individuals affected by Wilson's Disease."

For more information
please contact the:

WILSON'S DISEASE ASSOCIATION
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This brochure has been written to assist you and your medical advisors. It is not intended to replace any advice you receive from your treating physician.

References:

Brewer, George J. (2001) WILSON'S DISEASE: A Clinicians Guide to Recognition, Diagnosis, and Management. Norwell MA: Kluwer Academic Publishers

Roberts, EA. & Schilsky, ML. (2003) A Practice Guideline on Wilson Disease. Hepatology, 37(6), 1475-1491.

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A Clinical Tool For Physicians

A Diagnosis of Wilson's Disease

What Now?

WILSON'S DISEASE ASSOCIATION
INTERNATIONAL

TREATMENT AND MANAGEMENT

POSSIBLE TOXICITIES OF MEDICATIONS USED TO TREAT WILSON'S DISEASE

Penicillamine:

Ageusia
Agranulocytosis
Alopecia
Anorexia, epigastric pain, nausea, vomiting, diarrhea
Aplastic anemia
Blurred vision
Cutaneous macular atrophy
Degenerative changes of the skin (especially of the neck)
Depression of serum IgA levels
Diplopia
Elastosis perforans serpiginosa – EPS lesions
Goodpasture's syndrome
Hepatotoxicity
Hyperkeratosis
Hypogeusia
Initial hypersensitivity: hives, rash, fever, anaphylaxis, lymphadenopathy
Intrahepatic cholestasis
Leukopenia
Lichen planus
Lupus-like reaction
Mammary hyperplasia
Myasthenic syndrome
Nephrotic syndrome
Obliterative bronchitis
Optical axial neuritis
Oral ulcerations
Proteinuria
Ptosis
Serous retinitis
Thrombocytopenia or total aplasia

Trientine:

Ageusia
Aplastic anemia (rare)
Gastritis
Sideroblastic anemia

Zinc:

Biochemical pancreatitis
Gastritis
Leukopenia
Zinc accumulation

RECOMMENDATIONS UPON CONFIRMED DIAGNOSIS

TREATMENT

Goals:

- To stabilize disease symptoms and biochemical abnormalities in symptomatic patients
- To prevent disease symptoms and biochemical abnormalities in presymptomatic patients

In Symptomatic Patients:

- Initiate drug therapy with chelator alone or in combination with zinc
- Reduce excess copper deposits
- Initiate adjunctive evaluations/therapies as needed: speech, physical, psychiatric, neurological and hepatic—including for portal hypertension, ascites or edema.
- Transplant evaluation if necessary

In Presymptomatic Patients:

- Initiate drug therapy with zinc
- Reduce or prevent excess copper deposits

Diet:

Initial Phase:

- Generally, avoid foods with very high copper content: shellfish, nuts, chocolate, mushrooms, organ meat.
- Practicing vegetarians should consult a dietician
- Avoid copper cookware
- Avoid vitamin/dietary supplements containing copper, as well as mineral water
- Check copper content of household water for cooking or consumption, especially well water, or if brought in through copper pipes. Flush system of stagnant water before such use. A water purifying system may be advisable for high levels of copper (over 0.1 ppm)

Maintenance Phase:

- May be more liberal than in the initial phase of treatment, based on response to therapy
- Avoid organ meat and excessive shellfish consumption
- Careful evaluation of dietary supplements and nutraceuticals

MEDICATION GUIDELINES

Goal:

To maintain copper balance within the optimal range to avoid copper deposition or over-chelation/copper depletion

Medications:

Chelators – Usually the initial treatment recommended for symptomatic patients

- Trientine – Induces cupriuria
- D-Penicillamine – Induces cupriuria (Not recommended for patients presenting with neurological symptoms)
- Tetrathiomolybdate – Induces cupriuria and intestinal copper loss. Also blocks copper absorption. (As of this time, still experimental in U.S. and Canada)

Metallothionein inducer – A cellular protein that binds copper and blocks intestinal absorption of copper. Rarely used alone as initial treatment in symptomatic patients.

- Zinc salts – Blocks intestinal absorption of copper. (Must contain exactly 25 or 50mg of elemental zinc in combination with a salt)

Initial Treatment

Adult doses

Trientine – 750-1,500 mg/d in 2 – 4 divided doses.
Tetrathiomolybdate – no current dosing regimen established, still in clinical trials.
D-Penicillamine – 1,000-1,500 mg/d in 2 – 4 divided doses. Vitamin B6 (pyroxidine) – 25-50 mg/d taken away from Penicillamine to prevent B6 deficiency caused by Penicillamine.
Zinc salts – 150 mg/d in 3 divided doses.

Pediatric doses (<50 kg body weight)

Trientine – 20 mg/kg/d, rounded to nearest 250mg in 2 or 3 divided doses
Tetrathiomolybdate – not established
D-Penicillamine – 20 mg/kg/d, rounded to nearest 250mg, in 2 or 3 divided doses. B6 as above.
Zinc salts – 75 mg/d in 3 divided doses.

(Dosing not well established for children <20kg body weight and must be determined on an individual basis)

Maintenance Treatment

Adult doses

Trientine – 750-1,000 mg/d in 2 - 3 divided doses.
Tetrathiomolybdate – no current dosing regimen established, still in clinical trials.
D-Penicillamine – 750-1,000 mg/d in 2 divided doses.
Vitamin B6 (pyroxidine) – 25-50 mg/d taken away from Penicillamine to prevent B6 deficiency caused by Penicillamine.
Zinc salts – 150 mg/d in 3 divided doses.

Pediatric doses

Same as for Initial Phase until >50kg body weight

Medications must be taken daily, as prescribed, with water only, at least 1 hour before or after food consumption for proper absorption. Therapy must not be interrupted and must continue lifelong.

Maintenance phase: Typically 6-12 months after initiation of therapy when copper levels and lab values have begun to normalize.

MONITORING OF WILSON'S DISEASE THERAPY

Goals:

- To confirm clinical and biochemical improvement
- Ensure compliance and efficacy of therapy
- Identify adverse side effects in a timely fashion

The importance of monitoring for patient adherence and efficacy of therapy cannot be overemphasized.

Physical Exams:

- Evaluation for evidence of liver disease, psychiatric and neurological symptoms.
- Repeat exam for Kayser-Fleischer rings.
- Careful history including possible changes in behavior; or new psychiatric or neurological symptoms; fatigability. History of new symptoms related to liver disease: jaundice, ascites, edema.

Laboratory Testing:

Frequency is variable, but at least twice per year
More frequently is necessary during the initial phase of treatment, if worsening of symptoms or side effects of medication occurs, for suspected non-compliance, other interruption or change in therapy.

D-Penicillamine

- 24 hour urine copper 4 times per year initially, then at least twice per year
- Serum free copper 4 times per year initially, then at least twice per year
- CBC, liver biochemistries, INR, urinalysis: at 3, 6, 9, and 12 days, weekly for one month, twice weekly for one month, biweekly for two months, monthly for 6 months, every 3 months for one year, every 6 months for 2 years, then semi-annually
- Urinalysis to screen for proteinuria and cells

Trientine

- 24 hour urine copper 4 times per year initially, then at least twice per year
- Serum free copper 4 times per year initially, then at least twice per year
- CBC, liver biochemestries, INR, urinalysis: weekly for 1 month, biweekly for 2 months, monthly for 6 months, every 3 months for one year, every 6 months for 2 years, then semi-annually
- Urinalysis to screen for proteinuria and cells

Tetrathiomolybdate

- Not established

Zinc

- 24 hour urine copper and zinc twice in the first 6 months, every 6 months for 2 years, then semi-annually
- Serum free copper twice per year
- CBC, liver biochemistries, INR: twice per year

Target Result Ranges

- Serum Free Copper – 5 - 15µg/dL
- 24 hour urine copper:
  - Chelators – 200 – 500 µg/24 hours
  - Zinc – <125 µg/24 hours
- 24 hour urine zinc – >2.0 mg/d