

Clinical Commissioning Policy: Trientine for Wilson disease (all ages)

NHS England Reference: 170094P



NHS England INFORMATION READER BOX**Directorate**

Medical	Operations and Information	Specialised Commissioning
Nursing	Trans. & Corp. Ops.	Commissioning Strategy
Finance		

Publications Gateway Reference: 07603

Document Purpose	Policy
Document Name	Trientine for Wilson disease (all ages)
Author	Specialised Commissioning Team
Publication Date	21 December 2018
Target Audience	CCG Clinical Leaders, Care Trust CEs, Foundation Trust CEs , Medical Directors, Directors of PH, Directors of Nursing, NHS England Regional Directors, NHS England Directors of Commissioning Operations, Directors of Finance, NHS Trust CEs
Additional Circulation List	
Description	Routinely Commissioned - NHS England will routinely commission this specialised treatment in accordance with the criteria described in this policy.
Cross Reference	
Superseded Docs (if applicable)	
Action Required	
Timing / Deadlines (if applicable)	
Contact Details for further information	england.specialisedcommissioning@nhs.net

Document Status

This is a controlled document. Whilst this document may be printed, the electronic version posted on the intranet is the controlled copy. Any printed copies of this document are not controlled. As a controlled document, this document should not be saved onto local or network drives but should always be accessed from the intranet.

Clinical Commissioning Policy: Trientine for Wilson Disease (all ages)

First published: December 2018

Effective from: 1 April 2019

**Prepared by NHS England Specialised Services Clinical Reference Group for
Metabolic Disorders**

Published by NHS England, in electronic format only.

Contents

Policy Statement	5
Equality Statement	5
Plain Language Summary	6
1 Introduction	8
2 Definitions	8
3 Aims and Objectives	9
4 Epidemiology and Needs Assessment	9
5 Evidence Base.....	11
6 Criteria for Commissioning	18
7 Patient Pathway.....	20
8 Governance Arrangements.....	21
9 Mechanism for Funding	21
10 Audit Requirements	21
11 Documents Which Have informed this Policy.....	21
12 Date of Review	21
References	22

Policy Statement

NHS England will commission treatment for Wilson disease in all ages in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to suspend or rescind policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain Language Summary

About Wilson disease

Wilson disease is a complex disease which affects the liver, the brain and potentially most other organs in the body. It can lead to significant liver and brain dysfunction as well as mental health problems. Worldwide, the disease affects approximately one in 30,000 individuals. It is normally regarded as fatal unless diagnosed and treated.

Wilson disease is caused by an excess of copper in the body. Copper is present in most foods and is an essential element for humans. In Wilson disease patients, secretion of copper in the bile is impaired and copper accumulates in the tissues. In the liver this leads to progressive liver damage and potentially liver failure; in the brain, disturbances of motor function including seizures, movement disorders, psychosis and personality changes; in the cornea, brownish-yellow rings called Kayser-Fleischer rings; and in the kidney, functional disturbances.

About current treatments

There are three main treatments licensed for the treatment of Wilson disease:

- D- penicillamine
- Trientine dihydrochloride
- Zinc salts

The treatment for this disease is based on the drugs listed above which increase copper excretion from the body in the urine (copper chelation: D-Penicillamine and trientine dihydrochloride), or reduce copper absorption from the upper part of the intestine (zinc salts). A chelator is a chemical or medicine that, because of its structure, will associate or bind a particular ion, such as copper. D-Penicillamine (hereafter referred to as penicillamine except in references to clinical studies) is generally used as the first line treatment. Some patients have adverse reactions to penicillamine which makes it clinically inappropriate for patients to continue on this treatment. In this situation trientine dihydrochloride is a potential option (it is licensed for penicillamine intolerant patients in the United Kingdom). Zinc salts may be a clinical option, for example for patients who are non-symptomatic or whose disease has stabilised following use with a chelator.

About the new treatment

None of the three drugs, used in the treatment for Wilson disease, penicillamine, trientine dihydrochloride or zinc salts are new treatments for Wilson disease.

What we have decided

NHS England has carefully reviewed the evidence to treat Wilson disease with trientine. We have concluded that there is enough evidence to make the treatment available.

1 Introduction

Wilson disease is an autosomal recessive condition with a prevalence of approximately 1 in 30,000 of the population (Weiss KH. Wilson disease. Gene Reviews; last updated 2016).

The metabolic defect responsible for Wilson disease is failure of copper secretion into bile due to mutations in the gene coding for a copper transporter (ATP7B). Copper accumulates in the liver and then brain, giving a range of hepatic, neurological and psychiatric features. Patients have a high mortality rate from this condition if it is not effectively treated. This disease affects adults and children therefore the policy is for all ages.

The first line treatment for symptomatic Wilson disease is a copper chelator, and penicillamine is licensed for this use. Up to a third of patients have an adverse reaction to penicillamine and it is not clinically appropriate to continue with this treatment. Trientine dihydrochloride, another copper chelator, is the preferred second line treatment offered to patients with symptoms of Wilson Disease.

Zinc salts are also an alternative option for a selected group of patients.

2 Definitions

Chelation is the specific association of a metal ion, in this case copper, to chemical bonds in a molecule (called a ligand) with this specific affinity. It involves the formation or presence of two or more separate coordinate bonds between a polydentate (multiple bonded) ligand and a single central atom. Usually these ligands are organic compounds; they are called chelants, chelators, chelating agents, or sequestering agents.

Chelators are used in applications such as nutritional supplements, in chelation therapy to remove toxic metals from the body, and as contrast agents in magnetic resonance imaging (MRI) scanning.

D-Penicillamine is a copper chelator licensed for the first line treatment of Wilson disease.

Trientine dihydrochloride is a copper chelator licensed for the second line treatment of Wilson disease.

Zinc salts reduce copper absorption from the intestine by inducing the copper binding metalloprotein, in the intestinal mucosa.

3 Aims and Objectives

This policy considers NHS England's commissioning position for trientine dihydrochloride as second line therapy for a well-defined cohort of patients of all ages with Wilson disease who are intolerant of first line therapy with penicillamine.

The objectives are to:

- Provide an overview of the current clinical evidence for use of:
 - a) trientine dihydrochloride for second line treatment in patients with Wilson disease who are intolerant of Penicillamine and
 - b) trientine dihydrochloride as compared with zinc salts for second line or maintenance therapy,
- Provide a rationale, and propose criteria, for commissioning of trientine dihydrochloride and zinc salts in paediatric and adult patients in the second line setting aiming at improving health and care outcomes.

4 Epidemiology and Needs Assessment

Epidemiology

Wilson disease is an autosomal recessive condition with a prevalence of approximately 1 in 30,000 of the population (Weiss KH, 2016). The genetic frequency of the responsible mutations varies, leading to higher rates in populations with greater consanguinity. Wilson disease is a heterogeneous disease with a range of presentations and a wide age span, which affect treatment modalities. At present the number of patients with Wilson disease in England is not known, nor the number of newly diagnosed patients per year.

A patient registry has been established by the UK Wilson Disease Support Group, but this is voluntary and not an NHS supported database. On the basis that Wilson disease affects 1 in 30,000, in a population of 56 million the estimated number of patients who may have Wilson disease in England would be around 1854.

As the total number of patients with Wilson disease is not known, the number currently on trientine dihydrochloride is uncertain. The frequency of adverse events given in the European Association for the Study of the Liver (EASL) guidelines on Wilson disease suggests that 30% of patients could not be treated with penicillamine, therefore approximately 556 patients may be currently on trientine dihydrochloride. However, in England the experience of the clinical community is that the number of patients on trientine dihydrochloride is lower than this, and estimated to be around 100 patients.

Assessment of need

Three agents are licensed for the treatment of Wilson disease in the UK. Penicillamine and trientine dihydrochloride chelate copper leading to increased urinary excretion, while zinc salts reduce copper absorption from the intestine. These are long standing established treatments for this disease which follow the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines. Chelation therapy is very effective in treating this disease; where symptomatic patients with Wilson disease are treated with penicillamine or trientine dihydrochloride they have significantly reduced morbidity.

There are two groups of Wilson disease patients to be considered in this Policy:

- a. Newly diagnosed patients, who require chelation therapy, but in whom penicillamine is contra-indicated and second line therapy is required. In general, these patients will present with clinical disease markers including copper overload and symptoms of Wilson disease and will therefore require chelation therapy.
- b. Current patients, treated primarily with penicillamine but found intolerant to this treatment, who require a second line option – in this case zinc salts may

be an option where patients have normalised copper levels and have no symptoms.

Currently in England, life expectancy of patients with Wilson disease has been prolonged with chelator and transplant therapies. Treatment with a chelator has been the preferred treatment for people diagnosed with Wilson disease rather than zinc. The rationale for this is that chelators have a quicker effect on reducing the accumulated copper levels whilst zinc has a slower impact on copper balance; a concern if the patient has clinically significant disease. Patients who are intolerant to penicillamine would therefore have been prescribed trientine dihydrochloride in the past.

Treatment of Wilson disease is lifelong with treatment compliance issues often complicating the clinical response, stability and maintenance therapy. Thus, clinical features are monitored regularly with regard to liver, renal and neurological disease, and laboratory data. Laboratory test include full blood count (for haemoglobin, white cell and platelet count), renal and liver function tests, urinalysis, serum caeruloplasmin and copper levels, and urinary copper excretion. Depending upon the clinical scenario, monitoring of hepatic scarring/cirrhosis and brain scanning may be done. In England clinical protocols weigh the risk versus the benefits for each patient of all the above markers including duration of treatment (in relation to first administration of chelator) using established European and American Guidelines and landmark studies such as Weiss et al, 2011.

5 Evidence Base

There are two clinical evidence reviews that have informed this policy, one relating to trientine dihydrochloride and one relating to zinc salts.

Review of trientine dihydrochloride

One systematic review was identified, which assessed the efficacy of chelating agents and zinc for treating Wilson disease (Wiggelinkhuizen et al. 2009). However, it found no studies on trientine dihydrochloride that were suitable for inclusion.

Seven studies are included in this evidence review:

- One Randomised Controlled Trial (RCT) comparing tetrathiomolybdate (an experimental chelating agent, which is not currently available) with trientine dihydrochloride (Brewer et al. 2006)
- Two prospective observational studies (Ala et al. 2015 and Askari et al. 2003)
- Four retrospective observational studies (Arnon et al. 2007, Taylor et al. 2009, Walshe 2011 and Weiss et al. 2013)

Review of zinc salts

There were no studies that met the inclusion criteria specifically considering the use of zinc salts for treating people who were intolerant of penicillamine.

This evidence review includes 2 [systematic reviews](#) and 6 [observational studies](#) of which 1 systematic review and 3 observational studies are relevant to the policy.

- The systematic review ([Chen et al. 2015](#); 17 observational studies) assessed zinc salts and a chelating agent in combination for initial treatment of Wilson disease.
- The three observational assessed zinc salts taken alone as maintenance treatment for Wilson disease following treatment with a chelating agent ([Brewer et al. 2001](#), [Shimizu et al. 2010](#) and [Sinha et al 2008](#)).

Clinical effectiveness

Trientine dihydrochloride

The retrospective observational study by Weiss et al. (2013) is considered to provide the best available evidence for using trientine dihydrochloride compared with penicillamine in patients with Wilson disease. It included 141 patients who took trientine dihydrochloride monotherapy (36 first line and 105 second line) and outcomes in these patients were compared with outcomes in 326 patients who took penicillamine monotherapy (294 first line and 32 second line).

Weiss et al. (2013) found no statistically significant differences between trientine dihydrochloride and penicillamine for treating hepatic signs and symptoms of Wilson disease when used first or second line. In symptomatic patients after 6–48 months, improvement of hepatic signs and symptoms was seen with both trientine

dihydrochloride and penicillamine in 90.9% of treatment-naive patients and 70.5% of patients who switched treatments. Worsening of hepatic signs and symptoms was seen in only 8/467 patients in the study; 4/204 taking penicillamine first line and 4/45 taking trientine dihydrochloride second line, with no significant differences between the groups for line of treatment. There was also no significant difference between the groups in the number of patients who underwent liver transplantation (9/326 patients taking penicillamine and 3/141 patients taking trientine dihydrochloride).

When neurological symptoms were considered, Weiss et al. (2013) found no statistically significant differences in improvements between trientine dihydrochloride and penicillamine used first or second line. In symptomatic patients after 6–48 months, the proportion of patients whose neurological symptoms improved was lower than for hepatic symptoms (first line trientine dihydrochloride 55.0% compared with penicillamine 67.5%, second line trientine dihydrochloride 51.0% compared with penicillamine 23.1%: differences not statistically significant), with more than a third of patients' symptoms not improving or becoming worse. The number of patients with worsening of neurological symptoms was statistically different between the groups of patients who switched treatments. In treatment-naive patients, worsening occurred in statistically significantly more patients in the trientine dihydrochloride group. (10.5% compared with 2.0% for penicillamine in symptomatic and asymptomatic patients, $p=0.02$), although the number of patients taking trientine first line was relatively small (38 compared with 295 for penicillamine).

Taylor et al. (2009) retrospectively studied 16 children with Wilson disease (14 with liver disease) who took trientine dihydrochloride. After a median of 6.43 years, liver function became normal in the majority of children. However, 2/3 children taking trientine dihydrochloride first line and 4/13 children taking trientine dihydrochloride second line still had abnormal liver function. The authors reported that all children who presented with liver symptoms only became symptom-free; however, trientine dihydrochloride did not resolve accompanying neurological or psychiatric symptoms in children experiencing these.

The retrospective study by Arnon et al. (2007) evaluated the effects of first line trientine dihydrochloride in 10 children with Wilson disease and mixed presentations

that were followed up for at least 12 months. Trientine dihydrochloride monotherapy was used for 4–8 months before zinc was added (according to urinary copper levels). Alanine aminotransferase (ALT) liver enzyme levels were normal in 3 patients at 12 months and in a further patient after 30 months. In another 3 patients, ALT levels decreased but remained above the upper limit of normal: the authors noted that the clinical significance of a mild increase in liver enzymes is unclear. Similar results were seen for aspartate aminotransferase (AST) levels.

The retrospective study by Walshe (2011) looked at urinary copper excretion and its response to treatment for Wilson disease. In patients with neurological symptoms (n=124), 15 patients took trientine dihydrochloride (line of treatment unclear) rather than penicillamine. Urinary copper excretion fell over time, approaching the level considered to be normal at 2 years. Similar results were seen with penicillamine.

The RCT investigating ammonium tetrathiomolybdate and zinc for neurological symptoms of Wilson disease provides limited evidence on the efficacy and safety of first line trientine dihydrochloride plus zinc (Brewer et al. 2006). It found that 6/23 patients treated with trientine dihydrochloride and zinc for 8 weeks (followed by zinc monotherapy) experienced worsening of their neurological symptoms (compared with 1/25 patients taking tetrathiomolybdate and zinc, $p < 0.05$). No patients in either group reached the criteria for speech deterioration.

In their prospective observational study, Askari et al. (2003) found that 4 months' first line treatment with trientine dihydrochloride plus zinc (followed by zinc monotherapy) improved liver function in 9 patients with Wilson disease and hepatic decompensation who were potential candidates for liver transplantation. After 6 months, all patients no longer met the criteria for liver transplantation. Ascites, fatigue, nausea and vomiting resolved with treatment.

Another prospective observational study investigated once-daily trientine dihydrochloride in 8 patients with stable Wilson disease with liver involvement but mixed presentations (Ala et al. 2015). It found that, on changing from zinc (n=2), conventionally dosed trientine dihydrochloride (n=5) or penicillamine (n=1), physical

examination remained unchanged and no new neurological signs were detected over 12 months.

Zinc

Zinc salts alone or in combination with chelating agents for people who are intolerant of penicillamine

No studies that met the inclusion criteria specifically considered the use of zinc salts for treating people who were intolerant of penicillamine.

Zinc salts taken as maintenance therapy following treatment with a chelating agent

In their prospective observational study, Shimizu et al. (2010) found that hepatic and neurological symptoms did not worsen in 37 people who took zinc acetate alone for 48 weeks after previously being stable on penicillamine or trientine dihydrochloride (alone or in combination with other zinc salts), nor did any clinical signs or laboratory findings. Before being treated with zinc acetate, 9 people had hepatomegaly and this resolved in all of them at 16 weeks. Twelve people took trientine dihydrochloride initially (alone or with zinc salts), but results for this subgroup are not reported separately.

Safety and tolerability

Trientine dihydrochloride

In the retrospective study by Weiss et al. (2013), over a median of 13.3 years, adverse events leading to discontinuation of treatment were more common with penicillamine than with trientine dihydrochloride (94/326 [28.8%] compared with 10/141 [7.1%], $p=0.04$). Arthralgia occurred in 4 patients taking trientine dihydrochloride (2.8%), 2 patients had nausea or gastric pain (1.4%), and 1 patient (0.7%) experienced each of pruritus, myalgia, nephropathy, leukopenia, increase in antinuclear antibodies, erythema, lupus erythematosus and hirsutism. No patients died as a result of their treatment.

In the study by Taylor et al. (2009) ($n=16$), trientine dihydrochloride was discontinued in 3 children who took it second line. One had an allergic rash, 1 had low copper excretion and the third required liver transplantation, probably due to non-adherence.

After 5.1 years, trientine dihydrochloride was restarted in the patient who discontinued it because of a rash when his symptoms deteriorated during treatment with zinc, and was well tolerated.

According to the Summary of Product Characteristics (SPC) for trientine dihydrochloride, nausea has been reported at the start of treatment and, occasionally, skin rash can occur. Duodenitis, severe colitis and, very rarely, anaemia have also been reported.

Trientine dihydrochloride has been found to reduce serum iron levels, possibly reducing its absorption. Iron supplementation may be necessary in some cases and should be administered at a different time of the day to trientine dihydrochloride (SPC). According to the EASL guideline on managing Wilson disease, zinc should also be administered at a different time of day to trientine dihydrochloride to avoid it being chelated.

Safety and tolerability of zinc

Zinc salts taken as maintenance therapy following treatment with a chelating agent

In the total population in the study by [Brewer et al. \(2001\)](#), 11.8% (4/34) of children had mild gastric irritation with zinc acetate, and it had a small but statistically significant adverse effect on the children's high-density lipoprotein/total cholesterol ratio.

Adverse effects were seen in 54.1% (20/37) of people taking zinc acetate in the study by [Shimizu et al. \(2010\)](#). However, they were mild and did not require discontinuation of treatment. The most frequent adverse effects were gastrointestinal symptoms (such as stomach discomfort, 16.2% [6/37]) and decreased blood iron levels (45.9% [17/37]).

Evidence strengths and limitations

The studies included in this evidence review are of low quality and have significant limitations that affect their application to clinical practice. The majority are uncontrolled observational studies (generally, case series), which are subject to bias

and confounding factors. Two of the observational studies were undertaken prospectively, which may reduce some sources of bias and confounding factors; 4 were undertaken retrospectively. As is usual for a rare disease, many of the studies had small sample sizes. Surrogate or disease-orientated outcomes (such as liver function or urinary copper excretion) were used in some studies, rather than patient-orientated outcomes (such as hepatic or neurological symptoms).

One study was an RCT (Brewer et al. 2006) but it is unclear whether allocation was concealed, outcomes were poorly defined and many patients included in the study had received chelation therapy previously, which had not been controlled for. In addition, zinc was used concomitantly with trientine dihydrochloride.

Only Weiss et al. (2013) compared trientine dihydrochloride and penicillamine, and this comparison was retrospective. Nevertheless, this study included a large number of patients (n=405) and provides the most useful evidence on using these treatments in people with Wilson disease.

Many of the studies used a 250 mg formulation of trientine dihydrochloride. It is unclear how the bioavailability of this formulation compares with the 300 mg formulation that is licensed in the UK, and whether the effects of treatment would be the same. Dosage regimens differed in the studies or were not reported.

Some of the studies used trientine dihydrochloride plus zinc, whereas some used trientine dihydrochloride alone. It is unclear whether the combination has any advantages or disadvantages over monotherapy in terms of safety or efficacy. Compliance with treatment is likely to be an issue with combination therapy because the treatments cannot be taken at the same time. In some of the studies, trientine dihydrochloride was stopped after a period of time and zinc was used alone for maintenance therapy.

Wilson disease is a lifelong condition but the studies included in this evidence review have varied in the time span covered; those relating to zinc have been conducted over a relatively short period of time. A person's condition may take several years to deteriorate after stopping treatment ([Scheinberg et al. 1987](#)) and this should be

taken into account when considering the results of studies of maintenance treatment following discontinuation of a chelating agent. In practice, clinical and biochemical markers are used to determine when a person's treatment may be changed to zinc maintenance therapy. Some of the studies included in this evidence review monitored biochemical parameters when treatment was changed to zinc maintenance therapy; however, the studies do not provide sufficient information on when or why treatment was switched in the participants to help determine the optimal clinical condition or biochemical levels at which a change from a chelating agent could be considered.

Better quality studies are needed to compare the safety and efficacy of trientine dihydrochloride, penicillamine and zinc, and clarify their places in therapy. It is difficult to perform high quality RCTs with large sample sizes in rare diseases, although multicentre RCTs may be an option.

6 Criteria for Commissioning

The commissioning criteria for trientine dihydrochloride and zinc salts set out below apply for both adults and children with Wilson disease.

A. Patients intolerant of penicillamine with symptomatic disease

Trientine dihydrochloride will be commissioned as a second line option in patients with Wilson disease who are intolerant to or have a contra-indication to penicillamine and who have evidence of significant copper overload and its sequela requiring immediate treatment with a second line chelator. Patients are eligible for trientine dihydrochloride if they experience the following early side effects in the first weeks/months whilst on penicillamine and symptoms have not resolved and/or copper levels have not normalised:

1. Fever
2. Rash*
3. Enlarged lymph nodes
4. Neutropenia
5. Thrombocytopenia
6. Proteinuria

7. Severe persistent nausea

* Transient rashes and fever may occur early in therapy with penicillamine; if persistent, antihistamines or temporary withdrawal of treatment with or without a short course of steroids may be necessary. Penicillamine may be re-introduced at a lower dosage. If steroids are given, penicillamine should be reintroduced before steroid withdrawal.

Trientine dihydrochloride can be considered as an alternative to penicillamine in the following circumstances:

1. Patient has a past history of an autoimmune tendency
2. Patient has concurrent severe thrombocytopenia or renal disease
3. Patients who are hypersensitive to penicillin – patients may react rarely to penicillamine and thus trientine dihydrochloride needs to be available as alternative (BNF September 2016-March 2017;016).

B. Patients who become intolerant of penicillamine at a later time (see list below) and are without symptomatic disease and patients who have stable disease

Trientine hydrochloride is a recognised option but these patients could also be considered for zinc maintenance therapy by the tertiary care specialist centre, with the requirement for regular clinical and laboratory monitoring.

Late events (months to years after starting penicillamine) are usually but not exclusively in the list below:

1. Nephrotic syndrome
2. Glomerulonephritis
3. Total bone marrow aplasia
4. Skin changes (cutis laxa, elastosis perforans serpiginosa, pemphigus)
5. Myasthenia gravis
6. Polymyositis
7. Goodpastures syndrome
8. Optic neuritis
9. Proteinuria 1-2gm/day or equivalent in children (depending upon specialist Wilson disease and renal review)
10. Haematuria (if cause unknown) (see British National Formulary [BNF])

11. Thrombocytopenia, leukopenia (see BNF; note influence of hypersplenism)
12. Bleeding related to (11)
13. Lupus like syndrome (haematuria, proteinuria, positive antinuclear antibody).
14. Arthralgia

C: Patients who, after being prescribed trientine hydrochloride (or a combination of trientine and zinc), are on follow up without symptoms and have satisfactory parameters thought to reflect stable disease

These patients could also be considered for zinc maintenance therapy by a tertiary care specialist centre, with the requirement for their agreement to continue with regular monitoring.

* In the UK, zinc acetate dihydrate is the only zinc salt licensed for treatment of Wilson disease. Although the license does not preclude its use, the SPC states that it is not recommended for the initial treatment of people with symptoms of Wilson disease because of its slow onset of action.

7 Patient Pathway

Wilson disease is a rare condition with a complex range of presenting symptoms. Patients can be referred to a range of specialists, neurologists, metabolic physicians or liver specialists for, or following, diagnosis. As part of this policy, specialist centres will be recognised based upon the availability of consultant expertise in Wilson disease, hepatological, neurological (movement disorder expertise) and metabolic disorders. Specialist centres must provide all the range of specialists required or be able to enable patient access through a networked care model. Paediatric centres will also have to provide or be able to demonstrate clinical partnerships with centres with hepatology and neurological expertise.

In addition, access to ophthalmological, psychiatric, psychological, and clinical genetic services should be readily accessible, and physiotherapy and dietetic services available.

Where appropriate a formal shared care arrangement between a local hospital and the specialist centre could be put into place, with the patient being reviewed at this centre at least annually. This drug will be made available through homecare. The treatment of children with Wilson disease will follow the same structure.

8 Governance Arrangements

Trientine dihydrochloride treatment will normally only be initiated either in a specialist centre or by a non-specialist centre only after discussion with a specialist centre. All patients prescribed trientine dihydrochloride will have an annual review by their specialist centre to consider the appropriateness of continued prescribing. An established prior approvals system will be used for the prescribing of trientine dihydrochloride.

9 Mechanism for Funding

Trientine dihydrochloride will be routinely commissioned by NHS England through specialist neurology, liver and metabolic units, and in a formal shared care arrangement with such a centre. The activity will be invoiced through the contracts that the specialist trust has with NHS England.

10 Audit Requirements

The use of the drug will be audited through the NHS England prior approvals system.

11 Documents Which Have Informed this Policy

None.

12 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

References

Ala A., Walker A.P., Ashkan K., Dooley J.S., Schilsky M.L., 2007. Wilson Disease. *Lancet*, 369, p.397–408.

Ala A., Aliu E., and Schilsky M.L., 2015. Prospective pilot study of a single daily dosage of trientine for the treatment of Wilson Disease. *Digestive Diseases and Sciences*, 60, p. 1433–9.

Arnon R., Calderon J.F., Schilsky M. et al., 2007. Wilson Disease in children: serum aminotransferases and urinary copper on triethylene tetramine dihydrochloride (trientine) treatment. *Journal of Pediatric Gastroenterology and Nutrition*, 44.p. 596–602.

Askari FK, Greenson J, Dick RD et al., 2003. Treatment of Wilson Disease with zinc. XVIII. Initial treatment of the hepatic decompensation presentation with trientine and zinc. *Journal of Laboratory and Clinical Medicine*, 142.p. 385–90.

Bell CL, Graziano, FM, Arthritis Rheum. 1983 Jun; The safety of administration of penicillamine to penicillin-sensitive individuals. 26(6):801-3.

Brewer G.J., Askari F., Lorincz M.T., et al., 2006. Treatment of Wilson Disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease. *Archives of Neurology*, 63p. 521–7.

EASL Clinical Practice Guidelines: Wilson's disease. *J Hepatol* 2012;56 (3): 671-685.

Roberts EA, Schilsky ML. AASLD Practice Guidelines: Diagnosis and treatment of Wilson disease. *Hepatology* 2008; 47 (6):2089-2111.

Scheinberg, IH., and Sternlieb, I. Wilson Disease. In: Lloyd H, Smith J, editors. 1984. *Major Problems in Internal Medicine* Philadelphia: Saunders. pp134-145.

Scheinberg IH, Jaffe ME, Sternlieb I. The use of trientine in preventing the effects of interrupting penicillamine therapy in Wilson's disease. In *New England Journal of Medicine*. 1987 Jul 23;317(4):209-13.

Schilsky ML (2016) Treatment of Wilson Disease. www.uptodate.com. (last updated 29th November 2016, last accessed December 2016).

Taylor R.M., Chen Y., Dhawan A., on behalf of the EUROWILSON Consortium, 2009. Triethylene tetramine dihydrochloride (trientine) in children with Wilson Disease: experience at King's College Hospital and review of the literature. *European Journal of Pediatrics*, 168, p.1061–8.

Walshe J.M., 2011. The pattern of urinary copper excretion and its response to treatment in patients with Wilson Disease. *QJM*, 104, p. 775–8.

Weiss KH. In Pagon RA, Adam MP, Ardinger HH, Wallace SE, et al (1999 Oct 22, updated 2016 Jul 29) Wilson Disease In: GeneReviews (Internet). Seattle(WA): University of Washington;Seattle;1993-2016.

Weiss KH, Thurik F, Gotthardt DN et al. (2013) Efficacy and safety of oral chelators in treatment of patients with Wilson Disease. In: Clinical Gastroenterology and Hepatology 11: 1028–35

Weiss KH, Gotthardt DN, Klemm D et al. Zinc monotherapy is not as effective as chelating agents in treatment of Wilson disease. Gastroenterology 2011; 140:1189-1198.

Wiggelinkhuizen M, Tilanus ME, Bollen CW et al. (2009) Systematic review: clinical efficacy of chelator agents and zinc in the initial treatment of Wilson Disease In: Alimentary Pharmacology and Therapeutics 29: 947–58