CPAG Summary Report for Clinical Panel
trientine dihydrochloride for patients with Wilson's disease

The Benefits of the Proposition - trientine dihydrochloride for Wilson's disease			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured	
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Adverse events identified C	This outcome looked at how many people had side effects while they were taking trientine dihydrochloride or zinc salt as combination or maintenance therapy. It also considered how many people had to stop taking their treatment because of side effects. In a randomised control trial (Brewer et al. 2006), 48 patient with neurological symptoms were randomised to receive tetrathiomolybdate or trientine for 8 weeks in combination with zinc, 1 person in the trientine dihydrochloride group had leukopenia (low white blood cells) and 4 patients taking trientine died during the 3 year follow up. In an uncontrolled observational study

			(Arnon et al. 2007), 10 children with mixed disease presentation (5/10recorded as incidental presentation) were treated with trientine dihydrochloride first line for 4–8 months before zinc was added followed by stopping of trientine once urinary copper levels were 60–200 micrograms/24 hours. Follow up period was 12-18 months. No significant side effects were seen. 1 patient stopped trientine dihydrochloride after 12 months because of elevated liver enzyme levels (case may be linked to non-adherence). In a case review of medical notes (Taylor et al. 2009) including 16 children (2 had acute liver failure, 12 had chronic liver disease and 2 diagnosed via family screening) 3/16 had in addition neurological symptoms and a median follow up of 6.43 years.3 children took trientine dihydrochloride first line and the remaining second line. Trientine was discontinued in 3 children who took trientine as second line. 1 had an allergic rash, 1 had low copper excretion and the third required liver transplantation. A systematic review by Chen et al. (2015) of 271 treatment blocks included different clinical presentations of Wilson's disease with a mean follow-up was 10.6 years, found that, 97 resulted in side effects with combination treatment with zinc and a chelating agent(penicillamine or trientine), an overall side effect rate of 35.8%.Inter-study analysis found more adverse effects with combination treatment compared with trientine (RR 1.67, 95% CI 1.04 to 2.69) and compared with zinc salts (RR 2.25, 95% CI 1.36 to 3.73), but not compared with penicillamine (RR 1.10, 95% CI 0.87 to 1.38) In Shimizu et al. (2010), side effects were seen in 54.1% of 37 patients with mixed presentation of Wilson disease controlled or stable following treatment with chelating agents taking zinc acetate over 48 weeks. Side effects were mild and did

			not require discontinuation of treatment. The most frequent side effects were gastrointestinal symptoms (such as stomach discomfort, 16.2%) and decreased blood iron levels (45.9%). Only the study by Shimizu et al. (2010) was prospective but over a short period of time; the others were retrospective and either included asymptomatic patients or treatment with zinc sulphate. Outcome assessment was not blinded. The studies all reflect the experience of singe centres and a small number of people only received zinc therapy, therefore it does not support definitive conclusions. The above studies are of low-quality in which participants were either not randomised to treatment or treatment allocations were not concealed, leading to potential bias. The studies also did not correct for possible confounding factors that may have influenced the results (including demographic factors, environmental factors, duration of disease or treatment, comorbidity, co-medication and dietary composition). Due to differences in the study populations, in treatment pathways and outcome assessments, the results of the studies could not be pooled or support clear conclusions.
11.	Delivery of intervention	Not measured	

Other health metrics determined by the evidence review - trientine dihydrochloride for Wilson's disease			
No	Metric	Grade of evidence	Summary from evidence review
1.	Survival	There is a survival benefit [C]	This outcome describes the proportion of people who died or whose disease progressed until they needed a liver transplant. The systematic review by Chen at al. (2015) 3/17 studies assessed trientine plus zinc (1 each for zinc sulfate, zinc acetate, and another zinc salt or an

			unknown zinc salt), found that Combination versus trientine alone: 60.4% versus 82.6% (RR 0.73, 95% CI 0.65 to 0.82; p<0.00001) Combination versus zinc salts alone: 60.4% versus 71.6% (RR 0.84, 95% CI 0.72 to 0.98; p=0.03). This compares with a rate of 6.6% for mortality and liver transplant with monotherapy (44 had liver transplant and 103 died out of a cohort of 2,239 patients). A significantly higher mortality and transplantation rate was seen in the penicillamine plus zinc sulphate group (not licensed for this indication) compared to other treatments (16.3% vs 4.5%). Most of the 17 studies included in this review were observational and details of the quality and limitations are not provided. Observational studies are subject to bias and confounding and the authors of the systematic review note that there may be bias in some of their interpretations of the results due to the lack of substantive data. It is unclear whether the populations, treatment pathways and assessed outcomes were similar between the studies, and no information on heterogeneity is reported. Therefore, it is unclear whether the data was suitable to be pooled for comparison.
2	Liver function and hepatic outcomes (fibrosis, which is excessive accumulation of scar tissue that results from ongoing inflammati	Grade C	A case review of Wilson patients presenting with mixed symptoms (Weiss et al. 2013) noted no difference in effectiveness between penicillamine and trientine dihydrochloride over a mean 13.3 years follow up. 2.8% patients taking penicillamine and 2.1% (3/141) patients taking trientine underwent liver transplantation. In asymptomatic and symptomatic patients, worsening of hepatic outcomes was seen in 4/295 (1.4%) taking penicillamine first-line and 4/103 (3.9%) taking trientine second-line with no worsening seen with first-line trientine or second-line penicillamine.

	on and liver cell death that occurs in most types of chronic liver diseases. Nodules, abnormal spherical areas of cells, form as dying liver cells are replaced by regenerating cells. This regeneration of cells causes the liver to become hard. Fibrosis refers to the accumulation of tough, fibrous scar tissue in the liver)		There were no significant differences between the groups for either line of treatment (p=1 and p=0.6 respectively). Askari et al. 2003 an uncontrolled observational study including 9 patients with hepatic decompensation (8/9 candidates for liver transplant where 8 patients also had hyperbilirubinaemia (jaundice) and 7 had ascites (which is a build-up of fluid between the two layers of the peritoneum. This is a membrane that lines the abdomen) were treated with trientine and zinc for at least 4 months. Within 12 months in all patients', albumin levels, prolonged prothrombin time and bilirubin levels became normal. Ascites, fatigue, nausea and vomiting resolved. Benefits persisted in all patients during follow up (mean follow up was 6.2 years). Hepatic fibrosis was reduced in 3/9 patients who had serial liver biopsies. After 6 months, no patients met the criteria for liver transplantation (Child-Turcotte-Pugh score became 5 in all patients, a score of 8 is the minimum for a liver transplant). A pilot study (Ala et al. 2015) of single daily dose of trientine included 8 patients who were stable on current treatment (5 trientine, 2 zinc and 1 penicillamine) for over 1 year (median 8 years, range 3–50 years), with stable liver disease. Laboratory test results were generally stable in patients, although Alanine Aminotransferase Test (Alanine aminotransferase (ALT) is an enzyme found mostly in the cells of the liver and kidney. Much smaller amounts of it are also found in the heart and muscles. The function of ALT is to convert alanine, an amino acid found in proteins, into pyruvate, an important intermediate in cellular energy production. In healthy individuals, ALT levels in the blood are low. When the liver is damaged, ALT is released into the blood, usually before more obvious signs of liver damage occur, such as jaundice. This makes

			ALT a useful test for early detection of liver damage. Aspartate Transaminase Test, which tests for liver damage, increased in some patients, none of whom required treatment to be stopped. The above studies are of low-quality in which participants were either not randomised to treatment or treatment allocations were not concealed, leading to potential bias. The studies also did not correct for possible confounding factors that may have influenced the results (including demographic factors, environmental factors, duration of disease or treatment, comorbidity, co-medication and dietary composition). Due to differences in the study populations, in treatment pathways and outcome assessments, the results of the studies could not be pooled or support clear conclusions.
3	Neurological sign and deterioration	Grade C	In a randomised, double blind controlled study (Brewer et al. 2006) 48 patient randomised to receive tetrathiomolybdate or trientine dihydrochloride for 8 weeks, neurological deterioration was defined as an increase of 5 points on a quantitative neurological examination scale (range 0–38). 6/23 patients in the trientine group and 1/25 patients in the tetrathiomolybdate group experienced neurological deterioration. The difference between the groups was statistically significant ($p<0.05$). Weiss et al. 2013 a case review of patients with mixed symptoms of Wilson's disease noted in symptomatic neurological patients, no statistically significant differences between the rates of improvement for first line penicillamine/trientine (77/114 [67.5%] for 11/20 [55.0%] for trientine, p=0.3) compared with second line treatment (3/13 [23.1%] compared with 26/51 [51.0%] respectively, p=0.1). In asymptomatic and symptomatic patients, worsening of neurological outcomes was

			not statistically significantly different between the groups for second-line treatment (1/31 [3.4%] with penicillamine compared with 8/103 [7.8%] with trientine, p=0.7). However, a statistically significant difference was seen for first-line treatment, with more worsening seen with trientine (4/38 [10.5%] compared with 6/295 [2.0%] with penicillamine, p=0.02). Ala et al. 2015 a pilot study of single daily dose of trientine over 12 months included 8 patients who had been stable on current treatment (5 trientine dihydrochloride, 2 zinc and 1 penicillamine), neurological symptoms remained generally unchanged and a statistically significance worsening with trientine dihydrochloride used as first line therapy. In the systematic review by Wiggelinkhuizen et al. (2009), 5.7% (6/107) of people reported worsening of neurological symptoms with penicillamine compared with 0.8% (1/127 including pre-symptomatic patients) of people taking zinc salts. The systematic review comprises low-quality observational studies in which participants were not randomised to treatments. The number a people taking zinc to treat neurological symptoms was small (1/127 taking zinc salts). The above studies are of low-quality in which participants were either not randomised to treatment or treatment allocations were not concealed, leading to potential bias. The studies also did not correct for possible confounding factors that may have influenced the results (including demographic factors, environmental factors, duration of disease or treatment, comorbidity, co-medication and dietary composition). Due to differences in the study populations, in treatment pathways and outcome assessments, the results of the

			studies could not be pooled or support clear conclusions.
4	Copper excretion	Grade C	A case review of 192 pre-symptomatic and symptomatic patients (Walshe 2011) included15/124 patients with neurological Wilson's disease were treated with trientine monotherapy. The basal, pre-treatment copper excretion was the lowest in pre-symptomatic patients (207.93 µg/24 h) and the highest in the hepatic patients (465.75 µg/24 h). Those with neurological Wilson's disease gave an intermediate figure (305.58 µg/24 h).At 1 year, basal copper excretion had fallen from 193 micrograms/24 hours to 53 micrograms/24 hours. At 2 years, it fell further to 38 micrograms/24 hours, approaching the normal level of 30 micrograms/24 hours. The small subgroup treated with trientine, rather than penicillamine, showed similar results. Progress of clinical symptoms was not reported.
5	Speech deterioration	Grade C	Brewer et al. 2006 a randomised, double blind controlled study including 48 newly diagnosed patients with neurological symptoms randomised to receive tetrathiomolybdate or trientine dihydrochloride for 8 weeks, no patients in either group met the criteria for speech deterioration. Speech deterioration was defined as an increase of 3 points on a speech examination scale (range 0–7).
1.	Overall therapeutic success	Grade C	The systematic review of 17 studies by Chen et al. (2015) found that, of the 437 pooled treatment blocks, 264 responded well to combination treatment with zinc (including zinc sulphate which is not licensed for this indication) and a chelating agent; an overall effectiveness rate of 60.4%. The mean follow up period was 10.6 years. When compared with results from other studies looking at the efficacy of individual treatments for Wilson's disease (including asymptomatic patients 9.3% of the study

			population) combination treatment was found to be statistically significantly less effective (60.4%) than either penicillamine (73.7%), trientine (82.6%) or zinc (71.6%) alone. Combination treatment was effective in only 47.1% of people with mainly hepatic symptoms, compared with 78.6% of those with mainly neurological symptoms. Most of the 17 studies in the systematic review appear to be observational studies, although this is not clearly stated, and details of the quality and limitations of the included studies are not provided. Observational studies are subject to bias and confounding and the authors of the systematic review note that there may be bias in some of their interpretations of results due to the lack of substantive data. It is unclear whether the study populations, treatment pathways and outcome assessments were similar between the studies, and no information on heterogeneity is reported. Therefore, it is unclear whether the data was suitable to be pooled. In the prospective observational study Shimizu et al. (2010), followed up 37 patients with Wilson disease over 48 weeks of treatment with zinc acetate. In these patients disease had stabilised previously when treated with chelating agents. Nine out 29 patients with predominately hepatic symptoms had mild hepatomegaly (an enlarged liver), which resolved in all nine of them at 16 weeks of treatment with zinc acetate. The outcome may have been affected by previous treatments. Kayser-Fleischer rings disappeared in 3 out of the 11 patients. There was no change in neurological symptoms. Hepatic and neurological symptoms did not worsen in any of the 37 people in the study. The results provide no information on when a patient can be switched to zinc maintenance therapy but suggest careful monitoring of zinc treatments measuring 24-h urinary zinc excretion and spot

			urinary copper measurement. The 3 studies looking at this outcome are non-comparative observational studies, which are susceptible to bias, confounding and other methodological problems. Only the study by Shimizu et al. (2010) was prospective but was over a short period of time. The others studies were retrospective and either included asymptomatic patients or treatment with zinc sulphate. Outcome assessment was not blinded. The studies all reflect the experience of singe centres and a small number of people only. Thus they do not support definitive conclusions. Czlonkowska et al. (2014) found that there were no statistically significant differences between monotherapy with penicillamine and zinc sulphate (this treatment is not licensed for this indication) in subgroups of newly diagnosed patients over a median follow up period of four year). Whilst the likelihood of remaining on first-line therapy appeared to be higher in people treated with zinc alone in the group with hepatic symptoms (p=0.028) there were no statistically significant differences overall the treatments. Successful treatment was higher in the hepatic subgroup at 94.4% (34/36) for people taking penicillamine and 94.1% (48/51) for those on zinc sulphate, whilst for the neurological subgroup the treatment was successful in 82.8% (29/35) for patients treated with penicillamine compared with 71.4% (15/21) of patients taking zinc sulphate.
2.	7.Mortality or liver transplantation combined	Grade C	This outcome describes the proportions of people who died or whose disease progressed until they needed a liver transplant. The systematic review by Chen et al. (2015) found that, of 417 treatment blocks of combination treatment with zinc and a chelating agent, 13 required

			liver transplants and 40 resulted in death, a mortality or transplant rate of 12.7%. This compares with a mortality or transplant rate of 6.6% in studies of monotherapy with the 4 most common treatments (penicillamine, trientine, zinc salts and combination treatment), in which 44 out of 2,239 people required liver transplants and 103 died. A significantly higher mortality or transplant rate was seen with penicillamine plus zinc sulfate compared with all other groups (16.3% vs. 4.7%). Most of the 17 studies in the systematic review appear to be observational studies – see section 6 of this part.
8	Adherence	Grade C	Ala et al. 2015 a pilot study included 8 patients who had been stable on current treatment (5 trientine, 2 zinc and 1 penicillamine) for over 1 year and took trientine at 15 mg/kg /day over 12 months. Patients' questionnaires revealed once-daily trientine was easier to adhere to and preferable to having to time treatment around meals. In a case review study (Arnon et al. 2007), 10 children who were treated with trientine monotherapy for 4–8 months before zinc was added followed by stopping of trientine once copper levels reached 60–200 micrograms/24 hours, non-adherence was identified in 4 patients by increased Alanine Aminotransferase Test levels and low urinary levels of zinc, including 1 patient whose Alanine Aminotransferase Test had previously was normal. Czlonkowska et al. (2014) found that there were no statistically significant differences between monotherapy with penicillamine and zinc sulphate (this treatment is not licensed for this indication) in subgroups of newly diagnosed patients over a median follow up period of four year). Whilst the likelihood of remaining on first-line

			therapy appeared to be higher in people treated with zinc alone in the group with hepatic symptoms (p=0.028) there were no statistically significant differences overall the treatments. Noncompliance was more common in the neurologic group at 8.6% (3/35) in the penicillamine group and 19% (4/21) in the zinc group. In the hepatic group of patients noncompliance was less common at 2.9% (1/35) in the penicillamine treated group and 19.6% (10/51) in the zinc group. This study is an open-label, retrospective observational study and is, therefore, susceptible to bias, confounding and other methodological problems. Although it is a comparative study, it is a retrospective analysis and no randomisation was used and outcome assessment was not blinded. Thus it does not support definitive conclusions.