National Institute for Health and Care Excellence

Evidence review

Wilson's disease: trientine dihydrochloride

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Prepared by: The NICE Medicines and Technologies Programme on behalf of NHS England Specialised Commissioning

The content of this evidence summary was up-to-date in September 2016. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Key points from the evidence

Summary

A retrospective observational study of 405 patients provides the best available evidence for using trientine dihydrochloride compared with penicillamine for Wilson's disease. In the study, there were no statistically significant differences in the rates of hepatic and neurological improvement between trientine dihydrochloride and penicillamine. Hepatic signs and symptoms were reduced in about 90% of patients taking first-line therapy and 70% of patients taking second-line therapy with either drug. The proportion of patients experiencing improvement in neurological symptoms was lower (about 66% of patients taking first-line therapy and 45% of patients taking second-line therapy with either drug). More than a third of patients did not improve or became worse in both treatment groups.

Trientine was generally well tolerated. In the study, statistically significantly more patients discontinued treatment because of adverse events with penicillamine compared with trientine.

The other 6 studies included in the evidence review are smaller, including between 5 and 23 patients taking trientine. The evidence has significant

limitations and better-quality studies are needed to compare the safety and efficacy of trientine, penicillamine and zinc for Wilson's disease, and clarify their places in therapy.

Regulatory status: Trientine dihydrochloride (manufactured by Univar) is licensed in the UK for treating Wilson's disease in people who cannot tolerate penicillamine. First-line use of trientine dihydrochloride is off-label.

Effectiveness	**Safety**
In a retrospective observational study including 405 patients in which some people took more than 1 treatment: • There were no statistically significant differences in rates of improvement or worsening **of hepatic signs and symptoms** between penicillamine (n=326) and trientine (n=141) for first- or second-line treatment. 90.9% and 70.5% of symptomatic people improved with first- and second-line treatment respectively with either drug. Four patients taking each treatment became worse. • There were no statistically significant differences in rates of improvement of **neurological symptoms** between penicillamine and trientine for first- or second-line treatment. 65.7% and 45.3% of symptomatic people improved with first- and second-line treatment respectively with either drug. • Worsening of neurological symptoms occurred statistically significantly more often with trientine compared with penicillamine for first-line treatment, but the number of patients taking trientine first-line was relatively small (4/20 compared with 6/114 for penicillamine in symptomatic people, p=0.04). Similar proportions of patients taking penicillamine (1/31) and trientine (8/103) second-line became worse.	• In the retrospective observational study (n=405), discontinuation due to adverse events was seen statistically significantly more often with penicillamine compared with trientine (28.8% compared with 7.1%, p=0.04). No deaths related to adverse events were seen. Trientine was generally well tolerated. • According to the Summary of product characteristics 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.
Patient factors	**Resource implications**
• Trientine dihydrochloride should be stored in a refrigerator in the original container with the silica gel sachet.	• Trientine dihydrochloride costs £2,901.28 for 100 x 300 mg capsules (excluding VAT, local

• People taking trientine may need iron supplementation. • Iron and zinc should be administered at different times from trientine to avoid them being chelated. • Trientine should be administered on an empty stomach, usually 2 to 4 times daily. • Treatment regimens for trientine and other treatments for Wilson's disease may be difficult to adhere to.	procurement discounts and any costs incurred: personal communication Univar, July 2016). • The cost of trientine ranges from around £2,400 to £4,100 per 28 days for maintenance treatment compared with £130 to £260 for penicillamine and £80 for zinc.

Introduction and current guidance

Wilson's disease is a rare inherited genetic disorder in which biliary excretion of copper is impaired. Copper accumulates in the liver and, subsequently, other organs including the central nervous system, eyes and kidneys. Children may be asymptomatic while copper accumulates. Symptoms of the disease are usually non-specific but it should be considered in people with unexplained liver disease and neurological or psychiatric symptoms. Wilson's disease is fatal without treatment (Wilson's disease, Oxford Textbook of Medicine).

Chelating agents (such as penicillamine or trientine), which bond to copper in the body and are subsequently excreted, are recommended first-line for treating Wilson's disease. Zinc, which inhibits absorption of copper, may also be used. Lifelong treatment is required to avoid recurrence of symptoms and liver failure (Wilson's disease, Oxford Textbook of Medicine).

Full text of Introduction and current guidance.

Product overview

Trientine dihydrochloride (manufactured by Univar) is licensed in the UK for treating Wilson's disease in people who cannot tolerate penicillamine.

First-line use of trientine dihydrochloride is off-label. In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of

using trientine outside its authorised indications. Supporting information and advice is also available from the GMC.

Full text of Product overview.

Evidence review

- This evidence summary considers the best available evidence for using trientine dihydrochloride for treating Wilson's disease. It primarily looks at second-line treatment of people who cannot tolerate penicillamine (the licensed indication), although studies of first-line treatment are also included because of the limited amount and quality of evidence, and because trientine is sometimes used in this way (off-label). Seven studies are included: 1 randomised controlled trial (RCT), 2 prospective observational studies and 4 retrospective observational studies.
- The RCT compared **first-line** treatment with tetrathiomolybdate (an experimental chelating agent, which is not currently available) plus zinc with **trientine plus zinc** in 48 patients with **neurological symptoms** of Wilson's disease (Brewer et al. 2006). It found that 6/23 patients treated with trientine and zinc for 8 weeks (followed by zinc monotherapy) experienced worsening of their neurological symptoms compared with 1/25 patients taking tetrathiomolybdate and zinc ($p<0.05$).
- A prospective observational study also considered **first-line** treatment with **trientine plus zinc** (followed by zinc monotherapy) (Askari et al. (2003). It found that taking the combination for 4 months improved liver function in 9 patients with Wilson's disease and **liver failure** 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.
- The second prospective observational study was a pilot study of **once-daily trientine** in 8 patients with stable Wilson's disease with **liver involvement but mixed presentations** (Ala et al. 2015). It found that, on changing from zinc (n=2), conventionally dosed trientine (n=5) or penicillamine (n=1), physical examination remained unchanged and no new neurological signs were detected over 12 months.

- A retrospective observational study (Weiss et al. 2013) analysed data on 405 patients with Wilson's disease who were treated with chelating agents (some took more than 1 treatment). The study included 141 patients who took **trientine 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 and penicillamine for treating **hepatic signs and symptoms** of Wilson's disease when used **first- or second-line**. In symptomatic patients after 6–48 months, 90.7% of patients taking penicillamine first-line improved compared with 92.6% of patients taking trientine. Rates of improvement were lower for second-line treatment (75.0% compared with 68.9% respectively). Worsening of hepatic signs and symptoms was seen in only 8/467 patients taking first- or second- line treatments in the study; 4 taking penicillamine first-line and 4 taking trientine second-line, with no significant differences between the groups for line of treatment.
- Weiss et al. (2013) also found no statistically significant differences between trientine and penicillamine used **first- or second-line** for improving **neurological symptoms**. In symptomatic patients after 6–48 months, the proportion of patients whose neurological symptoms improved was lower than for hepatic symptoms (first-line trientine 55.0% compared with penicillamine 67.5%; second line trientine 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 significantly similar between the groups in patients who switched treatments. In treatment-naive patients, worsening occurred in statistically significantly more patients in the trientine group (20.0% compared with 5.3% for penicillamine in symptomatic patients, p=0.04), although the number of patients taking trientine first-line was relatively small (20 compared with 114 for penicillamine).
- Taylor et al. (2009) retrospectively studied 16 children with Wilson's disease (14 with **liver disease**) who took trientine. After a median of

6.43 years, liver function became normal in the majority of children. However, 2/3 children taking trientine **first-line** and 4/13 children taking trientine **second-line** still had abnormal liver function. The authors reported that all children who presented with liver symptoms only became symptom-free; however, trientine 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 in 10 children with Wilson's disease and **mixed presentations** who were followed up for at least 12 months. **Trientine monotherapy** was used for 4–8 months before **zinc was added**. 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. 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's disease. In patients with **neurological symptoms** (n=124), 15 patients took trientine (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.
- Trientine was generally well tolerated in the studies. In the study by Weiss et al. (2013), statistically significantly more patients discontinued treatment because of adverse events with penicillamine compared with trientine (28.8% compared with 7.1%, p=0.04). According to the Summary of product characteristics 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.
- 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. Many of the studies had small sample sizes and 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). In the RCT by Brewer et al. (2006), 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. Only Weiss et al. (2013) compared trientine and penicillamine, but this comparison was retrospective.

- Some of the studies used trientine first-line in newly diagnosed patients (off-label in the UK) and, therefore, have limited relevance to the licensed indication. There is more clinical experience of using penicillamine, rather than trientine first-line. In the study by Weiss et al. (2013), only 38 people took trientine first-line compared with 295 people taking penicillamine first-line. Dosage regimens differed in the studies or were not reported. It is unclear whether combining trientine plus zinc has advantages or disadvantages over monotherapy in terms of safety or efficacy.

Full text of Evidence review.

Context

The cost of trientine is substantially more than that of other treatments for Wilson's disease, ranging from around £2,400 to £4,100 per 28 days for maintenance treatment compared with £130 to £260 for penicillamine and £80 for zinc (excluding VAT, local procurement discounts and any costs incurred).

Full text of Context.

Estimated impact for the NHS

There is a lack of high-quality evidence to estimate the relative treatment effects of the available drugs for treating Wilson's disease. Guidelines from the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases recommend either penicillamine or trientine for treating Wilson's disease, but note that trientine may be better tolerated.

Full text of Estimated impact for the NHS.

About this evidence summary

Evidence summaries provide a summary of the published evidence for selected medicines that are considered to be of significance to the NHS including new medicines, off-label use of licensed medicines and unlicensed medicines.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary and provide information for healthcare professionals to inform their decision-making.

This summary is not NICE guidance.

Full evidence summary

Introduction and current guidance

Wilson's disease is a rare inherited genetic disorder with an incidence of about 1 in 30,000 people. In people with the disease, biliary excretion of copper is impaired leading to accumulation of copper in the liver, which causes toxicity. Eventually, copper is released into the bloodstream and deposited in extrahepatic tissues causing dysfunction of other organs including the central nervous system, eyes and kidneys. Wilson's disease is fatal without treatment (Wilson's disease, Oxford Textbook of Medicine).

Symptoms of Wilson's disease are usually non-specific but the condition should be considered in people with unexplained liver disease and neurological or psychiatric symptoms. Typical presentation is in the second and third decade of life, most commonly with liver disease (ranging from asymptomatic hepatomegaly to fulminant hepatic failure) or a neuropsychiatric disorder (dystonia, dysarthria, Parkinsonian tremor or psychiatric symptoms) (Wilson's disease, Oxford Textbook of Medicine).

Chelating agents (such as penicillamine or trientine), which bond to copper in the body and are subsequently excreted, are recommended first-line for treating Wilson's disease. Zinc, which inhibits absorption of copper, may also be used alone or in combination with a chelating agent. Lifelong treatment is required to avoid recurrence of symptoms and liver failure. Liver transplantation may be required for fulminant hepatic failure and decompensated liver disease that is unresponsive to medical therapy (Wilson's disease, Oxford Textbook of Medicine).

The European Association for the Study of the Liver (EASL) guideline on managing Wilson's disease advises that there is a lack of high-quality evidence to estimate the relative treatment effects of the available drugs. This evidence summary considers the best available evidence for trientine.

Product overview

Drug action

Trientine dihydrochloride (also referred to as trientine hydrochloride or triethylenetetramine dihydrochloride) chelates with copper, forming a stable soluble complex, which is excreted via the kidneys (Summary of product characteristics).

Licensed therapeutic indication

Trientine dihydrochloride (manufactured by Univar) is licensed in the UK for treating Wilson's disease in people who cannot tolerate penicillamine. The initial UK licence was granted in 1985, based on a series of case reports supported by references and information from UK specialists (personal communication Univar, July 2016 and August 2016).

First-line use of trientine dihydrochloride is off-label. In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using trientine outside its authorised indications. Supporting information and advice is also available from the GMC.

Trientine tetrahydrochloride was submitted to the European Medicines Agency for a licence in January 2016. It is currently not known what the indication will be. The tetrahydrochloride formulation of trientine is not discussed in this evidence summary and all references refer to the dihydrochloride formulation.

Course and cost

Trientine dihydrochloride (manufactured by Univar) is available as 300 mg capsules. The adult dosage of trientine dihydrochloride is 1200–2400 mg (4–8 capsules) daily in 2 to 4 divided doses, preferably 30–60 minutes before meals.

The dosage in children is lower than for adults and depends on age and body weight. A typical dosage for initiating therapy is 600–1500 mg (2 to

5 capsules) daily, which should be adjusted according to clinical response (Summary of product characteristics).

Trientine dihydrochloride costs £2,901.28 for 100 x 300 mg capsules (excluding VAT, local procurement discounts and any costs incurred, such as distribution costs: personal communication Univar, July 2016).

Evidence review

This evidence summary considers the best available evidence for using trientine dihydrochloride for treating Wilson's disease. It primarily looks at second-line treatment of people who cannot tolerate penicillamine (the licensed indication), although studies of first-line treatment are also included because of the limited amount and quality of evidence, and because trientine is sometimes used in this way (off-label).

In the searches undertaken for this evidence summary, studies of trientine for Wilson's disease were included if they:

- were published between 1996 and July 2016 to capture studies that reflect current clinical practice
- were systematic reviews, randomised controlled trials (RCTs), prospective or retrospective cohort studies or case series
- considered people with Wilson's disease taking any treatment (penicillamine, trientine or zinc) or trientine only, but not primarily other treatments
- included at least 5 people taking trientine (thereby excluding single case reports)
- primarily considered the efficacy or safety of individual treatments.

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

Seven studies are included in this evidence review:

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

Table 1: Summary of the RCT of tetrathiomolybdate compared with trientine dihydrochloride for Wilson's disease

Study	Patients	Interventions	Selected reported outcomes
Brewer et al. 2006 Randomised, double blind controlled study comparing tetrathiomolybdate[a] and trientine in patients with neurological symptoms of Wilson's disease. General Clinical Research Center of the University of Michigan Hospital.	48 primarily newly diagnosed patients with neurological symptoms of Wilson's disease were included. Patients who had received penicillamine or trientine for more than 28 days were excluded. Some included patients had stopped penicillamine more than a year ago and later developed new neurological symptoms. Mean age was 28 years (range 13–49 years). 30/48 patients were male.	Patients were randomised to receive tetrathiomolybdate 20 mg 6 times daily or trientine 500 mg twice daily (plus matching placebo) for 8 weeks. All patients received zinc 50 mg twice daily, which they continued on discharge from the hospital. Baseline characteristics appeared broadly similar between the groups. Follow up was 3 years.	6/23 patients in the trientine group and 1/25 patients in the tetrathiomolybdate group experienced neurological deterioration[b]. The difference between the groups was statistically significant ($p<0.05$). No patients in either group met the criteria for speech deterioration[c]. Over 8 weeks, 1 person in the trientine group had leukopenia. 4 patients taking trientine died during follow up.
[a] an experimental chelating agent, which is not currently available [b] Neurological deterioration was defined as an increase of 5 points on a quantitative neurological examination scale (range 0–38). [c] Speech deterioration was defined as an increase of 3 points on a speech examination scale (range 0–7).			

Table 2: Summary of the prospective studies of trientine dihydrochloride for Wilson's disease

Study	Patients	Interventions	Selected reported outcomes
Ala et al. 2015 Pilot study of a single daily dose of trientine for Wilson's disease. Yale University Medical Center.	This study included 8 patients who had been 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. Age ranged from 22–71 years. 7/8 patients were male.	Trientine 15 mg/kg (rounded upwards to the nearest 250 mg) was taken once daily for 12 months.	Physical examination remained unchanged and no new neurological signs were detected. Laboratory test results were generally stable, although ALT and AST (liver enzymes) increased in some patients, none of whom required treatment to be stopped. Patients' questionnaires revealed once-daily trientine was easier to adhere to and preferable to having to time treatment around meals.
Askari et al. 2003 Study of trientine plus zinc in patients newly diagnosed with liver failure caused by Wilson's disease. General Clinical Research Center of the University of Michigan Hospital.	This study included 9 patients with hepatic decompensation[a] who were potential candidates for liver transplantation based on their CTP scores (range 9–13). Patients with neurological symptoms were excluded, as were those who had been treated with another therapy for more than a month. Mean age was 25 years (range 19–32 years). 6/9 patients were female.	Trientine 1,000 mg/day and zinc 150 mg/day were taken for at least 4 months (initial 6–8 weeks in hospital). After 2 weeks, 1 patient with mild neurological symptoms was transferred to another clinical trial and randomised to receive tetrathiomolybdate 120 mg/day plus zinc 150 mg/day for 8 weeks then zinc alone. Mean follow up was 6.2 years (range 12 months to 14 years).	Within 12 months, in all patients, albumin levels, prolonged prothrombin time and bilirubin levels became normal. Ascites, fatigue, nausea and vomiting resolved with treatment. Benefits persisted in all patients during follow up. Hepatic fibrosis was reduced in 3 patients who had serial liver biopsies. After 6 months, no patients met the criteria for liver transplantation (CTP score became 5 in all patients). Adverse events were not reported.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTP score, Child-Turcotte-Pugh score for assessing the severity of cirrhosis and need for liver transplantation, a score of 8 is the minimum for a liver transplant (generally superseded by other scoring systems [Cholongitas et al. 2012]; p, p value

[a] Serum albumin less than 2.8 g/dL and prothrombin time prolonged by over 2.5 seconds. 8 patients also had hyperbilirubinaemia and 7 had ascites

Table 3: Summary of the retrospective studies of trientine dihydrochloride for Wilson's disease

Publication	Patients	Interventions	Selected reported outcomes
Arnon et al. 2007 Case review of the records of children with Wilson's disease to evaluate the efficacy of and adherence to trientine and/or zinc. Mount Sinai School of Medicine, New York.	10 children who were evaluated and treated between 1998 and 2006 received first-line trientine and were followed up for at least 12 months. Presentation was recorded as incidental in 5 patients, hepatic in 2 patients, mixed hepatic/neurological in 1 patient, neuropsychiatric in 1 patient and via screening in 1 patient. The median age at diagnosis was about 12 years (range 8–17 years). 8/10 patients were male.	Initial therapy was trientine 250–500 mg twice daily. After around 4–8 months zinc 25–50 mg twice daily was added[a]. All patients took zinc monotherapy by 18 months[b]. Follow up was 12–60 months	ALT levels were normal in 3 patients within 12 months and in a further patient after 30 months. In 3 patients, ALT levels decreased but remained above the upper limit of normal. Mean ALT levels decreased from 183 units/litre at baseline to 80 units/litre at 12 months (n=10) and 66 units/litre at 18 months (n=7). Similar results were seen for AST levels. Non-adherence was identified in 4 patients by increased ALT levels and low urinary levels of zinc, including 1 patient whose ALT had previously become normal. No significant side effects were seen. 1 patient stopped trientine after 12 months because of elevated liver enzyme levels.

Taylor et al. 2009 Case review of the medical notes of children taking trientine for Wilson's disease. King's College Hospital, London.	16/96 children diagnosed between 1981 and 2006 took trientine: 3 first-line (parental choice in 2 cases, 1 case had an allergic reaction to penicillamine during a challenge test) and 13 second-line following adverse reactions to penicillamine (including haematuria, bone marrow suppression and neutropenia) after a median of 0.84 years. On admission, 2 children had acute liver failure, 12 had chronic liver disease and 2 were diagnosed via family screening. Neurological symptoms or psychiatric symptoms were seen in 3 children. Median age was 10.5 years (range 6.6–15 years). 11/16 patients were male.	The initial dosage of trientine was 600 mg/day in children aged less than 12 years and 1200 mg/day in children aged over 12 years, increasing to 1500 mg/day or 2400 mg/day. Median follow up was 6.43 years (range 0.78–18.6 years).	2/3 children taking trientine first-line and 4/13 children taking trientine second-line still had abnormal liver function during trientine treatment. Nevertheless, all children who presented with liver symptoms only reportedly became symptom-free. Trientine did not resolve accompanying neurological or psychiatric symptoms. Trientine was discontinued in 3 children who took trientine second-line. 1 had an allergic rash, 1 had low copper excretion and the third required liver transplantation.

Walshe 2011 Case review to find out if urinary copper excretion shows a response to treatment for Wilson's disease. Middlesex Hospital, London.	192 cases seen between 1955 and 2000 included sufficient information. Patients were excluded if they were seen before best practice was established, were referred too late after diagnosis, or appeared to have inaccurate urinary copper readings. Patients were divided into groups of pre-symptomatic (n=31), hepatic (n=37) and neurological (n=124) Wilson's disease at diagnosis. The median age of the neurological group was 20 years (range 7–39 years). Gender was not reported.	15/124 patients in the neurological group took trientine rather than penicillamine for 2 years. No patients in the other groups took trientine. It is not reported if trientine was first- or second-line.	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. Similar results were seen in the other groups and with penicillamine. Progress of clinical symptoms was not reported.

Weiss et al. 2013 Case review of patients with Wilson's disease treated with chelating agents in tertiary care centres in Germany and Austria and the EUROWILSON registry.	380 patients from 3 tertiary care centres in each of Germany and Austria, plus 25 patients from the EUROWILSON registry were included (n=405). Patients were categorised according to symptoms at diagnosis: asymptomatic (n=54), hepatic (n=207) neurological (n=92) or mixed hepatic and neurological (n=52). 21 patients had liver failure at diagnosis. The median age at diagnosis was about 18 years. 238/405 patients were female.	Data were analysed for penicillamine (n=326) and trientine (n=141) monotherapy (total n=467 because some patients received more than one treatment). Zinc monotherapy and combination therapy were not analysed. Treatment blocks with less than 6 months' follow up were excluded. Baseline characteristics were generally similar between the treatment groups. Hepatic[c,e] and neurological[d,e] outcomes were assessed at 6, 12, 24, 36 and 48 months after initiation of the current treatment regimen and stratified according to first- (n=294 for penicillamine and n=36 for trientine) or second-line (n=32 and n=105 respectively) use. Median follow up was 13.3 years.	9/326 (2.8%) patients taking penicillamine and 3/141(2.1%) patients taking trientine underwent liver transplantation (no significant difference). In symptomatic hepatic patients, there was no statistically significant difference in rates of improvement between first-line penicillamine and trientine (185/204 [90.7%] compared with 25/27 [92.6%], p=1). Rates of improvement were lower for second-line treatment, with no statistically significant difference between the groups (12/16 [75.0%] compared with 31/45 [68.9%] respectively, p=0.8). 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. There were no significant differences between the groups for either line of treatment (p=1 and p=0.6 respectively). In symptomatic neurological patients, no statistically significant differences were seen between the groups in rates of improvement for first- (77/114 [67.5%] for penicillamine compared with 11/20 [55.0%] for trientine, p=0.3) or 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).

			No hepatic or neurological worsening was reported in patients who initially presented without these respective symptoms. Discontinuation due to adverse events was seen in 94/326 patients (28.8%) on penicillamine compared with 10/141 patients (7.1%) taking trientine (p=0.04). No deaths related to adverse events were seen.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; p, p value

[a] Zinc was added once evidence of chelation was seen (urinary copper levels below 200 micrograms/24 hours)

[b] Trientine was stopped when urinary copper levels were 60–200 micrograms/24 hours

[c] Hepatic outcome measures were based on clinical symptoms, course of liver enzymes and liver function tests and patients with any of these were considered 'symptomatic'

[d] The course of neurological disease was evaluated by the doctor

[e] Hepatic and neurological outcomes were scored as unchanged, improved to normal, improved but not normal, deteriorated or asymptomatic over duration

Clinical effectiveness

The RCT investigating tetrathiomolybdate for **neurological symptoms** of Wilson's disease provides limited evidence on the efficacy and safety of **first-line trientine plus zinc** (Brewer et al. 2006). It found that 6/23 patients treated with trientine 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 plus zinc** (followed by zinc monotherapy) improved liver function in 9 patients with Wilson's 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** in 8 patients with stable Wilson's disease with **liver involvement but mixed presentations** (Ala et al. 2015). It found that, on changing from zinc (n=2),

conventionally dosed trientine (n=5) or penicillamine (n=1), physical examination remained unchanged and no new neurological signs were detected over 12 months.

The retrospective observational study by Weiss et al. (2013) provides the best available evidence for using trientine compared with penicillamine in patients with Wilson's disease. It included 141 patients who took **trientine 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 and penicillamine for treating **hepatic signs and symptoms** of Wilson's 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 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 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). (See table 3 for more details.)

When **neurological symptoms** were considered, Weiss et al. (2013) found no statistically significant differences in improvements between trientine 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 55.0% compared with penicillamine 67.5%, second line trientine 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 significantly similar between the groups in patients who switched treatments. In treatment-naive patients, worsening occurred in statistically significantly more patients in the

trientine group (4/20 [20.0%] compared with 6/114 [5.3%] for penicillamine in symptomatic patients, p=0.04), although the number of patients taking trientine first-line was relatively small. (See table 3 for more details.)

Taylor et al. (2009) retrospectively studied 16 children with Wilson's disease (14 with **liver disease**) who took trientine. After a median of 6.43 years, liver function became normal in the majority of children. However, 2/3 children taking trientine **first-line** and 4/13 children taking trientine **second-line** still had abnormal liver function. The authors reported that all children who presented with liver symptoms only became symptom-free; however, trientine 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 in 10 children with Wilson's disease and **mixed presentations** who were followed up for at least 12 months. **Trientine 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's disease. In patients with **neurological symptoms** (n=124), 15 patients took trientine (line of treatment unclear) rather than penicillamine. Urinary copper excretion fell over time, approaching the level considered to be normal at 2 years (see table 3 for more details). Similar results were seen with penicillamine. Walshe (2011) suggested that the reduction in copper excretion indicates a reduction in the body load of copper.

Safety and tolerability

In the RCT (n=48) comparing tetrathiomolybdate and trientine (Brewer et al. 2006), over 3 years, 1 patient taking trientine had leukopenia (during the 8-week treatment phase) and 4 patients taking trientine died. Three of the patients who died had experienced worsening of neurological symptoms during treatment.

No patients stopped treatment or dropped out in the prospective study (n=8) investigating once-daily trientine (Ala et al. 2015).

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 (94/326 [28.8%] compared with 10/141 [7.1%], p=0.04). Of these adverse events, arthralgia (29 patients, 8.9%), increase in antinuclear antibodies (22 patients, 6.7%), albuminuria or proteinuria (20 patients, 6.1%) and erythema (11 patients, 3.4%) occurred most commonly with penicillamine. Arthralgia occurred in 4 patients taking trientine (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.

No significant side effects were seen in the study by Arnon et al. (2007) (n=10). One patient stopped trientine after 12 months because of elevated liver enzyme levels. The dosage of zinc was increased and levels normalised.

In the study by Taylor et al. (2009) (n=16), trientine was discontinued in 3 children who took trientine 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 was restarted in the patient who discontinued trientine because of a rash when his symptoms deteriorated during treatment with zinc, and was well tolerated.

Adverse events were not reported by Askari et al. (2003) or Walshe (2011).

According to the Summary of product characteristics 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 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 (Summary of product characteristics). According to the EASL guideline on managing Wilson's disease, zinc should also be administered at a different time of day to trientine to avoid it being chelated.

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. Two of the observational studies were undertaken prospectively, which may reduce some sources of bias and confounding; 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.

Only Weiss et al. (2013) compared trientine 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's disease.

Trientine dihydrochloride (manufactured by Univar) is licensed for treating Wilson's disease second-line in people who cannot tolerate penicillamine. The

definition of penicillamine intolerance is unclear. The EASL guideline on managing Wilson's disease notes that penicillamine is associated with numerous adverse effects and that severe adverse effects require the drug to be discontinued in approximately 30% of patients. (See the Summary of product characteristics for more information, for example, Distamine 250 mg). Taylor et al. (2009) reviewed the literature and found that adverse effects that were reported in studies in which patients were switched from penicillamine to trientine included rash, urticaria, proteinuria, nephrotoxicity, neutropenia, thrombocytopenia and arthritis.

Data from a UK study by Walshe (1982), was used to support the original licence application for trientine for Wilson's disease, which was made in 1983 (personal communication Univar, August 2016). The study is a case series that summarises the use of trientine over the previous 13 years in 20 patients with severe penicillamine intolerance (including rash, urticaria, bruising, neutropenia, thrombocytopenia, proteinuria and nephritis) who had taken trientine (1200–2400 mg daily) for more than 1 year. The study found that the adverse effects that forced a change in therapy resolved with trientine in most patients. Eight patients who developed penicillamine intolerance within a week of treatment responded well to trientine treatment, 3 patients who developed intolerance within the first year showed continued improvement, and 9 patients who developed late intolerance remained well controlled. No new adverse effects were seen, although some patients experienced iron deficiency, which was corrected with iron supplements.

Some of the studies included in the evidence summary used trientine first-line in newly diagnosed patients, which would be off-label in the UK. In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using trientine first-line outside its authorised indications.

There is more clinical experience of using penicillamine, rather than trientine first-line. In the study by Weiss et al. (2013), only 36 people took trientine first-line compared with 294 people who took penicillamine first-line. By contrast,

105 people took trientine second-line compared with 32 who used penicillamine second-line (some people took more than 1 treatment).

Many of the studies used a 250 mg formulation of trientine. In 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 plus zinc, whereas some used trientine 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 was stopped after a period of time and zinc was used alone for maintenance therapy.

Better-quality studies are needed to compare the safety and efficacy of trientine, 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. An observational study is currently underway, in which 90 patients with Wilson's disease who changed treatment from penicillamine to trientine are being reviewed retrospectively for 48 months and followed prospectively for a further 12 months (NCT02426905). Results are expected to be available in 2018 (personal communication Univar, July 2016).

Context

Alternative treatments

The EASL guideline on managing Wilson's disease recommends that initial treatment for symptomatic patients with Wilson's disease should include a chelating agent (penicillamine or trientine). Zinc may have a role as a first-line therapy in patients with neurological symptoms. Treatment of presymptomatic patients or those with neurological disease on maintenance therapy may be with a chelating agent or zinc. The guideline from the American Association

for the Study of Liver Diseases (AASLD) makes similar treatment recommendations.

The EASL guideline advises that typical dosages of trientine are 900–2700 mg/day in 2 or 3 divided doses, with 900–1500 mg/day used for maintenance therapy. In children, the weight-based dose is not established, but the dose generally used is 20 mg/kg/day rounded to the nearest 250 mg (also see the Summary of product characteristics).

According to the EASL guideline, the maintenance dose of penicillamine for adults is usually 750–1500 mg/day in 2 or 3 divided doses. (See the Summary of product characteristics for more information, for example, Distamine 250 mg). The guideline recommends that the dose of zinc is 150 mg/day in adults (see the Summary of product characteristics for more information).

Costs of alternative treatments

The table shows the comparative costs of maintenance dosages for treating adults with Wilson's disease for 28 days, using the dosage ranges in the EASL guideline on managing Wilson's disease. The costs are for the medicines only (excluding VAT) and do not include any local procurement discounts or any costs incurred, such as distribution costs.

Table 4: Comparative costs of treatments

Treatment	Maintenance dosage[a]	Cost per unit	Cost of 28 days' treatment
Trientine dihydrochloride	900–1500 mg/day	£2901.28 for 100 x 300 mg capsules[b]	£2437.08 to £4061.79
Penicillamine	750–1500 mg/day	£88.13 for 56 x 250 mg tablets[c]	£132.20 to £264.39
Zinc acetate	150 mg/day	£242.00 for 250 x 50 mg capsules[d]	£81.31

[a] Administered in divided doses
[b] Personal communication Univar, July 2016
[c] Drug tariff, July 2016
[d] Wilzin capsules: MIMS, July 2016

Estimated impact for the NHS

Place in therapy

Efficacy, safety, cost and patient factors should be into account when considering the place in therapy of trientine.

There is a lack of high-quality evidence to estimate the relative treatment effects of the available drugs for treating Wilson's disease (EASL guideline on managing Wilson's disease). From the largest observational study (Weiss et al. 2013), trientine was as effective as penicillamine for reducing hepatic and neurological signs and symptoms when used first- or second-line. Hepatic signs and symptoms were reduced in 90.9% of symptomatic patients taking first-line therapy and 70.5% of symptomatic patients taking second-line therapy with either drug. The proportion of patients experiencing improvement in neurological symptoms was lower, with more than a third of patients not improving or becoming worse in both treatment groups. Weiss et al. (2013) suggested that cerebral damage caused by copper toxicity may be at least partly irreversible.

Some limited evidence supports the use of trientine plus zinc to reduce hepatic and neurological signs and symptoms in newly diagnosed patients (Brewer et al. 2006 and Askari et al. 2003) However, it is unclear whether the combination has any benefits over trientine monotherapy.

Trientine was generally well tolerated in the studies. In the study by Weiss et al. (2013), statistically significantly more patients discontinued treatment because of adverse events with penicillamine compared with trientine (28.8% compared with 7.1%, p=0.04). Guidelines from the EASL and the AASLD recommend either penicillamine or trientine for treating Wilson's disease, but note that trientine may be better tolerated.

The cost of trientine is substantially more than that of other treatments for Wilson's disease, ranging from around £2,400 to £4,100 per 28 days for maintenance treatment compared with £130 to £260 for penicillamine and £80 for zinc (excluding VAT, local procurement discounts and any costs incurred).

Trientine should be stored in a refrigerator in the original container with the silica gel sachet. The EASL guideline on managing Wilson's disease advises that it should be administered 1 hour before or 3 hours after meals, but that taking it closer to meals is acceptable if this ensures compliance. Penicillamine and zinc should also be taken on an empty stomach. Zinc is chelated by trientine and penicillamine and, therefore, cannot be taken at the same time of day. The restricted timing of multiple daily doses of treatments for Wilson's disease mean it is unsurprising that compliance is reportedly poor (Ala et al. 2015).

Estimated usage

The NHS prescription cost analysis for England 2015 reports that approximately 600 community prescriptions for trientine dihydrochloride were dispensed in 2015, costing around £993,200 (net ingredient cost). These data do not include hospital prescriptions.

The report states that the average quantity per prescription was 187 capsules. Assuming a 28- or 30-day supply is typical; the estimated average dose is 6–7 capsules per day (NHS prescription cost analysis for England 2015).

Univar have advised that 2,210 bottles of trientine (containing 100 capsules) were sold in the UK in the financial year from April 2015 to March 2016 (personal communication Univar, July 2016).

Relevance to NICE guidance programmes

This use of trientine dihydrochloride is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme. NICE has not produced guidance on Wilson's disease.

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Development of this evidence summary

This evidence summary has been developed using the processes described in the integrated process statement for evidence summaries: new medicines. This statement sets out the process NICE uses to select topics for the evidence summaries, and explains how they are developed, quality assured and approved for publication.

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Declarations of interest

Godfrey Gillett has a shareholding in Oxford Biomedica, but no conflicts of interest with regard to Univar or Valeant.

Rupert Purchase is a freelance consultant for Univar. He provides an annual literature survey on trientine dihydrochloride.

James Dooley and Anette Schrag declared no relevant interests.

About this evidence summary

Evidence summaries provide a summary of the published evidence for selected medicines that are considered to be of significance to the NHS including new medicines, off-label use of licensed medicines and unlicensed medicines.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary and provide information for healthcare professionals to inform their decision-making.

This summary is not NICE guidance.