LMMG New Medicine Recommendation

Taurine capsules 500mg for Taurine deficiency in cystic fibrosis liver disease

LMMG Recommendation: BLACK

Taurine 500mg capsules are **not** recommended for supplementation in CF patients with liver disease.

Available evidence is very limited and of poor quality. Having consulted with colleagues at specialist centres, who have confirmed the poor evidence base, the requesting clinician has withdrawn his proposal for the use of taurine.

Summary of supporting evidence:

- Trials of taurine supplementation in CF patients are typically small and assess effects on biochemical and physiological parameters over the short-term.
- The few longer-term trials that have assessed important outcomes have failed to demonstrate consistently that changes in biochemical and physiological parameters observed with taurine supplementation translate into improved nutritional status, weight gain or height velocity; however, these are still limited to assessment of 6 months of treatment.
- Collectively, the available evidence is very limited and of poor quality to address the long term use of taurine in CF patients.

Author:	**Warren Linley/Hillary Smith**
Version:	**Recommendation**
Clinical Reference Group (if appropriate)	
Reviewer:	**Brent Horrell**
Date of formal consultation:	**October 2013**
Date of recommendation to member organisations by LMMG:	**14 November 2013**

Details of Review

Name of medicine (generic & brand name)**:** Taurine (unlicensed product, various manufacturers)
Strength(s) and Form(s): 500mg capsules
Licensed indication(s): Not licenced.
Reason for Review: Requested by Dr Ned Rowlands, Consultant Paediatrician, Blackpool, Fylde & Wyre Hospital Trust
Proposed use (if different from or in addition to licensed indication above): This is a nutritional supplement requested for patients with assumed taurine deficiency in cystic fibrosis liver disease (CFLD).

Background and context

Cystic fibrosis (CF) is an autosomal recessive genetic disorder that results in thick, viscous secretions that inhibit the function of the lungs, pancreas, intestines and liver. Chronic liver disease and failure is a potential complication due to plugging of intrahepatic bile ducts with thickened bile, which may lead to abnormal drainage and biliary cirrhosis. As survival of patients with CF has improved, the clinical issue of diagnosis and treatment of cystic fibrosis liver disease has become more relevant.[1,2,4]

Treatment is aimed at improving biliary excretion and bile acid composition. Ursodeoxycholic acid (UDCA) is a naturally occurring hydrophilic bile acid which augments bile flow, displaces toxic hydrophobic bile acids, stimulates biliary secretion by hepatocytes and has a general cytoprotective cholangiocyte effect.[3]

Taurine deficiency is frequently found in CF patients as a result of bile acid malabsorption. Long-term administration of UDCA, aimed at improving biliary function, may also critically increase the demand for taurine needed for bile acid conjugation.[2] Based on animal models and observational data it is suggested that taurine deficiency may be associated with poor nutritional status and adverse cardiovascular profile in humans.[12] A guideline on the treatment of cystic fibrosis liver disease, produced in 2008 by regional adult and paediatric CF units in Leeds, suggests taurine supplementation (30mg/kg/day in two or three divided doses) in those treated with UDCA, as this may improve serum pre-albumin levels (an indicator of nutritional status) and may reduce fat malabsorption.[2] In contrast, best practice guidance on the diagnosis and management of CF-associated liver disease, produced by the European Cystic Fibrosis Society in 2011, makes no reference to the use of taurine.[17]

A request was received from a consultant paediatrician to use taurine to prevent deficiency in patients with CF taking UDCA for liver disease. As taurine is not licensed as a medicinal product in the UK, unlicensed taurine capsules are normally obtained and supplied.

The requesting clinician has since consulted with specialist colleagues at other centres and has concluded that, although the Leeds guideline suggests its use, taurine is not being used routinely in other centres, including Leeds. This review has been completed in order to meet the obligations of LMMG to consider the original request and provide a Lancashire-wide recommendation.

Evidence in Proposed Use

Summary of Efficacy Data in Proposed Use:

The main evidence in support of the use of taurine in the Leeds guideline was a small, one-year, double-blind placebo-controlled RCT of UDCA, which also included the use of taurine in half of enrolled patients.

Patients: 55 CF patients with chronic liver disease (hepatomegaly and abnormal liver biochemistries of at least 1 year's duration) with persistent alterations of serum liver enzymes at least 1.5 times the upper limit of normal were recruited from 12 centres across Italy. Patients were excluded if aged below 3 years, had serum bilirubin > 3mg/dL, ascites, chronic viral hepatitis, concomitant severe pulmonary disease, previous episodes of variceal bleeding, encephalopathy or portosystemic shunting. Patients who had been treated with corticosteroid or immunosuppressives within the last 6 months and those who had taken part in other clinical studies were also excluded.

Interventions and Comparators: The patients were randomly assigned by a centrally computer-generated list to receive either UCDA (15mg/kg/day) + placebo (n=15), UCDA + taurine (30mg/kg/day) (n=15), placebo + taurine (n=12) or double placebo (n=13) for one year.

Outcomes: The study was powered for differences in gamma-glutamyl trans peptidase (GGT) levels between those receiving UDCA and those not, rather than for the efficacy of taurine. Four patients withdrew, and results were analysed on an intention-to-treat basis. It is reported that there was a significant improvement in pre-albumin concentrations (however, the reported p-value was 0.053) with taurine treatment compared with placebo. It is also reported there was a non-significant improvement in faecal fat excretion with taurine treatment compared with placebo.

An earlier one-year, placebo-controlled cross over trial compared medium dose UDCA against UDCA plus taurine in patients with or without liver disease.[18] This reports that after 6 months of treatment, mean body weight and mid arm muscle circumference were significantly increased compared with baseline in those receiving UDCA plus taurine, but not in those receiving UDCA alone. However, these effects were also observed during a 6 month placebo phase in patients randomised to the combination therapy arm. The authors concluded that nutritional status and fat absorption were not significantly modified with either UDCA or taurine treatment, and liver function tests improved after UDCA treatment only in those with liver disease at baseline. The primary endpoint of this study was not specified and no power calculations are apparent. There is no indication of whether treatment allocation was concealed or whether patients or investigators were blinded to treatment assignment. There were important differences in baseline characteristics relating to liver disease, 9 out of 51 (18%) randomised patients dropped out and analyses were conducted on a per protocol basis. The dose of UDCA (12mg/kg/day) and taurine (18-22mg/kg/day) employed in this study are lower than those suggested in the Leeds guideline. Collectively, the results are subject to a high risk of bias and the results uncertain.

Several other small, short term studies have been conducted to explore the influence of taurine supplementation on lipid and vitamin E blood concentrations, bile composition, and fatty acid and

sterol excretion. These report mixed results, with some improvements in these parameters over the short follow up periods.[5-10] However, in two cross-over studies that monitored more meaningful outcomes over two successive 4 to 6 month periods, no significant differences were noted in height and weight velocity, or lung function.[8,9]

Other Efficacy data:

The European Society for Clinical Nutrition and Metabolism recently drafted guidelines on nutritional support in CF, which were presented at conference in 2012.[18] These included a systematic literature review and Delphi panel methods to formulate recommendations. These make no specific reference to taurine, but do not recommend routine supplementation with any single protein or amino acid in malnourished children due to very low quality of the available data.

Summary of Safety Data:

Safety data from trials in CF patients are limited by their short term follow-up periods. A review of safety data for amino acid supplements across a range of trials (not specific to CF) concluded the evidence for the absence of adverse effects is strong for taurine at supplemental intakes up to 3g per day, although higher doses have been used.[11]

Summary of Evidence on Cost Effectiveness and Patient Outcomes:

No evidence on the cost effectiveness of taurine supplementation has been identified. This is to be expected given the paucity of efficacy data, in particular that relating to patient orientated outcomes.

Key Points to Note from the Available Evidence:

- Trials of taurine supplementation in CF patients are typically small and assess effects on biochemical and physiological parameters over the short-term.
- The few longer-term trials that have assessed important outcomes have failed to demonstrate consistently that changes in biochemical and physiological parameters observed with taurine supplementation translate into improved nutritional status, weight gain or height velocity; however, these are still limited to assessment of 6 months of treatment.
- Collectively, the available evidence is very limited and of poor quality to address the long term use of taurine in CF patients.

Productivity, Service Delivery and Implementation Considerations:

No productivity, service delivery or implementation impacts are anticipated.

Innovation, Need and Equity Considerations:

There is no evidence to suggest taurine is an innovative nutritional supplement. There are no anticipated issues related to equity.

Recommended Place in Therapy

Taurine 500mg capsules are **not** recommended for supplementation in CF patients with liver disease.

Available evidence is very limited and of poor quality. Having consulted with colleagues at specialist centres, who have confirmed the poor evidence base, the requesting clinician has withdrawn his proposal for the use of taurine.

Financial and Service Implications

Comparative unit costs:

Taurine is available as capsules only. There is a variety of manufacturers, with different list prices[13,14] (See **Table 1**). The Lambert product below is black listed in the Drug Tariff however other taurine preparations can be prescribed in primary care. The costs for taurine preparations supplied through primary care could be significantly higher than those listed below.

Table 1. Example ingredient costs for taurine capsules

Product	Cost price	Pack size
HealthAid L-Taurine Tab 550mg	£4.46	60
Lambert Healthcare Taurine Cap 500mg	£4.97	60
Unichem (own brand) 500mg	£48.00	100

Based on the Leeds guidance[2] a dose of approximately 30mg/kg/day is suggested in 2 or 3 divided doses where feasible. **Table 2** provides annual cost estimates per patient based on the costs of the Lambert Healthcare Ltd product.

Table 2. Estimated annual costs of taurine capsules, based on body weight

Weight	Dose	Annual cost
10-20kg	500mg daily	£30.23
25-40kg	500mg twice daily	£60.46
> 40kg	500mg three times daily	£90.70

Anticipated patient numbers and net budget impact:

Based on the estimated prevalence of 1 in 2,500 patients having CF, there may be as many as 600 patients with cystic fibrosis across Lancashire. A third of cystic fibrosis patients develop clinically significant liver disease[2], assuming all patients who develop liver disease receive treatment with taurine would result in 200 patients requiring treatment.

At an average cost of £60.46 per patient per year, the total cost impact of the drug if the Lambert Healthcare product was supplied would be around £12,092 per annum. The costs for taurine preparations supplied through primary care could be significantly higher.

Impact of Implementation:

No Impact on service delivery is expected.

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