Gastrointestinal Subcommittee of PTAC meeting held 19 December 2012

(minutes for web publishing)

Gastrointestinal Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

Note:

- that this document is not necessarily a complete record of the Gastrointestinal Subcommittee meeting; only the relevant portions of the minutes relating to Gastrointestinal Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.
- that any part of the minutes relating to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML) will be released, in a complete publication with the original Hospital Pharmaceuticals Subcommittee minutes and final recommendations made by PTAC, once PTAC have reviewed each therapeutic group.

The Gastrointestinal Subcommittee may:

(a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes were reviewed by PTAC at its meeting on 14 & 15 February 2013, the record of which will be made available in April 2013.

1 Ursodeoxycholic acid for total parenteral nutrition induced cholestasis

Application

1.1 The Subcommittee reviewed a clinician lead proposal to fund ursodeoxycholic acid (UDCA) for the treatment of total parenteral nutrition induced cholestasis (TPN-IC).

Recommendation

1.2 The Subcommittee recommended that UDCA be listed in the Pharmaceutical Schedule for paediatric patients with TPN-IC with a medium priority subject to the following Special Authority criteria:

> Initial application – (Total Parenteral Nutrition induced cholestasis) - from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
> Both:
>
> 1. Paediatric patient has developed abnormal liver function as indicated on testing which is likely to be induced by TPN; and
> 2. Liver function has not improved with modifying the TPN composition.
>
> Renewal from any relevant practitioner. Approvals valid for 6 months for paediatric patients continuing to require TPN and who are benefiting from treatment, defined as a sustained improvement in bilirubin levels.

1.3 The Subcommittee recommended that funding for UDCA to treat TPN-IC in adults be declined.

The Decision Criteria particularly relevant to this recommendation are: *(iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

1.4 The Subcommittee noted that TPN-IC has been recognised as a cause of severe morbidity and is more common in paediatric patients than in adults.

1.5 The Subcommittee noted that this indication for UDCA had previously been discussed at its April 2012 meeting at which it noted that further evidence needed to be reviewed prior to recommending funding for this group. The Subcommittee considered five studies (De Marco et al. Aliment Pharmacol Ther 2006; 24:387-94, Chen et al. J Pediatr. 2004; 145:317-21, Peyret et al. B Eur J Clin Nutr. 2011;65:743-9, Lloyd et al. Proc Nutr Soc. 2007 Nov;66:530-8 Kelly et al. Gastroenterology 2006: 130; 70-77).

1.6 Overall, the Subcommittee considered the evidence to be weak, however it appears that there is stronger evidence supporting the use of UDCA in neonates with TPN-IC and some evidence for its effect in infants. The Subcommittee noted that it was not aware of any evidence to support the use of UDCA in adult patients with TPN-IC.

1.7 The Subcommittee considered that in paediatric patients, TPN-IC can be treated or prevented by manipulating the TPN composition and cycling formulations, and by addressing bacterial overgrowth however UDCA would be considered in the event that other interventions had failed, other causes of liver dysfunction had been ruled out and liver function tests remained abnormal. The Subcommittee considered that prophylactic treatment for paediatric patients using TPN would be inappropriate.

1.8 The Subcommittee considered that most patients would require treatment for several months however if effective its likely patients would continue treatment for as long as TPN continued. The Subcommittee considered that bilirubin levels would be the most appropriate indicator of the response to treatment and levels would be assessed at least monthly.

1.9 The Subcommittee considered that there are likely to be 7 to 10 patients per annum who would require treatment as a result of TNP-IC and noted that the cost of UDCA for these patients would be low.

2 Ursodeoxycholic acid for patients with cystic fibrosis related cholestasis

Application

2.1 The Subcommittee reviewed a clinician lead proposal to fund ursodeoxycholic acid (UDCA) for the treatment of patients with cystic fibrosis related cholestasis.

Recommendation

2.2 The Subcommittee recommended that the proposal to fund UDCA for patients with cystic fibrosis be deferred. The Subcommittee recommended that further evidence be sought including expert opinion and that this be reviewed at its next meeting.

Discussion

2.3 The Subcommittee noted that at its previous review in April 2012 there was insufficient evidence to recommend funding for this indication.

2.4 The Subcommittee considered the effect of UDCA in patients with cystic fibrosis liver disease (Cheng et al. Cochrane Database Syst. Rev. 2000;(2):CD000222, Siano et al. Dig Liver Dis. 2010 Jun;42:428-31, Desmond et al.Liver Int. 2007; 27:1402-8, Nousia-Arvanitakis S. J Clin Gastroenterol. 2001; 32:324-8). Overall, the Subcommittee considered the strength and quality of the evidence to be weak.

2.5 The Subcommittee considered that in general, there appears to be supportive evidence for the effect of UDCA on improving liver function tests, however this does not appear to result in improved survival. The Subcommittee considered that the results of some studies are likely to be affected by the inclusion of children with established liver disease.

2.6 The Subcommittee noted that liver dysfunction and decline is expected as part of the natural progression of cystic fibrosis. The Subcommittee considered that if UDCA was used, it is likely to be more effective if started early, targeting patients who were more likely to develop early hepatic complications.

2.7 The Subcommittee noted that there are no reliable predictors of patients who are likely to develop early liver disease however there may be a correlation with patients born with meconium ileus and with a severe cystic fibrosis phenotype. The Subcommittee noted that Siano et al. 2010 studied the effect of early treatment with UDCA in 26 patients with cystic fibrosis and meconium ileus to prevent chronic hepatic involvement, in which one group were treated early (following diagnosis of CF) and the other group treated from the onset of cystic fibrosis liver disease with a mean dose of 15 mg/kg per day UDCA. The authors reported a higher prevalence of cystic fibrosis chronic liver disease at age 9 in patients who started UDCA later ($p<0.05$). The Subcommittee considered that the study involved very small patient numbers and that further evidence is needed to prior to recommending funding for this patient group.

2.8 The Subcommittee considered that beginning treatment prior to detection of ultrasound abnormalities, sustained elevation of liver enzymes following exclusion of other causes and splenomegaly is likely to be more beneficial than commencing treatment once those indicators had been observed. The Subcommittee noted that the complications of liver disease are costly.

2.9 The Subcommittee considered that it is likely that up to 20% to 30% of children born with cystic fibrosis would access treatment which is likely to be continued indefinitely. The Subcommittee noted that higher doses of 20 mg/kg to 30 mg/kg per day may be used for cystic fibrosis patients.

2.10 The Subcommittee considered that further evidence be sought to establish the effect of early UDCA treatment on the development of cystic fibrosis liver disease both in the form of expert opinion and any other available published evidence.