Gastrointestinal Subcommittee of PTAC meeting held 13 April 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 2 & 3 August 2012, the record of which will be made available in September 2012.

Contents

1 Therapeutic Group Review

1.1 The Subcommittee considered a review of the alimentary tract and metabolism therapeutic group provided by PHARMAC staff.

1.2 The Subcommittee noted the recently amended criteria for budesonide, which it considered to be appropriate, and that there has been an increase in expenditure primarily attributable to use by patients with microscopic colitis. The Subcommittee considered that should an alternative budesonide product become available, its equivalence in terms of release profile would need to be established prior to any brand switch in this market.

1.3 The Subcommittee considered that there is an unmet need for children who require treatment with mesalazine and recommended that mesalazine sachets be listed in the Pharmaceutical Schedule, noting that the tablets form an unpleasant mixture when dispersed in water. The Subcommittee suggested the following Special Authority criteria should apply to mesalazine sachets:

> **Initial application** from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:
> Both:
> 1 The patient is unable to swallow tablets; and
> 2 The patient is aged 16 years or below.
>
> **Renewal** from any relevant practitioner. Approvals valid for 12 months for patients meeting the following criteria:
> Both:
> 1 The treatment remains appropriate and the patient is benefiting from treatment; and
> 2 The patient is aged 16 years or below.

1.4 The Subcommittee noted that there has been some use of peppermint oil capsules in DHB hospitals, and that PHARMAC staff were seeking advice around this product in the context of further evaluating it for possible funding in the community. The Subcommittee noted that hyoscine and mebeverine are fully funded anti-spasmodic agents and therefore there is no significant unmet need, however members considered that it is possible that peppermint oil would be useful for some patients. The Subcommittee considered that whilst there may not be a great deal of evidence to support its use, there may be a place for peppermint oil in therapy and recommended that PHARMAC staff approach a supplier to submit a funding application.

1.5 The Subcommittee noted that famotidine has been discontinued and that no replacement brand has been found. The Subcommittee considered that famotidine has a longer half-life than ranitidine and it is often preferred for this reason. The Subcommittee considered that should an alternative supplier be known, PHARMAC could consider relisting famotidine.

1.6 The Subcommittee noted that there is a lack of funded second line treatment options for H. Pylori. Members noted that resistance to clarithromycin is increasing, and is up to 25% in some areas of New Zealand. The Subcommittee noted that quadruple therapy

which includes bismuth and tetracycline is an option, or triple therapy which includes levofloxacin. The Subcommittee noted that ciprofloxacin could be looked at for its efficacy in these patients. The Subcommittee recommended that PHARMAC seek a funding application for bismuth, tetracycline and levofloxacin for this indication.

1.7 The Subcommittee noted the usage of omeprazole suspension in paediatrics and whilst it considered usage to be high, members noted that omeprazole is often empirically prescribed due to the nonspecific presentation of GORD and the requirement for invasive gastroscopy for diagnosis. Members noted that young patients are likely to take omeprazole for approximately 3 to 6 months as the majority of patients will outgrow GORD by 8 to 9 months of age. Overall, the Subcommittee considered that prescribing rates in this age group were likely to be appropriate.

1.8 The Subcommittee noted that an oral liquid form of omeprazole is important for paediatrics and for patients with naso-gastric tubes. The Subcommittee considered that a dispersible tablet preparation would be much more palatable compared with the extemporaneously compounded preparation for paediatric patients and considered that the compounded form is not appropriate for patients with a naso-gastric tube. The Subcommittee **recommended** that dispersible tablets form or omeprazole or esomeprazole be listed in the Pharmaceutical Schedule, subject to the following Special Authority criteria:

> **Initial application** from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:
> Any of the following:
> 1 Both:
> 1.1 The patient is a child who requires a 10 mg dose or less, for whom sprinkling the contents of omeprazole capsules on soft food has not been tolerated or is not appropriate; and
> 1.2 Patient has trialled an adequate course of sodium alginate powders and an H_2 antagonist and both products have been unsuccessful or not tolerated; or
> 2 Patient is fed via a naso-gastic tube.

1.9 The Subcommittee noted that several low dose pancreatic enzyme preparations have been discontinued in New Zealand recently and considered that there may be an issue for paediatric patients who require small doses and that the option of funding a powder or granule should be investigated. Members noted that funding powder or granule preparation would also be useful for patients with naso-gastric tubes.

1.10 The Subcommittee also noted that Pancrex V, which has been discontinued, was the only non-enteric coated product in this range, and that having an alternative non-EC product funded would be beneficial, as these achieve early enzymatic activity in the gastrointestinal tract when administered.

1.11 The Subcommittee considered the current listing and Special Authority for macrogol 3350. The Subcommittee **recommended** that the current restriction of 60 sachets per prescription be removed, or raised to at least 90 sachets per prescription. Members noted that patients will be receiving as many prescriptions as necessary to get the correct number of sachets and therefore the restriction places administrative burden on both patients and clinicians.

1.12 The Subcommittee **recommended** that a half-dose preparation of macrogol 3350 or a preparation more palatable for paediatric patients be funded. Members noted that the palatability issue for children with this product is more related to the electrolyte components rather than the flavouring. The Subcommittee noted that an unflavoured product without electrolytes is available and considered that this would be more suitable for children.

1.13 The Subcommittee considered that the requirement in the Special Authority criteria for macrogol 3350 for paediatric patients to have trialled intra-rectal products was unnecessarily invasive, and recommended that this be removed.

1.14 The Subcommittee considered that there is likely to be a group of patients receiving radiation therapy to the head and neck who would benefit from receiving benzydamine solution fully funded. The Subcommittee considered that further advice should be sought from the relevant radiology or oncology specialists.

1.15 The Subcommittee considered that the currently funded cholecalciferol high dose tablet is the preferred supplement option for gastroenterology at this time as patients get good results and adhere easily to treatment. The Subcommittee noted that there may be a requirement to fund a product suitable for paediatrics and for use during pregnancy and recommended that further advice be sought from relevant specialties.

1.16 The Subcommittee **recommended** that the Special Authority criteria for the combination fat soluble vitamin preparation Vitabdeck excluded some adults who would benefit from treatment. The Subcommittee **recommended** that the criteria be amended as follows (addition in bold):

> Initial application from any relevant practitioner. Approvals without further renewal for applications which meet the following criteria:
> Either
> 1. Patient has cystic fibrosis with pancreatic insufficiency; or
> 2. Patient is an infant or child with liver disease or short gut syndrome; or
> 3. **Patient has severe malabsorption syndrome**

1.17 The Subcommittee considered that such a change would affect fewer than 100 patients per year.

1.18 The Subcommittee considered the Special Authority criteria recommended by PTAC for adalimumab for fistulising Crohn's disease. The Subcommittee considered that the 4 month initial trial was acceptable to determine whether a patient is responding to treatment and that whilst the 'fistula grading tool' adopted from the PBAC was not an official tool, members considered it to be an acceptable way of measuring treatment response. The Subcommittee noted that magnetic resonance imaging (MRI) could be performed at baseline and then at intervals determined by clinical progress, and is considered to be the optimal method of assessing complete healing of fistulae. The Subcommittee considered that MRI is not universally used and should not be used in the stopping criteria.

1.19 The Subcommittee noted that PTAC has previously recommended against funding weekly doses of adalimumab. Members considered that this assessment may not have accurately reflected the place of such 'rescue therapy' in Crohn's disease. The Subcommittee noted that a small number of patients receiving maintenance therapy with

TNF inhibitors experience a loss of remission; in this situation, either a short burst of weekly administration (6 additional doses) or re-induction (5 additional doses) may result in patients regaining control of symptoms. The Subcommittee noted that this would entail up scaling treatment frequency or dose for no more than 12 weeks per year and should a remission not be regained, clinicians would need to cease or switch treatments. The Subcommittee **recommended** that PHARMAC staff remodel previous cost-effectiveness estimates for this therapy and for 'rescue therapy' to be reconsidered for funding.

1.20 The Subcommittee considered there may be 120 patients per annum who would benefit from treatment for fistulising Crohns.

1.21 The Subcommittee considered the availability of funded magnesium supplements. Members noted that current practice is to use magnesium sulphate injections administered orally, as this provides the best response in short gut syndrome. Members noted that internationally, magnesium glycerophosphate tablets are available and could be investigated for funding in New Zealand should a supplier be willing. The Subcommittee **recommended** funding of magnesium tablets and suggested the following Special Authority criteria apply:

> **Initial application** from a Renal Physician or Gastroenterologist. Approvals valid for 12 months where the patient has severe malabsorption with hypomagnesaemia or severe hypomagnesaemia.

1.22 The Subcommittee noted that a topical intra-rectal tacrolimus preparation is being studied in Australia for treating proctitis and Crohn's disease. The Subcommittee noted that it would be interested to view further data on this as it becomes available.

2 Removal of Special Authority on short acting octreotide injections

Application

2.1 The Subcommittee reviewed a proposal from PHARMAC staff to remove the Special Authority applying to octreotide short-acting injections and considered the potential population of patients who would access treatment for a gastroenterology indication.

Recommendation

2.2 The Subcommittee considered that there would be little increased use of short-acting octreotide for gastroenterology indications should the Special Authority be removed and therefore **recommended** that the Special Authority be removed with a medium priority.

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (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; and (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

2.3 The Subcommittee considered potential indications for short-acting octreotide which are not funded under the current Special Authority. The Subcommittee considered that there is good evidence to support the use of octreotide for gastrointestinal neuroendocrine tumours.

2.4 The Subcommittee considered a Cochrane Review 2012 which assessed the efficacy of somatostatin analogues in treating acute bleeding oesophageal varices. The authors reported that the number of patients failing initial haemostasis was reduced (relative risk 0.68 (0.54 – 0.87) however the number of patients with re-bleeding was not significantly reduced, relative risk 0.84 (0.52 – 1.37). The authors concluded that the need for blood transfusions corresponded to half a unit of blood saved per patient and that treatment with somatostatin analogues had no significant effect on mortality. The Subcommittee considered that terlipressin is usually used first line however somatostatin analogues may be used in patients with cardiovascular disease and also have a role in Non-variceal upper gastrointestinal bleeding. The Subcommittee considered that if funded for this use short acting octreotide would be used in only small number of in-patients for a short period of time, approximately 3 to 5 days.

2.5 The Subcommittee considered a systematic review (Gurusamy et al. Cochrane Database of Systematic Reviews 2010; 2: CD008370) which assessed the use of somatostatin analogues for pancreatic surgery. The authors reported that treatment did not reduce the length of hospital stay or peri-operative mortality however was effective at reducing fistulae (relative risk 0.64; 95% CI 0.53 to 0.78) and the number of patients with postoperative morbidity (relative risk 0.71; 95%CI 0.62 to 0.82). The Subcommittee considered that short acting octreotide would be used occasionally for this indication, the population was small, and it would be administered as an in hospital treatment for 1-7 days post operation.

2.6 The Subcommittee considered that there is less evidence to support the use of short acting octreotide use for enterocutaneous fistulae. The Subcommittee considered a meta-analysis of the role of somatostatin and its analogues in the treatment of enterocutaneous fistula (Stevens et al. Eu J Gastroent Hep 2011; 23:912-922). The authors reported that octreotide reduced fistulae closure time but not spontaneous closure rate and there was no decrease in fistula output. The Subcommittee noted that octreotide is not standard of care for treating enterocutaneous fistulae and considered that there was a trend away from using it in this setting.

2.7 The Subcommittee considered the use of short acting octreotide for high output stomas and intractable diarrhoea. The Subcommittee considered that high doses of octreotide over a short period of time may be useful for chemotherapy-induced acute diarrhoea; however, the data in this setting is poor.

2.8 The Subcommittee considered the use of short acting octreotide for short bowel syndrome. Members considered that octreotide may reverse sodium water loss but that the short acting preparation slows down blood supply to the gut therefore was not considered a standard care treatment, Members considered that there was evidence for the long acting preparation for use in patients with short bowel syndrome and it may be better than the short acting product, perhaps with a different mode of action.

2.9 The Subcommittee considered the use of octreotide in patients with rapid gastric emptying, so called "dumping syndrome". Members noted that the incidence of dumping syndrome was rising mainly due to increases in gastric bypass surgery. The Subcommittee considered a review of randomised controlled trials (Postgrad Med J 2001;77:441-442 doi:10.1136/pmj.77.909.441) that showed that octreotide can be a successful treatment in this setting. The Subcommittee considered that while the population of patients who can't control the symptoms by using dietary measures alone is quite small (about 5%), numbers are increasing due to increases in gastric bypass surgery procedures and that use in these patients may be chronic.

2.10 The Subcommittee considered that short acting octreotide may be used for treating diarrhoea associated with Acquired Immunodeficiency Syndrome (AIDS) or gut graft vs. host disease, or AIDS however there is little evidence to support these uses.

2.11 Overall, the Subcommittee considered that the financial risks of removing the Special Authority restriction from short acting octreotide to be low for gastroenterological indications.

3 Glyceryl trinitrate 0.2% (Rectogesic) for anal fissure

Application

3.1 The Subcommittee reviewed a funding application from Care Pharmaceuticals Australia to fund glyceryl trinitrate 0.2% (Rectogesic) ointment for the treatment of anal fissure and for the relief of pain and discomfort associated with haemorrhoids and haemorrhoidectomy.

Recommendation

3.2 The Subcommittee **recommended** that glyceryl trinitrate 0.2% ointment be funded for the treatment of anal fissures subject to the following Special Authority criteria with a high priority:

> **Initial Application** from any practitioner. Approvals valid for 3 months for applications meeting the following criteria:
> Both:
>
> 1. Patient has chronic anal fissure defined as fissure persisting for longer than three weeks

3.3 The Subcommittee **recommended** that the application to fund glyceryl trinitrate 0.2% ointment for the treatment of pain and discomfort associated with haemorrhoids or haemorrhoidectomy be declined.

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (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; and (vii) the direct cost to health service users.*

Discussion

3.4 The Subcommittee noted that surgical treatment of chronic anal fissures is generally very successful; however this intervention can result in transient or permanent incontinence and is a more invasive option than non-surgical treatments. The Subcommittee considered that there is an increasing preference to attempt chronic fissure healing by using non-surgical options.

3.5 The Subcommittee considered that a high proportion of acute anal fissures generally resolve often with the use of bulk forming laxatives and anti-haemorrhoidal ointments or suppositories. The Subcommittee noted that chronic anal fissures are usually fissures which persist for longer than 3 to 4 weeks.

3.6 The Subcommittee considered the systematic review reported by Nelson (Cochrane Database of Systematic Reviews 2006; 4: CD003431) which assessed non-surgical treatments for anal fissure. The authors reported that glyceryl trinitrate (GTN) was marginally but significantly better than placebo in healing anal fissure (48.6% vs 37%, $p<0.004$), but late recurrence of the fissure was observed in 50% of patients who were originally cured. Members noted that higher response rates are observed in practice.

3.7 The Subcommittee considered the randomised, prospective, double-blind, placebo-controlled trial which assessed the efficacy of glyceryl trinitrate in treating chronic anal fissure in 80 patients (Lund et al. Lancet 1997; 349: 11-14). Patients applied either GTN or placebo ointment twice daily to the anal canal and the primary endpoint of fissure healing was assessed after 8 weeks of treatment. The authors reported that healing occurred in 68% of patients treated with GTN and 3% of patients treated with placebo ($p<0.0001$).

3.8 The Subcommittee considered that there are two alternative non-surgical treatments used for chronic anal fissure; diltiazem ointment which is likely to have a similar effect to GTN but there is no registered preparation in New Zealand, and botulinum toxin (botox) which is injected into the anal sphincter. The Subcommittee considered that botox is likely to be more effective than GTN, however it is also more expensive and must be administered in an out-patient setting.

3.9 The Subcommittee noted that there are no treatments currently funded for chronic anal fissure and that there is an unmet need. The Committee considered that there could be approximately 2000 patients per annum.

3.10 The Subcommittee considered that the evidence to support the use of GTN for the reduction of pain associated with haemorrhoids or haemorrhoidectomy was weak and that there are alternative funded treatments for these indications.

4 Sorafenib tosylate (Nexavar) for the treatment of Hepatocellular Carcinoma

Application

4.1 The Subcommittee considered a funding application from Bayer New Zealand Ltd for the funding of sorafenib tosylate (Nexavar) for patients with advanced inoperable hepatocellular carcinoma (HCC) with preserved liver function (Child Pugh score 5-7).

Recommendation

4.2 The Subcommittee **recommended** that sorafenib be funded with a medium priority for patients with preserved liver function (Child Pugh A, score 5-6) subject to the following Special Authority criteria:

Initial Application only from an oncologist or gastroenterologist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:

1. Patient has treatment naïve, advanced, inoperable hepatocellular carcinoma; and
2. The patient has preserved liver function (Childs Pugh score 5-7); and
3. The patient has good performance status (ECOG 0-1); and
4. Sorafenib to be given for a maximum of 12 weeks, and
5. Sorafenib to be given as monotherapy at a maximum does of 400 mg twice daily.

Renewal only from and oncologist or gastroenterologist. Approvals valid for 6 months for applications meeting the following criteria:

1. Radiological Evaluation by CT shows no evidence of disease progression (no new lesions or metastases or increase in size of target lesion(s)); and
2. Patient is tolerating treatment.

The Subcommittee noted that sorafenib was poorly cost effective at the pricing offered and noted that its priority rating would increase if the cost of sorafenib was reduced.

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (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; and (vii) the direct cost to health service users.*

Discussion

4.3 The Subcommittee noted that PTAC and its Cancer Treatments subcommittee (CaTSoP) had previously reviewed the funding of sorafenib for patients with advanced, inoperable, hepatocellular carcinoma (HCC), on a number of occasions, most recently in November 2011. Members noted that these committees had declined funding because sorafenib was not considered cost-effective.

4.4 The Subcommittee considered that key evidence for sorafenib in HCC patients comprised two randomised, phase III studies comparing sorafenib with placebo: the "SHARP" study conducted in the USA, Europe, South America and Australia (Sorafenib Hepatocellular Carcinoma Assessment Randomised Protocol, study 100554, Llovet et al NEJM 2008, 359:378-90) an Asia-pacific Study (Chen et al Lancet Oncology 2009;10:25-34). . The Subcommittee noted that this evidence has previously been reviewed by PTAC and its Cancer Treatments Subcommittee (CaTSoP) and that no new evidence had been provided.

4.5 The Subcommittee considered that overall the evidence demonstrated that sorafenib treatment was associated with a 2 month increase in overall survival in patients with HCC. Members noted that sorafenib was associated with significant adverse effects including diarrhoea, hand foot syndrome, alopecia, rash, weight loss, anorexia, fatigue

and thrombocytopenia. Members considered that the majority of adverse events were manageable with dose reduction or delay, however, approximately 10% of patients discontinue sorafenib treatment completely due to toxicity.

4.6 The Subcommittee noted that overall sorafenib did not improve quality of life, however, members considered that QOL benefits were not uniform in all patients and a subset of patients responded well to treatment, whilst others had extreme side effects.

4.7 The Subcommittee considered that the degree of cirrhosis appeared to be an important predictor of outcome in patients treated with sorafenib for advanced HCC. Members considered that overall survival was longer in patients with preserved liver function (Child Pugh A, score 5-6) compared with patients with more severe liver disease (Child Pugh B (score 7-9) or higher).

4.8 The Subcommittee considered that there was a high unmet clinical need for effective treatments for patients with HCC and that sorafenib was the only treatment registered, and to have demonstrated a survival benefit in, this setting. However, members noted that because of its high price relative the benefits demonstrated in the clinical trials sorafenib was poorly cost-effective.

4.9 The Subcommittee noted that HCC is associated with hepatitis B or C infection, and that HCC cases were increasing (approximately 20% per annum) due to the increased diagnosis of, and screening for hepatitis infection.

4.10 The Subcommittee noted that approximately 142 new patients presented with HCC in Auckland last year (which see's approximately 75% of all cases nationally) 58 of whom presented with intermediate or advanced disease (Childs-Pugh A or B (score of 5-6 or 7-9)). Members considered 50% of the advanced patients would not be eligible for treatment, therefore approximately 30-40 patients would be eligible for treatment each year, which equates to around 40-50 nationally.

4.11 The Subcommittee considered that patients with hepatitis B often improve following antiviral treatment and liver function can often be improve from Childs Pugh B to Childs Pugh A and this should be considered in analysis.

4.12 The Subcommittee considered that should sorafenib be funded the Special Authority criteria should require disease monitoring by CT scan every 3 months with stopping rules in the event of radiological progression. Members noted that such criteria may reduce the overall median duration of treatment in the CUA model, which was based on the SHARP study, since in this study patients were continued on treatment until both radiological and symptomatic progression. Members considered that symptomatic progression was generally apparent 6-12 weeks after radiological progression. The Subcommittee considered that the majority of patients who cannot tolerate treatment would discontinue within one month, and those still responding to treatment after 3 months would likely do well.

4.13 [withheld under OIA (section 9(2)(b)(ii))]

5 Widening access for ursodeoxycholic acid

Application

5.1 The Subcommittee reviewed a funding proposal from PHARMAC staff to widen access to ursodeoxycholic acid (UDCA) for drug induced liver disease (DILI), Total Parenteral Nutrition (TPN) induced cholestasis, Alagille syndrome, cystic fibrosis related cholestasis, progressive familial intrahepatic cholestasis (PFIC), non-alcoholic steatohepatitis and for chemo-prophylaxis of colon cancer in patients with inflammatory bowel disease.

Recommendation

5.2 The Subcommittee **recommended** that ursodeoxycholic acid be funded for the treatment of Alagille syndrome, progressive familial intrahepatic cholestasis and chronic drug induced liver injury subject to the following Special Authority criteria with a medium priority:

Initial application – (Alagille syndrome or progressive familial intrahepatic cholestasis) - from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
Either:

1. Patient has been diagnosed with Alagille syndrome
2. Patient has progressive familial intrahepatic cholestasis

Initial application – (chronic severe drug induced cholestasic liver injury) - from any relevant practitioner. Approvals valid for 3 months for applications meeting the following criteria:
Either:

1. Patient has chronic severe drug induced cholestatic liver injury; and
2. Treatment with UDCA may prevent hospital admission or reduce duration of stay

Renewal application – from any relevant practitioner. Approvals valid for 6 months where the patient continues to benefit from treatment.

5.3 The Subcommittee **recommended** that the current criteria applying to ursodeoxycholic acid for the level of bilirubin constituting decompensated cirrhosis be amended with a medium priority (additions in bold, deletions in strikethrough):

Initial application – (Pregnancy~~/Cirrhosis~~) - from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
Either:

1. Patient diagnosed with cholestasis of pregnancy; or
2. ~~Both:~~
   - 2.1. ~~Primary biliary cirrhosis confirmed by antimitochondrial antibody titre (AMA) > 1:80, and raised cholestatic liver enzymes with or without raised serum IgM or, if AMA is negative, by liver biopsy; and~~
   - 2.2. ~~Patient not requiring a liver transplant (bilirubin > 170~~ **100** ~~umol/l; decompensated cirrhosis)~~

Note: Liver biopsy is not usually required for diagnosis but is helpful to stage the disease.

Initial application – (Cirrhosis) - from any relevant practitioner. Approvals valid without further renewal for applications meeting the following criteria:

1. **Both:**
   - **1.1. Primary biliary cirrhosis confirmed by antimitochondrial antibody titre (AMA) > 1:80, and raised cholestatic liver enzymes with or without raised serum IgM or, if AMA is negative, by liver biopsy; and**
   - **1.2. Patient not requiring a liver transplant (bilirubin > ~~170~~ 100 umol/l; decompensated cirrhosis)**

Note: Liver biopsy is not usually required for diagnosis but is helpful to stage the disease

Initial application – (Haematological Transplant) - from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
Both:

1. Patient at risk of veno-occlusive disease or has hepatic impairment and is undergoing conditioning treatment prior to allogenic stem cell or bone marrow transplantation, and
2. Treatment for up to 13 weeks.

Renewal – (Pregnancy/Cirrhosis) - from any relevant practitioner. Approvals valid for 2 years where the treatment remains appropriate and the patient is benefiting from treatment.

Note: Ursodeoxycholic acid is not an appropriate therapy for patients requiring a liver transplant (bilirubin > ~~170~~ **100** micromol/l; decompensated cirrhosis). These patients should be referred to an appropriate transplant centre. Treatment failure – doubling of serum bilirubin levels, absence of a significant decrease in ALP or ALT and AST, development of varices, ascites or encephalopathy, marked worsening of pruritus or fatigue, histological progression by two stages, or to cirrhosis, need for transplantation.

5.4 The Subcommittee **recommended** that the funding proposal for ursodeoxycholic acid in patients with TPN induced cholestasis, cystic fibrosis related cholestasis, non-alcoholic steatohepatitis and for chemo-prophylaxis of colon cancer in patients with inflammatory bowel disease be declined.

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iv) The clinical benefits and risks of pharmaceuticals; and the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule; (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

5.5 The Subcommittee noted that UDCA improved liver function tests (LFTs) in all patients with abnormal LFTs however there was a lack of evidence that it altered the natural history of disease in the patient groups identified in this review and this evidence would be difficult to obtain in view of the small size of these patient groups. Members noted that there was no long term outcome data for any of the patient groups identified following UDCA treatment.

5.6 The Subcommittee considered that a small population of patients with chronic drug induced liver injury (DILI) may benefit from UDCA treatment, approximately 10 to 20 patients nationally. The Subcommittee noted that there is little evidence to support the effect of treatment on the pace of liver recovery, as the evidence is mainly from isolated

case reports; however UDCA may reduce bilirubin levels enough to facilitate discharge from hospital.

5.7 The Subcommittee considered that there would likely be 7 to 10 cases of TPN induced cholestasis per annum. Members noted that this would often be managed by adjusting the TPN composition. The Subcommittee noted that some paediatric cases can be more difficult to manage in this way, and that treatment with UDCA may be useful however further evidence is required.

5.8 The Subcommittee considered that UDCA may be useful for patients with Alagille syndrome and for progressive familial intrahepatic cholestasis (PFIC) to improve liver function tests. However the Subcommittee considered that there was anecdotal evidence to support the effect of UDCA on symptomatic improvement for patients with cystic fibrosis but that there was little known evidence to support any survival benefit.

5.9 The Subcommittee considered that there was a lack of data to support the effect of UDCA on symptoms associated with non-alcoholic steatohepatitis (NASH). The Subcommittee noted that there could be a large population of patients affected by this condition. Members considered that there was no survival benefit shown with UDCA in this patient population and recommended that access not be widened for this group.

5.10 The Subcommittee considered the EASL guidelines (J Hepat 2009; 51: 237-267) which discuss the use of UDCA in patients with inflammatory bowel disease. The Subcommittee considered that UDCA may significantly reduce the risk of developing colonic dysplasia in some patients however the evidence is limited. The Subcommittee considered that UDCA may be considered in high-risk groups such as those with a strong family history of colorectal cancer, previous colorectal neoplasia or longstanding extensive colitis. The Subcommittee noted that there are approximately 300 to 400 patients with ulcerative colitis and primary sclerosing cholangitis in New Zealand and that UDCA would be a chronic treatment. The Subcommittee considered that a funding application should be sought with further evidence of the use of UDCA for this indication.

5.11 The Subcommittee noted that cholestyramine resin (Questran Lite) which is often used to treat pruritus associated with cholestasis is not fully subsidised. The Subcommittee considered that the possibility of fully funding this product be investigated.