Gastrointestinal Subcommittee of PTAC
Meeting held 21 May 2014

(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.

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 6 &7 November 2014, the record of which will be available in February 2015

Record of the GASTROINTESTINAL SUBCOMMITTEE of PTAC meeting held on 21 May 2014

1 Therapeutic Group Review

1.1 Members noted bismuth and tetracycline are now available for helicobacter pylori eradication. The Subcommittee **recommended** the requirement of a Special Authority be reviewed for tetracycline. Members noted levofloxacin would also be desirable if supply was able to be secured.

1.2 The Subcommittee reiterated its previous **recommendation** to amend the VitABDECK Special Authority criteria to include patients with severe malabsorption syndrome.

1.3 Members noted previous recommendations from the Subcommittee regarding access to macrogol sachets for constipation are still being assessed by PHARMAC. The Subcommittee reiterated its previous **recommendation** that restrictions to macrogol be reviewed. The Subcommittee reiterated its previous **recommendation** that a half-dose preparation of macrogol 3350 or a preparation more palatable for paediatric patients be funded.

1.4 Members noted the HML restrictions for infliximab for ulcerative colitis (UC) use a score system (the Simple Clinical Colitis Activity Index, SCCAI ≥ 4) that is not appropriate for children with UC. Members considered the Paediatric Ulcerative Colitis Activity Index (PUCAI) score of 60 to 85 would be an appropriate measure of severe disease activity in children and **recommended** PHARMAC consider incorporating the PUCAI into the HML restrictions for UC.

2 Matters arising and Correspondence

Mesalazine

2.1 The Subcommittee noted a proposal from Pharmaco to consider funding Pentasa 2g sachets as an extension to the existing funding of Pentasa 1g sachets and a proposal from Baxter Healthcare to consider funding Asacol 800mg tablets as an extension to the existing funding of Asacol 400mg tablets.

2.2 The Subcommittee considered the availability of the higher strength mesalazine products (Pentasa 2g sachets and Asacol 800mg tablets) may improve patient compliance with medication. The Subcommittee considered the Asacol 800mg tablet could reduce the number of tablets a patient would need to take each day which may be helpful for patients taking a number of other medicines. Members considered the larger size of the Asacol 800mg tablet would not be a problem.

2.3 The Subcommittee noted the proposed price was equivalent per mg to existing strengths and considered there would be minimal financial risk as a result of dose creep or wastage if patients required dose adjustments if these preparations were to be funded.

2.4 The Subcommittee **recommended** Pentasa 2g sachets and Asacol 800mg tablets be listed in the Pharmaceutical Schedule with medium priority.

Cimetidine

2.5 The Subcommittee noted that the supplier of cimetidine intends to discontinue supplying the New Zealand market and stock would be available until early 2015.

2.6 The Subcommittee considered it is helpful to have an alternative H2 antagonist available for people that are unable to tolerate ranitidine. Members considered that famotidine would be the preferred second H2 antagonist if this was available in New Zealand.

Vitadol C

2.7 The Subcommittee noted the recent recommendations from PTAC regarding Vitamin D preparations for pregnant women and infants.

2.8 The Subcommittee noted that Vitadol C (contains vitamins A, C and D) is used in neonates who require vitamin D supplementation and this product is funded with no restrictions, however PHARMAC is aware that there is a preference from some clinicians and dieticians to use a vitamin D only product in the neonate population, without vitamin A or C.

2.9 Members noted Vitadol C is also used for infants with liver disease or Cystic Fibrosis requiring vitamin A supplementation who are unable to take fat soluble vitamin capsule preparations. Members were not aware of any other patients groups who would require Vitadol C.

2.10 The Subcommittee **recommended** that vitamin D only liquid be listed on in the Pharmaceutical Schedule if cost neutral or cost saving to Vitadol C. Members considered a vitamin A containing liquid would still be required on the Pharmaceutical Schedule for some patients.

Adalimumab rescue therapy for Crohn's

2.11 The Subcommittee noted the recommendations from PTAC regarding the funding of adalimumab as rescue therapy for Crohn's disease.

2.12 The Subcommittee **recommended** the Special Authority criteria should be as follows:

Initiation – rescue therapy Crohn's disease – gastroenterologist
Approval valid for 3 months for applications meeting the following criteria:
All of the following

1. Patient has confirmed Crohn's disease; and
2. Crohn's Disease Activity Index (CDAI) increase by greater than 100 points whilst taking fortnightly adalimumab (ADA);
3. Adalimumab to be administered weekly at doses no greater than 40 mg every week for a total of 12 weeks including maintenance dose; and
4. The number of additional adalimumab doses for rescue therapy would not exceed 6 doses per year.

Continuation – rescue therapy Crohn's disease – gastroenterologist
Approval valid for 3 months for applications meeting the following criteria**:**
All of the following:

1. Crohn's Disease Activity Index (CDAI) increase by greater than 100 points whilst taking fortnightly adalimumab (ADA);

2. Patient has not received a course of rescue therapy (6 additional doses) in the last 9 months; and
3. Adalimumab to be administered at doses no greater than 40 mg every week for a total of 12 weeks.
4. The number of additional adalimumab doses for rescue therapy would not exceed 6 doses per year.

2.13 The Subcommittee noted PTAC has recommended this application be a low priority for funding, however the Subcommittee considered the priority for this application should be high due to the clinical need for this patient group, rescue therapy is already happening with infliximab treatment for Crohn's disease, and that patients who experience disease relapse on adalimumab are moving to infliximab treatment, which, at this time is a more expensive treatment.

Rifaximin

2.14 The Subcommittee reviewed the proposed Special Authority criteria for rifaximin for hepatic encephalopathy.

2.15 The Subcommittee considered there may be a small number of patients, as indicated by recent NPPA applications, that present to hospital with severe hepatic encephalopathy requiring rifaximin, who would not meet the requirements of two previous episodes of HE but had tried an adequate trial of max tolerated doses of lactulose and other treatments (LOLA is currently listed on HML only). Members considered the proposed criteria would not allow access to these patients in the hospital setting.

2.16 The Subcommittee considered criteria should be the same for community special authority and hospital restrictions, otherwise patients would be started on rifaximin in hospital and would be unable to meet criteria for community access.

2.17 The Subcommittee considered it would be appropriate to extend applicant restrictions to allow a practitioner to apply for rifaximin on the recommendation of a gastroenterologist or hepatologist. Members considered this would not substantially change the number of patients that would be treated and would improve access to timely and appropriate treatment.

2.18 The Subcommittee considered it would be reasonable to amend the proposed Special Authority criteria and HML restrictions as follows (changes in bold and strikethrough).

> Rifaximin
> Initial application only from a gastroenterologist **or hepatologist or Practitioner on the recommendation of a gastroenterologist or hepatologist**. Approvals valid for six months where the patient has ~~had two previous episodes of~~ hepatic encephalopathy despite an adequate trial of maximum tolerated doses of lactulose.
>
> Renewal only from a gastroenterologist **or hepatologist or Practitioner on the recommendation of a gastroenterologist or hepatologist**. Approvals valid without further renewal where the treatment remains appropriate and the patient is benefiting from treatment.

2.19 The Subcommittee noted that several NPPA applications have been received for rifaximin for bacterial overgrowth and would welcome an application for funding this indication in the future.

3 Adalimumab (Humira) for Ulcerative Colitis

Application

3.1 The Subcommittee considered a resubmission from Abbvie for the listing of adalimumab on the Pharmaceutical Schedule for the treatment of moderately to severely active Ulcerative Colitis (UC) in adults.

Recommendation

3.2 The Subcommittee recommended that the Application for adalimumab for Ulcerative Colitis 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; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

Discussion

3.3 The Subcommittee noted that PTAC had previously reviewed an application for adalimumab at its November 2013 meeting where it recommended that the application be declined because of limited evidence for sustained clinical effectiveness, lack of long term safety data and high financial risk. Members noted PTAC had also recommended the application be referred to the Gastro-intestinal Subcommittee for further advice, including advice on the appropriate scoring scale for assessing disease severity.

3.4 The Subcommittee noted the clinical evidence presented in the submission consists of two pivotal randomised, double-blind, multicentre, placebo-controlled trials. The Subcommittee further noted that the supplier had provided additional information to that provided to PTAC which included updated data to 180 weeks from the open label study.

3.5 The Subcommittee noted the ULTRA 1 trial (Reinisch et al. 2011 Gut 2011;60:780-787) and the minutes from PTAC's previous discussion on this study. Members noted patients with UC were initially randomised to adalimumab (160 mg/80 mg) or placebo at weeks 0 and 2, respectively. Subsequently, after an amendment of the protocol, a third arm, with adalimumab at 80 mg/40 mg, was included. All patients enrolled were naïve to anti-TNFα therapy and had active disease (defined by a full Mayo score of 6–12 and an endoscopic subscore of 2–3), despite stable doses of concomitant steroids, immunomodulators, or both. The primary endpoint, assessed in 390 patients, was defined as the proportion of patients achieving clinical remission (full Mayo score ≤ 2, with no individual subscore > 1) by week 8 in each treatment arm. Week 8 clinical remission was achieved in 18.5% of patients in the adalimumab 160/80 mg group and in 9.2% of patients in the placebo arm (P = 0.031). The week 8 clinical remission rate in the adalimumab 80/40 mg group was similar to that of the placebo group (10% vs 9.2%) (P = 0.833). The clinical response and mucosal healing among the three groups (secondary endpoints) were not significantly different. Members noted 390 patients entered an open-label extension study after week 8 and were maintained on adalimumab 40 mg every other week (EOW) for 52 weeks, with the possibility of dose-escalation to 40 mg weekly. Members noted that clinical

remission at week 52 was reported in 25.6% of patients maintained with 40 mg of adalimumab EOW.

3.6 The Subcommittee noted the ULTRA 2 trial (Sandborn et al. Gastroenterology 2012;142:257-265), where 494 active UC patients were randomised to receive adalimumab 160 mg at week 0, 80 mg at week 2, and 40 mg EOW, or placebo, through to 52 weeks. Members noted the eligibility criteria were similar to those associated with the ULTRA 1 study, except with the inclusion of UC patients (40% of the population studied) previously treated with anti-TNFα agents with a discontinuation period of at least 8 weeks. Members noted the mean Mayo score was 9 and 60% of the population studied were on corticosteroids and 35% were on azathioprine or 6-mercaptopurine at baseline. Members noted patients who were considered primary non-responders to infliximab were excluded. The two co-primary endpoints were defined as the proportion of patients achieving clinical remission (defined as full Mayo score ≤ 2, with no individual subscore > 1) at week 8 and the proportion of patients achieving clinical remission at week 52. Members noted that the clinical remission at week 8 was achieved in 16.5% of patients in the adalimumab arm and in 9.3% of patients in the placebo arm (P = 0.019). The corresponding values at week 52 were 17.3% and 8.5% (P = 0.004), respectively, with an absolute difference of adalimumab versus placebo of 8.8%. Members noted a clinical response was achieved in 50.4% of patients receiving adalimumab and 34.6% on placebo (P < 0.001) at week 8 and in 30.2% and 18.3%, respectively (P = 0.002) at week 52. Members noted that a subgroup analysis, stratifying patients based on prior exposure to anti-TNFα, indicated these patients did not respond as well. Among naïve patients, a week 8 clinical remission was achieved in 21.3% of patients in the adalimumab group and in 11% in the placebo group (P = 0.017); the corresponding values at week 52 were 22% and 12.4%, respectively (P = 0.029). In the anti-TNFα-exposed group a significant difference in clinical remission was found only at week 52 (10.2%, adalimumab and 3%, placebo) (P = 0.039).

3.7 The Subcommittee noted the short duration of the ULTRA 1 study and considered the key evidence was from ULTRA 2, a randomised controlled trial for 52 weeks. The Subcommittee also noted the post hoc intention-to-treat analysis of ULTRA 2 (Sandborn et al. Aliment Pharmacol Ther 2013;37:204–213). Members noted it would be preferable to have longer term data available. Members noted the additional data provided in the resubmission was from an open-label extension study.

3.8 The Subcommittee noted that in general the magnitude of clinical benefit gained from adalimumab compared to placebo in UC was small. Members noted that there was a notable decrease in the proportion of patients in clinical remission with the progression of time in the ULTRA 2 Trial (Sandborn et al., 2012).

3.9 The Subcommittee noted that in the ULTRA 2 absolute remission rates difference between adalimumab and placebo are smaller than that observed in the infliximab trials for induction and maintenance therapy for UC, however the ability to compare these trials is somewhat limited due to differences in trial design.

3.10 The Subcommittee noted the updated information provided in the resubmission from the supplier. Members noted the study M10-223 (ULTRA 3) provides data up to 180 weeks and evaluates the safety and efficacy of adalimumab for the long term maintenance of response in subjects with UC who had successfully completed either the ULTRA 1 study or the ULTRA 2 study and responded well to adalimumab treatment. Members noted of the 588 patients entered the extension study, 52.25% were in remission on entry (baseline) and this was maintained at 180 weeks (52%). Members considered that the information from the updated extension study did not

add sufficient long term safety data to that previously submitted and further evidence is required.

3.11 The Subcommittee noted that the efficacy of adalimumab and infliximab has not been directly compared, and considered adalimumab is unlikely to be more efficacious than infliximab. Members noted that patients in the ULTRA 2 study (Sandborn et al., 2012) who had not responded to infliximab did worse on adalimumab if used second line. Members noted there may be a role for adalimumab for treating patients who are hypersensitive to infliximab therapy.

3.12 The Subcommittee noted that infliximab is the appropriate comparator for the cost-utility analysis.

3.13 The Subcommittee noted that there are approximately 6000 patients in New Zealand with UC, most of which have mild disease. Members considered approximately 1000 patients would have moderate to severe UC, of which approximately 500 would be intolerant or refractory to other treatments and therefore would be eligible for adalimumab if it were to be funded. Members noted there was substantial estimation involved in the prediction of patient numbers and considered the assumptions made regarding the proportion of patients that would achieve clinical response in the modelling were high and consider 50% a more appropriate estimate.

3.14 The Subcommittee noted that PTAC had recommended the application be referred to them for advice on the appropriate scoring scale for assessing disease severity. The Subcommittee noted that the Simple Clinical Colitis Activity Index (SCCAI) (Walmsley, et al. Gut 1998 1998;43(1):29-32) has been widely adopted for use in New Zealand to assess disease severity and monitor patients during therapy. Members noted that SCCAI is different from the Mayo scoring system which is used in the clinical trials provided. Members noted that the SCCAI and Mayo scoring system are not interchangeable. The current threshold, SCCAI of ≥ 4 may reflect a less severe presentation than a Mayo score of ≥ 4. The Subcommittee noted that due to the different scoring activities indices, comparison of results from different trials is difficult. Members noted that the most common scoring systems, the Mayo Scoring System and the SCCAI have different activity indices. Members considered that there was a potential for inter- observer variation with the Mayo Scoring System. The Subcommittee considered the SCCAI should be the preferred scoring system in New Zealand.

3.15 The Subcommittee agreed with PTAC's recommendation that the application be declined because of limited evidence for sustained clinical effectiveness, as well as a lack of long term safety data and high financial risk. The Subcommittee considered the additional information provided in the resubmission was not sufficient to alter this recommendation.

4 Sodium picosulfate

Application

4.1 The Subcommittee reviewed an application from a clinician for the listing of sodium picosulfate oral liquid on the Pharmaceutical Schedule for treatment of chronic constipation.

Recommendation

4.2 The Subcommittee **recommended** that if a registered sodium picosulfate oral liquid product became available in New Zealand, it should be listed in the Pharmaceutical Schedule with a high priority subject to Special Authority criteria.

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;*

Discussion

4.3 The Subcommittee noted that PHARMAC had received a clinician application for the listing of sodium picosulphate oral solution on the Pharmaceutical Schedule. Members noted that the clinician proposes that the target population would be children who have chronic constipation (disimpaction and maintenance) and also for children and adults who are unable to tolerate large volumes of laxative. Members noted that the application is supported by other paediatricians.

4.4 The Subcommittee further noted that PHARMAC had also received correspondence from the "New Zealand Nurses Organisation" on behalf of their members working with children with encopresis, the "New Zealand College of Primary Health Care Nurses" and the "Nurses for Children and Young People of Aotearoa" stating that there is a lack of safe, appropriate medication for children with encopresis.

4.5 The Subcommittee noted that since the introduction of the Hospital Medicines List in July 2013 PHARMAC had received 13 NPPA applications for sodium picosulfate (Dulcolax Pico) liquid for children between the ages of 2 and 10 with chronic constipation. The Subcommittee noted the high frequency of correspondence received by PHARMAC related to the lack of an alternative laxative to those currently listed for chronic idiopathic paediatric constipation.

4.6 The Subcommittee considered that the prevalence of chronic constipation in children to be high, possibly accounting for as much as 25% of consultations with paediatric gastroenterologists and also a significant portion for general paediatricians. Members noted that there were a large number of patients with autism spectrum disorder and other neurodevelopmental disorders who present with chronic idiopathic paediatric constipation as a co-morbidity.

4.7 The Subcommittee considered that there is little published evidence to guide health professionals regarding the pharmacological management of chronic constipation in children. Members considered that it is unlikely that there is one treatment regimen that will suit all children. Members noted the paucity of evidence related to laxatives and that the available evidence was of weak strength and poor quality. The Subcommittee noted the NICE commissioned guidelines for the diagnosis and management of idiopathic childhood constipation in primary and secondary care includes sodium picosulphate as a second-line therapeutic option but noted the lack of supporting evidence.

4.8 The Subcommittee noted that the applicant has requested the funding of a 5mg/5ml oral sodium picosulphate solution. Members noted the usual dose of sodium picosulfate would be between 2.5 – 20 mL per day. Members noted that sodium picosulphate oral liquid is not currently registered with Medsafe. The Subcommittee noted that currently any sodium picosulfate solution prescribing or dispensing in New Zealand would need to comply with the requirements of Sections 29 and 25 of the Medicines Act 1981. Members noted that a 5mg/5ml oral solution is registered in the

United Kingdom. Members also noted that a 7.5mg/mL liquids drop presentation is a registered in Australia.

4.9 The Subcommittee considered a macrogol-based iso-osmotic laxative such as Lax Sachets, to be a suitable comparator to sodium picosulphate solution. Members considered that there were palatability issues and the large dose volume with macrogol products frequently impacts on patient adherence and tolerability to therapy.

4.10 The Subcommittee noted that there were no "head-to-head" comparison trials between sodium picosulphate and macrogol in chronic constipation.

4.11 The Subcommittee noted the availability of PicoPrep (sodium picosulfate powder for oral solution) and noted the issues with palatability and large dose volume with the product.

4.12 The Subcommittee considered that due to the palatability and dose volume issues with the currently available products that there was an unmet clinical need for a low dose volume, pleasant tasting New Zealand registered product. Members noted that PHARMAC was working on a proposal to list an electrolyte free macrogol product. Members noted there were no other alternative laxative products that would be a similar alternative to sodium picosulfate oral liquid currently available in New Zealand that PHARMAC should consider.

4.13 The Subcommittee considered that it was difficult to estimate patient numbers and considered that numbers would be large and there was a high risk of slippage if this product was listed. Members noted that there could be significant fiscal risk if used extensively in the community setting. The Subcommittee considered that although there is no supporting evidence, the availability of sodium picosulphate may have the potential to reduce the need for colonic lavage and other clinical intervention (e.g. abdominal x-ray, manual disimpaction) requiring hospital admission.

4.14 The Subcommittee considered it would be appropriate to restrict use to treatment after macrogol, based on the lack of evidence for sodium picosulfate. Members also noted restricting access could help minimise the fiscal risk. Members noted children would benefit the most from sodium picosulfate liquid, however it could be used for adults or children with chronic constipation who were intolerant or unresponsive to other treatments.

4.15 The Subcommittee recommended that if a registered sodium picosulfate oral liquid product became available in New Zealand, it should be listed in the Pharmaceutical Schedule with a high priority subject to Special Authority criteria.

5 Biosimilar Infliximab

Application

5.1 The Subcommittee reviewed an application from Hospira (New Zealand) Ltd for the listing of its biosimilar infliximab (CT-P13, Inflectra/Remsima) in Section H of the Pharmaceutical Schedule.

Recommendation

5.2 The Subcommittee **recommended** that subject to Medsafe approval, Hospira's biosimilar infliximab should be listed in Section H of the Pharmaceutical Schedule subject to the same restrictions as the Remicade (Janssen) brand of infliximab.

5.3 The Subcommittee further **recommended** widening of access to infliximab to enable dose increases in patients not responding to treatment.

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; (v)The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health & disability support services; and (vi) the budgetary impact of any changes to the pharmaceutical schedule.*

Discussion

5.4 The Subcommittee noted that PTAC had reviewed the application at its 8 & 9 May 2014 meeting and requested the opinion of the Gastrointestinal Subcommittee.

5.5 The Subcommittee noted that infliximab (Remicade, Janssen) is currently funded in DHB hospitals subject to restrictions for a range of inflammatory conditions including severe active Crohn's disease, fistulising Crohn's disease and severe ulcerative colitis (UC).

5.6 The Subcommittee noted that since the Hospital Medicines List (HML) came into effect on 1 July 2013 the cost to DHBs of infliximab has increased significantly, in some cases doubling, and it was dominating local drug budgets. Members considered that the growth was mainly driven by increased use in UC and some price relief on this product was essential for DHBs.

5.7 The Subcommittee noted that infliximab and other TNF inhibitors were immunogenic molecules and the development of anti-TNF antibodies can cause reduced efficacy. Members noted discussions at recent conferences on the use of drug trough concentrations and anti-TNF antibody measurements to drive treatment decision making, for example stopping treatment or dose escalating. Members considered that this may become routine practice for infliximab and other TNFs over the next few years.

5.8 The Subcommittee noted that Hospira's biosimililar infliximab (Inflectra/Remsima) was not currently approved by Medsafe but that it was approved by the European Medicines Agency (EMA), had been launched in some European countries and Medsafe is currently considering a submission. Members noted that in order to satisfy the EMA for approval a biosimilar must demonstrate that its variability in any parameter falls within the range of variability for the reference product and that any differences between it and the reference product have no clinically meaningful differences in quality, safety or efficacy.

5.9 The Subcommittee reviewed evidence comparing Hospira's biosimilar infliximab with Remicade including evidence from two comparative clinical studies in patients with ankylosing spondylitis (AS) (Study CT-P13 1.1, PLANETAS, Park et al Ann Rheum Dis. 2013;72(10):1605-12) and rheumatoid arthritis (RA) (Study CT-P13 3.1,

PLANETRA, Yoo et al Ann Rheum Dis. 2013;72(10):1613-20) and unpublished data in patients with inflammatory bowel diseases (IBDs).

5.10 The Subcommittee noted some minor differences in characteristics but considered these to be of no clinical significance. Members considered that overall these data indicated that Hospira's infliximab demonstrated same or similar quality, safety and efficacy to Remicade.

5.11 The Subcommittee considered that Remicade was already effectively a "biosimilar" version of infliximab since commercial lots had undergone multiple manufacturing changes since the molecule was originally approved (Schiestl et al Biotechnology Nature Biotechnology 2011;29,310–312).

5.12 The Subcommittee noted that the pathology of disease was different in synovitis compared with IBDs and the exact mode of action of anti-TNF drugs was not well characterised. However, members considered that despite this and the known molecular differences between various innovator anti-TNF drugs themselves, e.g. adalimumab, etanercept, infliximab, they all have similar efficacy across various disease settings. Members considered that differences would need to be very large for a biosimilar TNF to have a different clinical profile to its innovator TNF. Members considered that because even different TNF molecules have similar activities there was minimal likelihood that Hospira's biosimilar infliximab would be different to Remicade in IBD's.

5.13 The Subcommittee noted some clinicians and patients may be concerned about switching to biosimilar infliximab. Members considered educational and implementation support would be necessary if biosimilar infliximab was funded.

5.14 The Subcommittee considered that it would be appropriate for PHARMAC to run a Sole Supply process for infliximab for all indications currently funded. Members further considered that it would be appropriate to award Hospira Sole Supply Status to Hospira's biosimilar infliximab if it was the preferred bid, subject to it gaining approval from MedSafe. The Subcommittee noted that if the price was low enough it would be desirable to allow dose increases for some patients who do not respond to standard dosing of infliximab.

6 Ursodeoxycholic acid for Cystic Fibrosis Liver Disease

Application

6.1 The Subcommittee reviewed further information provided by PHARMAC staff, including expert opinions and updated literature search, regarding the use of ursodeoxycholic acid (UDCA) for patients with cystic fibrosis liver disease.

Recommendation

6.2 The Subcommittee **recommended** that the Application for ursodeoxycholic acid for patients with cystic fibrosis liver 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.*

Discussion

6.3 The Subcommittee noted that at its previous reviews in April and December 2012 that there was insufficient evidence to recommend funding for this indication. The Subcommittee noted that the decision regarding funding of UDCA for patients with cystic fibrosis was deferred at a Gastro-Intestinal Subcommittee teleconference meeting held in December 2012 with the request that further evidence be sought to establish the effect of early UDCA treatment on the development of cystic fibrosis liver disease including expert opinion and that this be reviewed at its next meeting.

6.4 The Subcommittee noted there is little new evidence available since its previous review in 2012. The Subcommittee noted the Cochrane review updated in late 2012 (Cheng et al. Cochrane Database Syst. Rev. 2012;10:CD000222. Ursodeoxycholic acid for cystic fibrosis-related liver disease [updated from 2000 review]) did not include any new references and hence the conclusions remain the same as the review previously considered by the Subcommittee.

6.5 The Subcommittee noted Kappler M et al. (Ursodeoxycholic acid therapy in cystic fibrosis liver disease – a retrospective long-term follow-up case-control study. Alimentary Pharmacology and Therapeutics 2012;36:266-73) published a retrospective case-control study assessing the long-term effects of continuous UDCA therapy (20mg/kg) in 98 CF patients with constantly elevated serum liver enzymes. Early treatment with UDCA was found to reduce serum liver enzyme elevations significantly and persistently in CF patients. Members noted meconium ileus was not identified as a risk factor for development of CF-related liver disease, however liver disease did start earlier in this subset of patients (p=0.01). Members noted the long-term primary endpoint 'development of overt liver disease' was used. Study design issues meant cases were matched to 2 control groups; one well-matched and one historic group. Members noted one of the 98 patients treated with UDCA developed overt liver disease, compared to no patients in the well-matched control group and 9 patients in the historic group (p=0.09). Members noted the limitations of this study, particularly the retrospective comparative group from a different medical era where clinical care may have been very different.

6.6 The Subcommittee noted the expert opinions from specialists in the area. . Members considered that the information presented did not include any new information or evidence to support that long-term UDCA for CF-related liver disease prevents disease progression, liver-related complications, liver related death, liver transplant or impacts overall survival. Members noted international guidelines (the European Cystic Fibrosis Society and the North American Cystic Fibrosis Foundation) recommend the use of UDCA to limit progression of CFLD on the basis of expert opinion and clinical practice. Members considered that further studies in this patient population may be unlikely as use of UDCA is already established practice in many countries.

6.7 The Subcommittee reiterated its previous view that in general, there appears to be supportive evidence for the effect of UDCA on improving liver function tests (LFTs), however this does not appear to result in improved survival. Members noted that evidence in Primary Sclerosing Cholangitis (PSC), another biliary liver disease with similarities to CF-related liver disease, use of UDCA was associated with a small but significant increase in liver related complications (despite improvement in LFTs). Members questioned the safety of using UDCA for CFLD when there is insufficient evidence of benefit or to rule out possible harm.

6.8 The Subcommittee considered that although the price of UDCA has decreased in recent years, there would still be significant financial risk should restrictions be removed.

6.9 The Subcommittee considered the strength and quality of the evidence to be weak. The Subcommittee **recommended** the application for UDCA for patients with CLFD be declined, due to insufficient evidence to support use and concerns regarding safety. Members noted they would be willing to reconsider the application if new evidence became available.