Gastrointestinal Subcommittee of the Pharmacology and Therapeutics Advisory Committee (PTAC)

Meeting held on 28 March 2017

(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 2016.*

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 will be reviewed by PTAC at its meeting on 10 & 11 November 2017, the record of which will be available in due course.

Record of the Gastrointestinal Subcommittee of PTAC meeting held at PHARMAC on 28 March 2017

1 Record of the previous Subcommittee meeting

1.1 The Subcommittee noted and accepted the record of its previous meeting held on 21 May 2014.

2 Factors for Consideration

2.1 The Subcommittee noted a presentation by PHARMAC staff outlining PHARMAC's new decision making criteria, the Factors for Consideration (FFC), which replaced the previous nine Decision Making Criteria on 1 July 2016. Members noted that all recommendations made by the Subcommittee should be provided in the context of the FFC.

3 Matters Arising and Correspondence

Levofloxacin

3.1 The Subcommittee noted that following an ongoing supply issue with bismuth, PHARMAC staff had submitted an application to the Anti-Infective Subcommittee (AISC) in October 2016 to consider the clinical appropriateness of funding levofloxacin for the treatment of *H. pylori*. Members noted that the AISC had recommended that the application be declined and referred to the Gastrointestinal Subcommittee for further advice.

3.2 The Subcommittee disagreed with the AISC's assessment. The Subcommittee noted the concerns of the AISC regarding antimicrobial resistance, however considered this did not outweigh the clinical importance of securing a second-line treatment *H. pylori* treatment. The Subcommittee noted the difficulties with a decreasing number of options available for the treatment of *H. pylori*.

3.3 The Subcommittee noted that there was data from Middlemore Hospital which had shown that the resistance rate of moxifloxacin was 10% which it considered would be similar to the resistance rate of levofloxacin. The Subcommittee considered this resistance rate did not preclude the use of levofloxacin for *H. pylori* treatment.

3.4 The Subcommittee considered that the number of patients accessing bismuth in the community would be an appropriate surrogate for the patient numbers requiring access to levofloxacin. Members considered that with levofloxacin funded as a second-line therapy only, numbers would remain small – approximately 500 patients per year. Members considered that there would be little use in funding levofloxacin as a third line therapy and further considered that it would be clinically appropriate to have two options available as a second-line therapy.

3.5 The Subcommittee **recommended** that levofloxacin be funded as a second-line treatment for *H. pylori* with a high priority.

3.6 The Subcommittee noted that international guidelines for the treatment of *H. pylori* stated that first line treatment should be for a duration of 10-14 days and that due to that, the Subcommittee **recommended** that patients have access to 28 tablets of clarithromycin for initial treatment of *H. pylori*. Members considered that it would be appropriate to educate prescribers on the most effect duration of first line treatment in a BPAC article.

Bismuth

3.7 The Subcommittee noted that PHARMAC had located a supplier of colloidal bismuth subcitrate tablets which was being supplied to Australia and had been recommended by an Australian Clinical Gastroenterologist.

3.8 The Subcommittee considered that this formulation of bismuth was acceptable for use in New Zealand as a replacement for the product currently out of stock.

Fat Soluble Vitamins for Patients with Severe Malabsorption Syndrome

3.9 The Subcommittee noted that PHARMAC sought advice on the definition of severe malabsorption syndrome in regards to widening access to Vitabdeck.

3.10 The Subcommittee considered that the majority of the intended patient group had short gut syndrome and that those patients, along with any other relevant patient subgroups, would be under the care of a nutrition team. The Subcommittee **recommended** that the proposed access criteria for Vitabdeck be worded to include "initial application from a specialist" for severe malabsorption syndrome. Members considered it would be clinically appropriate for an initial application to be for 1 year with life-long renewals to be given by a specialist only.

Half-dose Macrogol 3350 / Electrolyte-free Macrogol 3350

3.11 The Subcommittee noted that PHARMAC sought advice on tender bids for half-dose macrogol 3350 and electrolyte-free macrogol 3350 preparations that are not currently listed on the Pharmaceutical Schedule.

3.12 The Subcommittee considered that the half-dose formulation would be useful for paediatric patients who required a half-dose, but would not be necessary for adult patients. Members further considered that there was little or no need for the electrolyte-free formulation for adults. Members considered that if a half dose macrogol was available it should be no greater than half the cost of the full dose macrogol.

3.13 The Subcommittee considered that it was important for paediatric patients, particularly those with developmental disorders and very young patients, to have access to a tasteless formulation such as the electrolyte-free macrogol 3350. Members considered that the taste of the macrogol 3350 to be a barrier to compliance in those paediatric patients as even mixing it with juice did not disguise the taste. The Subcommittee considered that it would be appropriate to require patients to trial the standard macrogol 3350 before being eligible for the electrolyte-free formulation.

3.14 The Subcommittee **recommended** that the half-dose macrogol 3350 and electrolyte-free macrogol 3350 be listed on the Pharmaceutical Schedule with a high priority.

Vitamin D Liquid (100 iμ/drop)

3.15 The Subcommittee noted that the currently funded vitamin D gel capsule could not be compounded or prepared into an oral liquid, unlike the previously funded tablets that could be crushed. Members noted that parents or nursing staff were withdrawing the contents of the capsule with a needle which can be unsafe. The Subcommittee considered that for patients who could not take the gel capsules, the liquid formulation would be appropriate using the following Special Authority criteria.

Initial application from any relevant practitioner. Approvals valid for two years.

Both

1. Patient is less than 12 years old; and
2. Patient has proven vitamin D deficiency and requires supplementation

Renewal application from any relevant practitioner. Approvals valid for two years.
Both

1. Patient is less than 12 years old; and
2. Patient continues to have proven vitamin D deficiency and requires supplementation.

Vitamin D Gel Capsule (1.25 mg: 50,000 iμ) – Cholecalciferol – Soy and Nut Allergies

3.16 The Subcommittee noted that PHARMAC sought advice on the possible issues with the soy and nut allergens warning on the listed brand of cholecalciferol gel capsules Medsafe datasheet. Members considered that the proportion of nut/soy allergens in the capsules was so small it would be clinically irrelevant. Members noted that it would be difficult to explain this to caregivers of patients with soy/nut allergies.

3.17 The Subcommittee suggested that PHARMAC check with the Centre for Adverse Reactions Monitoring (CARM) to see if there had been any reports regarding the allergens.

Rifaximin

3.18 The Subcommittee noted that as a result of the 2016/2017 Annual Tender, PHARMAC had received bids for rifaximin 200 mg and rifaximin 550mg tablets and sought advice on the standard dose and frequency of rifaximin.

3.19 The Subcommittee noted that the standard adult dose was 550 mg twice daily but could take 600 mg twice daily if only the 200 mg tablets were funded. Members noted that the 200 mg tablet was used in New Zealand prior to the listing on the Schedule. Members considered that the 200mg was likely the formulation used for Small Intestinal Bacterial Overgrowth (SIBO) indication.

Zinc sulphate (50 mg elemental zinc)

3.20 The Subcommittee noted that during the 2016/2017 Annual Tender, PHARMAC had received a bid for a zinc sulphate tablet rather than the specified capsule. Members noted that the capsules were preferable for paediatric patients whereby the powder inside the capsule could be mixed with water and the patient given a proportion of the liquid according to the dose prescribed.

Paediatric Crohn's Disease Activity Index (PCDAI) for Adalimumab

3.21 The Subcommittee noted that PHARMAC had received correspondence from the supplier of adalimumab, Abbvie, requesting the use of the PCDAI scoring system in the Special Authority (SA) for adalimumab for patients under 40 kg with Crohn's disease. Members noted that for adalimumab the current SA utilises CDAI scoring for adult and paediatric patients, whereas for infliximab HML restrictions, PCDAI is used for children and CDAI for adults. The Subcommittee **recommended** that the adalimumab SA criteria for Crohn's disease be amended to include paediatric appropriate criteria in-line with the infliximab HML restriction for Crohn's disease in children and considered that PHARMAC should propose new wording to be reviewed by the Subcommittee by email.

4 Macrogol Correspondence and Clozapine Coroner's Report

Recommendation

4.1 The Subcommittee **recommended** that the Special Authority (SA) criteria for macrogol 3350 (13.125 g with potassium chloride 46.6 mg, sodium bicarbonate 178.5 mg and sodium chloride 350.7 mg) be amended to include first-line use to prevent constipation in patients receiving clozapine with a high priority.

4.2 The Subcommittee **recommended** that the Special Authority (SA) criteria for macrogol 3350 (13.125 g with potassium chloride 46.6 mg, sodium bicarbonate 178.5 mg and sodium chloride 350.7 mg) be removed for all patients with a high priority.

Discussion

4.3 The Subcommittee noted that PHARMAC sought advice regarding widening access to macrogol 3350 (13.125 g with potassium chloride 46.6 mg, sodium bicarbonate 178.5 mg and sodium chloride 350.7 mg) for the prophylaxis and treatment of constipation in patients with schizophrenia prescribed clozapine following a recommendation received in a coroner's report (Warburton [2017] NZCorC 4 (26 January 2017).

4.4 The Subcommittee also noted PHARMAC had received correspondence from a South Island PHO requesting macrogol 3350 sachets be listed without any restrictions.

Macrogol 3350 for patients treated with clozapine

4.5 The Subcommittee noted that clozapine was an antipsychotic used for treatment resistant schizophrenia. Members noted that clozapine has many potential side effects included in the Medsafe data sheet with emphasis on its haematological adverse reactions including agranulocytosis which requires frequent blood testing. Other precautions are noted included its effect on the gastrointestinal tract.

4.6 The Subcommittee noted the Coroner's report regarding a patient who had been treated with clozapine for schizophrenia for 16 years who subsequently died of toxaemia secondary to megacolon and paralytic ileus.

4.7 The Subcommittee noted that the Coroner's report provided a number of recommendations, including a request for PHARMAC and its Gastrointestinal Subcommittee of PTAC to consider broadening the eligibility criteria for accessing macrogol to include clozapine use without having to trial lactulose first.

4.8 The report highlighted the lack of clarity between primary and secondary care clinicians on the identification and management of patients taking clozapine and the risk of Clozapine Induced Gastrointestinal Hypomotility (CIGH).

4.9 Members noted that the Coroner, in producing its report, had engaged Dr Susanna Every-Palmer as an expert in the subject of CIGH. Capital and Coast DHB (CCDHB) and Hutt Valley DHB (HVDHB) both use the Porirua Protocol as a means of managing the risk of CIGH in patients treated in those DHBs. The report mentions that there is not a nationally consistent approach to the management of CIGH in New Zealand although noting that some DHBs have procedures and pathways in place.

4.10 The Subcommittee considered two papers published by Dr Every-Palmer.

Every-Palmer et al, Clozapine-treated Patients Have Marked Gastrointestinal Hypomotility, the Probable Basis of Life-threatening Gastrointestinal Complications. EBioMedicine 2016

- For 17 patients not prescribed clozapine, median colonic transit time was 23 h. For 20 patients prescribed clozapine, median transit time was 104.5 h, over four times longer than those on other antipsychotics or normative values (p = 0.0001). Eighty percent of clozapine-treated patients had colonic hypomotility, compared with none of those prescribed other antipsychotics (olanzapine, risperidone, paliperidone aripiprazole, zuclopenthixol or haloperidol). In the clozapine group, right colon, left colon and rectosigmoid transit times were all markedly abnormal suggesting pan-colonic pathology.

Every-Palmer et al, The Porirua protocol in the treatment of Clozapine-induced GI hypomobility and constipation: a Pre and Post Treatment Study. CNS Drugs 2017;31: 75-85.

- A follow on study of the clozapine patients of who were in the previous study (Every-Palmer et al, 2016). Colonic transit times (CTTs) of clozapine-treated inpatients not receiving laxatives were compared with their transit times when receiving laxatives with treatment prescribed according to the Porirua Protocol for clozapine related constipation (docusate and senna augmented by macrogol 3350 in treatment resistant cases). Overall, 14 patients (10 male) were enrolled, transit times improved markedly with laxative treatment. Median CTT without laxatives was 110hours (95% CI 76-144 h), over four times longer than normative values (p<0.0001). Median CTT with laxatives was 62 h (95% CI 27-96 h), a two day reduction in average transit time (p=0.009). Severe gastrointestinal hypomotility decreased from 64-21% (p=0.031). Four of the 14 patients were treated with Macrogol 3350 in addition to docusate with senna.

4.11 The Subcommittee considered that, as a result of the research and published papers by Dr Every-Palmer, constipation cannot be relied on as a demonstrated symptom of serious CIGH. Members noted that in the study the addition of macrogol 3350 sachets to the treatment of clozapine patients was following a comprehensive induction of docusate with senna alongside a frequent review of gastrointestinal function. Members noted it was not stated what was the indicator of constipation and at what stage the four patients that commenced macrogol 3350 sachet started treatment.

4.12 Members noted that patients enrolled in the study were prophylactically started on docusate with senna. The author considered that macrogol 3350 is likely to be clinically more effective and superior to lactulose, albeit more expensive, although published evidence demonstrating superiority in this clinical setting is lacking. Members considered that published papers have demonstrated patients treated with clozapine should commence prophylactic use of laxatives, up to 2-4 docusate with senna tablets per day as first line. There is also evidence that traditional symptoms of constipation are not a reliable diagnostic marker for CIGH and patients that are not managed proactively are at risk of developing serious CIGH.

4.13 The Subcommittee noted that macrogol 3350 sachets (Lax-Sachets) were funded in the community and DHB hospitals for patients in whom other oral laxatives, including lactulose, have been ineffective and the patient would otherwise need a per-rectal presentation. In DHB hospitals there was an additional criteria that allowed macrogol 3350 to be use short term for faecal disimpaction. The Subcommittee considered that there are not inequities in access between DHB hospitals and community as the only difference in criteria was ‘for short term use of faecal disimpaction’.

4.14 The Subcommittee noted community prescribing data that demonstrated that patients prescribed clozapine are prescribed a regular laxative less than 30% of the time. Members considered that this percentage should be much higher given the risk of these patients developing CIGH.

4.15 The Subcommittee considered that, based on the high risk of these patients achieving potentially life threatening CIGH, patients taking clozapine should have access to macrogol 3350 without restriction as their condition and treatment make treating constipation quite different to the general population.

Macrogol 3350 for the treatment of constipation in all patients

4.16 The Subcommittee considered evidence provided by a primary health organisation and also two Cochrane reviews provided by PHARMAC comparing lactulose to macrogol 3350.

Lee-Robichaud et al, Lactulose versus Polyethylene Glycol (PEG) for Chronic Constipation. Cochrane Database Syst Rev. 2010;7:CD007570

4.17 This meta-analysis considered ten trials which enrolled a total of 868 participants and were conducted between 1997 and 2007. The trials were conducted in six different countries. Participant age ranged from 3 months to 70 years. Adults only were recruited for 4 studies. Five trials reported stool frequency per week. Singularly taken, all showed that macrogol 3350 resulted in a higher stool frequency per week when compared with lactulose. Two trials reported form of stool on the Bristol Stool Scale, both studies reported a higher Bristol Stool Score when using macrogol 3350 compared with lactulose (softer stool). Three trials reported relief of abdominal pain. Two favoured macrogol 3350 in this outcome; one found lactulose and macrogol 3350 to be comparable in this outcome. Three trials reported on use of additional products, all favoured macrogol 3350 as requiring less use of additional products.

4.18 The analysis indicated that polyethylene glycol is better than lactulose in outcomes of stool frequency per week, form of stool, relief of abdominal pain and the need for additional products. On subgroup analysis, this is seen in both adults and children, except for relief of abdominal pain. The report concluded that polyethylene glycol should be used in preference to lactulose in the treatment of chronic constipation.

Every-Palmer et al. Pharmacological treatment for antipsychotic-related constipation. Cochrane Database Syst Rev. 2017 Jan 24;1:CD011128.

4.19 A review evaluating the effectiveness and safety of pharmacologic treatment (versus placebo or compared against another treatment) for antipsychotic-related constipation (defined as constipated patients of any age, who are treated with antipsychotics, regardless of dose, in which constipation is considered to be an antipsychotic-related side effect).

4.20 Overall, there is insufficient trial-based evidence to assess the effectiveness and safety of pharmacological interventions for treating antipsychotic-related constipation, due to limited, poor quality data (few studies with high risk of bias and no meta-analyses). The author considered methodological limitations in the included studies were obvious, and any conclusions based on their results should be made with caution. Methodologically rigorous RCTs evaluating interventions for treating antipsychotic-related constipation are needed.

4.21 The Subcommittee considered that, based on the evidence provided, macrogol 3350 was at least as clinically effective as lactulose and potentially better tolerated. Members noted that since listing the price per sachet has reduced significantly through the tender process and that wider access could now be considered. Members considered that access to macrogol 3350 should not require a trial of lactulose due to the relative price difference and evidence of efficacy and tolerability.

4.22 The Subcommittee considered that the patient group who would use macrogol would be the same as the patient group taking lactulose and that it was unlikely that the patient group would increase as patients would simply be switching from one treatment to the other.

4.23 The Subcommittee noted the current restriction of a maximum of 90 sachets per prescription, members considered that there would be a small patient sub-group which would require more than one sachet per day, but noted that this could be managed by the patient's clinician by providing more than one script at a time.

4.24 The Subcommittee considered the average usage of macrogol sachets per patient compared with average usage of lactulose. Members noted that comparable average use of lactulose is much less than macrogol 3350 and therefore patients switching would be a cost to the CPB. Based on current use and number of patients on lactulose and other laxatives, listing without restriction of macrogol 3350 would be a significant cost to the Community Pharmacy Budget.

5 Biologics for Ulcerative Colitis

Discussion

5.1 The Subcommittee noted that PTAC had considered an application for the funding of golimumab for the treatment of moderate to severe ulcerative colitis (UC) in February 2017 and, while the minutes from that meeting were not signed at the time of this Subcommittee meeting, it was understood that PTAC had declined the application based on a lack of long-term evidence for sustained clinical benefit. The Subcommittee noted evidence for golimumab was limited to TNF-α inhibitors treatment naïve patients and more data is required to determine its role in patients who have not responded to other agents.

5.2 The Subcommittee considered that monitoring serum levels of biologics (adalimumab and infliximab) and measurement of drug antibodies showed promising results for treatment optimisation. The Subcommittee considered that the monitoring of serum levels and drug antibodies could reduce the incidence of under and overdosing of biologic agents. This could potentially result in additional costs or savings for pharmaceutical expenditure compared to standard recommended dosing currently used in clinical practice, and it may be cost-neutral overall to the Combined Pharmaceutical Budget.

5.3 The Subcommittee noted that currently infliximab is weight based dosing and adalimumab is fixed dosing based on indication from the Medsafe datasheet. Members noted that the Medsafe datasheet for adalimumab does not contain dose information based on weight or serum levels. Members considered that an application to consider serum level based dosing of infliximab and adalimumab would need to consider the licencing and approved use of these agents in New Zealand.

5.4 The Subcommittee considered that the evidence suggested that a loss of response to a TNF-α inhibitor agent was directly related to a lack of concentration or the presence of antibodies and considered that it would be necessary for clinicians to monitor their patients and test for serum concentrations annually. Members noted that the serum level test was currently available in Christchurch with a turnaround time of approximately ten days and cost approximately $80 per test. Members considered that testing would need to continue during remission phases as well as at induction. Members considered that the point-of-care testing was currently too inaccurate to use.

5.5 The Subcommittee considered it would be possible to develop a treatment algorithm for use of biologic agents used in inflammatory bowel disease (IBD) indications based on serum levels and antibodies.

- For patients that do not respond to TNF-α inhibitors – use another biologic with a different mode of action.
- If loss of response to TNF-α inhibitors – measure drug trough concentration – if low, consider increasing dose and or decreasing interval of treatment; if high and lost response, change to another agent.
- If loss of response due to antibodies – try another TNF-α inhibitor. If already tried both, no current options for further biologics.

5.6 Members noted that Australia is developing consensus guidelines of therapeutic drug monitoring of biologics in IBD and considered these should be reviewed by this Subcommittee when published.

5.7 The Subcommittee considered that the immediate clinical gap is second line treatment for ulcerative colitis following lack of response to infliximab as there is no funded biologic agent for patients to move on to. The Subcommittee considered that New Zealand has fallen behind internationally as many countries already fund adalimumab, golimumab and vedolizumab for moderate to severe ulcerative colitis as well as for Crohn's disease.

5.8 The Subcommittee noted that lack of data on hospital use of infliximab based on indications. Members considered that it was difficult to make funding recommendations without this data.

5.9 The Subcommittee noted that ustekinumab was another agent that could be considered for IBD indications and this is likely to come to the Subcommittee for consideration in the future, pending Medsafe approval.

5.10 The Subcommittee noted that the clinical trials for ulcerative colitis use a Mayo or partial Mayo scoring scale for disease severity whereas New Zealand uses the SCCAI scale. The Subcommittee noted that disease severity scores on these scales are not aligned and therefore make direct comparisons difficult. Members also noted that the SCCAI assessment does not require an endoscopic examination. This may have reduced accuracy but does have the advantage of allowing better access and reduced waiting time for patients who are being considered for biologics.

6 Adalimumab Resubmission for Ulcerative Colitis

Recommendation

6.1 The Subcommittee **recommended** that adalimumab be funded as a second-line biologic therapy only for patients who were secondary non-responders to infliximab with a high priority.

6.2 The Subcommittee **recommended** that adalimumab as first-line biologic therapy in the treatment of moderate to severe ulcerative colitis be declined.

Discussion

6.3 The Subcommittee noted that both PTAC and this Subcommittee had previously considered adalimumab for use in adult patients with moderately to severely active ulcerative colitis (UC) in 2013 and 2014 respectively and had recommended that the application be declined due to a lack of evidence for sustained clinical benefit. Members noted that the supplier, Abbvie, had since provided additional information to support a re-application.

6.4 The Subcommittee noted the new long-term follow up data, ULTRA-3 (Colombel et al. Am J Gastroenterol 2014;109:1771-80), an open-label extension study of 4-year maintenance treatment with adalimumab in 600/1094 patients enrolled in ULTRA 1 or 2 with moderate to severe active UC. Of these, 199 patients remained on adalimumab after 4 years of follow-up. Rates of remission per partial Mayo score, remission per IBDQ score, mucosal healing, and corticosteroid discontinuation at week 208 were 24.7%, 26.3%, 27.7% (non-responder imputation(NRI)), and 59.2%, respectively. Of the patients followed up in ULTRA 3 (588/1,094), 360 patients remained on adalimumab 3 years later. Remission per partial Mayo score and mucosal healing at 3 years were maintained by 63.6% and 59.9% of patients, respectively (NRI). Adverse event rates were stable over time.

6.5 The Subcommittee noted that 264 patients from ULTRA 1 and 183 from ULTRA 2 entered ULTRA 3 on every other week dosing regimen (EOW), 120 of those patients switched to weekly dosing (EW) during the ULTRA 3 phase. The Subcommittee noted that 261 of the 588 patients followed up during ULTRA 3 were on weekly dosing of adalimumab, however the results reported did not differentiate between the two dosing regimens. The Subcommittee noted that the supplier application was for fortnightly dosing and considered that there would be desire among patients and clinicians to move to weekly dosing based on treatment response.

6.6 The Subcommittee noted that 1,010 patients received one or more doses of adalimumab during the course of ULTRA 1,2 or 3. Exposure adjusted rates of adverse events in all adalimumab-treated patients during the entire treatment period were similar to or lower than those observed during the double-blind treatment period for patients receiving placebo or 160/80/40 mg adalimumab. Adverse events were stable over time and no new safety signals were reported.

6.7 The Subcommittee noted the INSPIRADA study (Travis et al, Gastroenterology. 2016;150(4):s633) which was a single-arm, multi-country, open label study that evaluated the effect of adalimumab on clinical outcomes, Health Related Quality of Life (HRQoL) and costs of care in patients with UC treated according to usual clinical practice. Data from 461 patients were analysed, 84% had no prior exposure to TNF-α inhibitors. Mean Simple Clinical Colitis Activity Index (SCCAI) at baseline was 7.7, which equates to moderate disease activity (Mild-Moderate = 5, Moderate-Severe=11). At week 2, 79% achieved SCCAI response (defined as a decrease of greater than or equal to two points compared with baseline), 49% were in remission (defined as an SCCAI less than or equal to two) and 55% had no blood in their stool. At week 26, 67% achieved SCCAI response, 48% were in remission and 57% had no blood in their stool

(significance values for these results were not provided). Significant improvements in Short Inflammatory Bowel Questionnaire (SIBDQ) and EQ-5D-5L were reported from baseline to week 26. The Subcommittee noted that these results had yet to be published.

6.8 The Subcommittee noted the review of real world effectiveness studies of adalimumab in adult patients with UC against the outcomes from pivotal randomised controlled trials (Armuzzi et al, Real-world effectiveness of adalimumab in patients with ulcerative colitis 2016; Abstract P365, ECCO. unpublished). This study identified 30 publications that included comparable outcomes of 'remission' or 'response', these outcomes however were not consistently measured across all studies and therefore a direct comparison was not accurately measured. The results indicated that real-world outcomes were consistently higher than those reported in the clinical trials. The Subcommittee noted that these results had yet to be published.

6.9 The Subcommittee noted that in the reviewed trials the difference in absolute remission rates 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 limited due to differences in trial design and an absence of head to head trials. 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.

6.10 The Subcommittee considered that there would be a substantial budget impact with listing a second line biologic treatment for UC. The Subcommittee considered that 20-40% of patients do not respond to first line biologic treatment with infliximab (primary non-responders). Members considered that primary non-responders to TNF-α inhibitors are better managed with optimisation of their therapy with serum monitoring, followed by a biologic with a different target as opposed to trialling another TNF-α inhibitor. Members consider that 8-10% of patients lose response to biologic treatment in UC (secondary non-responders). Members considered that immunogenicity underlies secondary non-response, however there is not adequate published evidence as yet.

6.11 The Subcommittee considered that there is good evidence for sustained response from adalimumab treatment in ulcerative colitis patients who respond to TNF-α inhibitors initially. Members considered that the Special Authority for adalimumab would need to clearly define what a secondary non-responder to infliximab was as all patients that did not respond to first line biologic therapy would want to trial adalimumab as second line agent. The Subcommittee noted that there is limited paediatric data for use of adalimumab for UC and evidence supports using infliximab in this population.

6.12 The Subcommittee considered that subcutaneous administration of adalimumab offered significant benefits over infliximab which requires intravenous infusion administered in an outpatient setting. The Subcommittee considered that currently hospital outpatient infusion services are at capacity and this treatment option could help alleviate such pressures. It was noted however that this application should be considered in isolation of such pressures. The Subcommittee considered that community infusion services are needed to make barriers to accessing such treatments less of an issue.

6.13 The Subcommittee considered that there are health sector savings that can be attributed to a reduction in hospital time for patients being treated with adalimumab instead of infliximab in outpatient infusion clinics. Members also considered that for patients that fail to respond to biologic therapy there could be an attributable savings

from a reduction in hospitalisation where UC is severe and not managed by biologic therapy.

6.14 The Subcommittee noted there were other biologic agents also under consideration for the treatment of UC with a different mechanism of action and this may be preferred over adalimumab in some patients.

7 Vedolizumab for Ulcerative Colitis and Crohn's Disease

Recommendation

7.1 The Subcommittee **recommended** that vedolizumab be funded for ulcerative colitis, in a first-line setting if cost neutral with infliximab if a registered product becomes available.

7.2 The Subcommittee **recommended** that vedolizumab be funded for ulcerative colitis, in a second-line setting for primary non-responders to infliximab and secondary non-responders to infliximab with a high priority if a registered product becomes available.

7.3 The Subcommittee **recommended** that vedolizumab be funded for Crohn's disease, in a first-line setting if cost neutral with infliximab and adalimumab if a registered product becomes available.

7.4 The Subcommittee **recommended** that vedolizumab be funded for Crohn's disease, in a second-line setting for primary non-responders to infliximab or adalimumab with a high priority if a registered product becomes available.

Discussion

7.5 The Subcommittee noted that the New Zealand Society of Gastroenterologists had submitted a clinician funding application for vedolizumab for the treatment of moderate to severe ulcerative colitis (UC) and Crohn's disease (CD).

7.6 Members noted that vedolizumab was not registered in New Zealand but was registered and funded in Australia (funded only for ulcerative colitis). The Subcommittee noted that vedolizumab is given via intravenous infusion of 300 mg (fixed dose) at 0,2 and 6 weeks, then given 8 weekly thereafter.

7.7 The Committee noted the evidence for vedolizumab was limited to three key trials. Member considered that the evidence was of high strength and high quality. Members noted that vedolizumab binds to integrin α4β7, which is a different target to currently available biologic agents for crohns or ulcerative colitis in New Zealand. Members noted that patients with crohns and ulcerative colitis have a high clinical need and have few options if they do not respond to treatment or become refractory to treatment.

Ulcerative colitis

7.8 The Subcommittee noted the GEMINI I trial for ulcerative colitis (UC) (Feagan BG et al., NEJM 2013;369:699-710). Patients were randomised to vedolizumab 300 mg or placebo via intravenous infusion at day 1 and 15 for the induction phase. For maintenance, the induction responders plus an additional 521 patients were administered vedolizumab every four or eight weeks for maintenance.

- At week six, 47% (106/225) of patients receiving vedolizumab and 26% (38/149) of patients in the placebo group had a clinical response (reduction in Mayo Clinic score of at least three points and a decrease of at least 30% from the baseline score) (adjusted difference 22%; 95% Confidence Interval [CI] 12 to 32, p<0.001). In the TNF-α inhibitor naïve subgroup, 53% (69/130) of patients in the vedolizumab group achieved a clinical response at week 6 compared with 26% (20/76) of patients in the placebo group. In the TNF-α inhibitor failure subgroup, 39% (32/82) of patients in the vedolizumab group achieved a clinical response at week 6 compared with 21% (13/63) of patients in the placebo group.

- At week 52, 42% (51/122) and 45% (56/125) of patients allocated to vedolizumab every eight weeks and every four weeks respectively were in clinical remission (CR, defined as Mayo Clinic score of less than or equal to 2 and no subscore higher than one), compared with 16% (20/126) of patients in the placebo group. The adjusted difference compared with placebo was 26 for vedolizumab every eight weeks % (95% CI: 15 to 37, p<0.001) and 29% vedolizumab every four weeks (95% CI: 18 to 40, p<0.001).

- Subgroup analysis of the TNF-α inhibitor naïve patients (n=224), demonstrated similar results: CR in 46% (33/72) and 48% (35/73) of patients receiving vedolizumab every eight weeks and every four weeks respectively at week 52, compared with 19% (15/79) in the placebo group. In the TNF-α inhibitor non-responder subgroup (n=121), CR was reported in 37% (16/43) and 35% (14/40) of patients allocated to vedolizumab every eight weeks and vedolizumab every four weeks respectively at week 52, compared with 5.3% (2/38) in the placebo group.
  The Subcommittee considered that the GEMINI I trial demonstrated treatment induction efficacy for vedolizumab in UC with a durable response. Members noted that the primary outcome of six weeks was likely to be too early and a better result would have been reported at weeks 8 to 10. Members noted that treatment patients that have failed TNF-α inhibitor treatment already had a poorer response to vedolizumab than those that were treatment naïve.

Crohn's disease

7.9 The Subcommittee noted GEMINI II, a phase 3 randomised, parallel group, double-blind, placebo controlled study with separate induction and maintenance trials for patients with Crohn;s disease (Sandborn WJ et al., NEJM 2013;369:711-21).

7.10 In the induction phase, primary outcomes were CR (CDAI score less than or equal to 150) at week 6 and CDAI-100 response (greater than or equal to 100 point decrease in CDAI score). At week 6, CR was achieved by significantly more vedolizumab (15%, 32/220) than placebo patients (6.8%,10/148); difference 7.8% (95% confidence interval [CI]: 1.2 to 14.3), p=0.02. The CDAI-100 response was achieved by numerically but not significantly more vedolizumab than placebo patients: 31% (69/220) and 26% (38/148) respectively; difference 5.7% (95% CI: -3.6 to 15.0), (p=0.23).

7.11 In the subgroup of patients who had non-responded to TNF-α inhibitor therapy, there were no significant differences between vedolizumab (11%) and placebo (4.3) in CR at week 6 and CDAI-100 at week 6 (24% and 23% respectively). The key secondary outcome in the induction phase, change in serum C-reactive protein levels at week 6, was not significantly different between the groups.

7.12 In the maintenance phase, the primary outcome was CR (CDAI score less than or equal to150) at week 52 was significantly more in patients in the vedolizumab every 8 weeks

and 4 weeks groups than placebo: 39% and 36% versus 22% respectively (p<0.001 and p=0.004). Subgroup analysis of patients who had not responded to TNF-α inhibitors indicated higher rates of CR at week 52 in vedolizumab than placebo groups: 28%, 27% and 13%.

7.13 Key secondary outcomes included the proportion of patients with CDAI-100 response at week 52, which was 44%, 45% and 30% respectively (p<0.05 for both vedolizumab groups versus placebo); the proportion of patients using oral corticosteroids at baseline who discontinued corticosteroids at week 6 and were in CR at week 52 was 32%, 29% and 16% respectively (p<0.05 for both vedolizumab groups versus placebo). The proportion of patients with durable CR (defined as CR at _80% of study visits) was not statistically different between the vedolizumab and placebo groups: 21%, 16% and 14% respectively.

7.14 The Subcommittee considered that Gemini I and II demonstrated that, for Crohn's disease, vedolizumab is less efficacious than it is in UC in both induction and maintenance response for biologic primary and secondary non-responders with respect to clinical remission and clinical response. Members considered that, for IBD, it was important that a non-TNF-α inhibitor agent was available for patients if a TNF-α inhibitor was used initially.

7.15 The Subcommittee noted GEMINI III, a randomised trial of 416 patients Crohn's disease comparing response in those who were TNF-α inhibitor naïve and those who had not responded TNF-α inhibitor treatment (Sands BE et al. Gastroenterology 2014;147:618-27).

- The primary outcome was the proportion of patients achieving CR (CDAI score less than150) at week 6 in the TNF-α inhibitor non-responder subgroup and there was no significant difference between vedolizumab and placebo: 15% (24/158) versus 12% (19/157) respectively: difference 3.0% (95% CI: -4.5 to 10.5), p=0.433.

- The proportion of patients with CR at week 10 was 27% (42/158) for vedolizumab patients and 12% (19/157) placebo patients; CR at weeks 6 and 10 was 12% (19/158) for vedolizumab patients and 8.3% (13/157) for placebo patients and CDAI- 100 response at week 6 was 39% (62/158) for vedolizumab and 22% (35/157) placebo.

Discussion- ulcerative colitis and crohns

7.16 The Subcommittee considered that vedolizumab has been studied in patients that have not responded to TNF-α inhibitors. The Subcommittee considered that there is stronger evidence for the use of vedolizumab after TNF-α inhibitor non-response than other TNF-α inhibitors such as golimumab and adalimumab. Members considered that there is insufficient data to demonstrate that vedolizumab is more efficacious than TNF-α inhibitors agents in the treatment of Crohn's disease or UC.

7.17 The Subcommittee considered the time to clinical response for vedolizumab was longer than that of infliximab and adalimumab. Outcomes measured at week six showed very little difference to those patients on placebo, however at week 14 vedolizumab appeared to reach its peak effectiveness.

7.18 The Subcommittee noted that vedolizumab is not currently registered in New Zealand and PHARMAC intend to discuss a possible submission to Medsafe with the supplier.

7.19 The Subcommittee noted that funding of vedolizumab would not be further considered by PHARMAC until the product had Medsafe approval and a funding application was received from the supplier, Takeda Pharmaceuticals, and reviewed by PTAC along with the minutes from this discussion. The Subcommittee requested that data on paediatric patients should be provided by the supplier with the funding application.

8 Creon Micro

Application

8.1 The Subcommittee reviewed a funding application from Mylan New Zealand for Creon Micro (scoopful EC 5,000 BP u lipase, 3,600 BP u amylase and 200 BP u protease) for paediatric patients with cystic fibrosis (CF).

Recommendation

8.2 The Subcommittee **recommended** that Creon Micro be listed on the Pharmaceutical Schedule for paediatric patients with a high priority.

Discussion

8.3 The Subcommittee noted one study (Muncke et al., Journal of Cystic Fibrosis 2009;8:14-8) comparing efficacy and preference of Creon Micro to Creon 10,000 capsules in cystic fibrosis (CF) infants aged between 6 and 36 months with pancreatic enzyme insufficiency (PEI). This was a multi-centre, open, randomised, cross over study that randomised 40 infants and toddlers. Members noted the preference of parents of young CF children of Creon Micro over capsules (51% prefer Creon Micro, 23% prefer Creon 10,000) due to practicality and less gastrointestinal symptoms. There were no clinical relevant differences between patient symptoms or adverse events.

8.4 The Subcommittee noted that the evidence for the efficacy and safety of pancreatic enzyme use in PEI had already been established and these products are currently used in New Zealand practice. Members noted that the benefits of Creon Micro are mostly due to an increase suitability for use in young patients.

8.5 The Subcommittee considered that the lower levels of lipase in Creon Micro is more appropriate for children under 5 years as they consume smaller amounts of food and fat and therefore require smaller amounts of lipase and enzymes per serve than an adult. Members considered that if a Special Authority was required to manage fiscal risk then it should be restricted to patients under 5 years of age.

8.6 The Subcommittee considered that carers of patients under 5 years who require pancreatic enzyme supplementation currently empty a whole Creon 10,000 capsule over a measure of apple puree. Then, depending on whether the dose is half or quarter of the Creon 10,000, the apple puree is divided up accordingly with the unrequired part discarded. The Subcommittee considered that there is significant burden of care for these patients who need to divide off doses of pancreatic enzymes 5-8 times per day for breast/bottle fed infants, 5-6 times per day for toddlers.

8.7 The Subcommittee considered that most patients five years and older would be able to swallow a capsule and Creon Micro would be particularly useful for infants and children under five. Based on average dosage of pancreatic enzymes the 0-1 year old children would waste approximately 13-17 bottles of Creon 10,000 per annum and the 1-5 year

old patients would waste 11-14 bottles of Creon 10,000 per annum. Members noted there are 40 children under 5 years old with CF that are pancreatic insufficient and of that, 10 would be less than 1 year old.

8.8 The Subcommittee considered that Creon Micro would likely be cost saving to Creon 10,000 due to the reduced amount of wastage per dose and would potentially improve adherence and therefore clinical outcomes. The Subcommittee considered that this formulation should be no more expensive than Creon 10,000.

9 Oral Viscous Budesonide

Application

9.1 The Subcommittee reviewed two clinician funding applications for budesonide 0.5 mg/mL nebules for the compounding of oral viscous budesonide for the treatment of eosinophilic oesophagitis (EO).

Recommendation

9.2 The Subcommittee **recommended** that budesonide 0.5 mg/mL nebules be listed on the Pharmaceutical Schedule for paediatric patients with eosinophilic oesophagitis who cannot tolerate, or where swallowed fluticasone is ineffective with a high priority.

9.3 The Subcommittee **recommended** that the application for funding of budesonide 0.5 mg/mL nebules for adult patients with eosinophilic oesophagitis be declined.

Discussion

9.4 The Subcommittee considered that currently paediatric and adult patients with eosinophilic oesophagitis are clinically managed in the same way with proton pump inhibitors used first line and then an elimination diet for 8 and 8-12 weeks respectively. Swallowed inhaled corticosteroids and mechanical dilation of the oesophagitis is the next step if proton pump and diet treatment is ineffective.

9.5 The Subcommittee considered the significant health need of patients with EO and in particular children whom have to coordinate using a meter dose inhaler and swallowing the dose instead of inhaling it. The Subcommittee noted that children often had difficulty using a fluticasone inhaler and coordinating their breathing with the dispensing button, though it did not appear to be an issue for most adult patients. The Subcommittee also noted that the inability to control this disease will put children at the risk of malnutrition due to the impact that this disease has on the ability to swallow, food impaction and vomiting.

9.6 The Subcommittee considered that the incidence of EO in New Zealand is approximately 20 paediatric and 50 adult new patients per annum. Members noted that 12 of the paediatric patients would be managed at Starship Hospital in Auckland. The Subcommittee considered that 30-40% of both children and adults would be intolerant/refractory or unable to use oral swallowed fluticasone from an inhaler device. Members estimated there would be 5 to 10 paediatric patients that would be eligible for treatment with oral viscous budesonide each year

9.7 The Subcommittee considered that there is only one clinical trial (Albert et al. Dig Dis Sci. 2016;61:1996-2001) and one case report (Krishna et al. Gastroenterology and Hepatology. 2011; 7(1): 55-59) comparing the efficacy of budesonide versus

fluticasone in EO. Members considered that the evidence for budesonide is weak with no head to head comparison. The Subcommittee considered that budesonide showed promise of being slightly superior to swallowed fluticasone for EO however there is no published evidence demonstrating this. The Subcommittee considered that the evidence was studied in short duration and there was no long term data on safety for budesonide in eosinophilic oesophagitis. Members considered that patients currently using oral swallowed fluticasone long term were at risk of hypopituitary axis suppression due to absorption of this steroid and budesonide offered an advantage of less oral absorption.

9.8 The Subcommittee noted there is no commercial oral viscous preparation of budesonide available internationally and that the nebule formulation is compounded into a viscous solution. The Subcommittee noted that if the budesonide nebules were listed, there would still be a cost for the compounding elements, such as a sucralose-based artificial sweetener (such as Splenda). The Subcommittee considered that patients or carers would self-fund the compounding agents and mix the nebules with the Splenda or equivalent themselves on the direction of the prescriber. Members noted that if a pharmacist was required to compound this product, it would result in a significant part charge for the patient.

9.9 The Subcommittee considered that, if listed, budesonide ampoules should be restricted to paediatric patients less than 18 years of age and only prescribed by gastroenterologists and immunologist or a medical practitioner on the recommendation of a gastroenterologist or an immunologist.

9.10 The Subcommittee considered that budesonide nebuliser solution ampoules were delisted from the Pharmaceutical Schedule due to low usage in December 2005. The Subcommittee considered that PHARMAC should investigate if there is a supplier that would be willing to register a budesonide product in New Zealand, noting that this indication would be off label.

9.11 The Subcommittee noted that budesonide nebules are listed on the PBS in Australia for a different indication. Members noted that there were different rules for compounding in Australia than in New Zealand. Members noted issues with supply of this product to the New Zealand market alongside compounding issues for a pharmaceutical not registered or intended for use in this indication or administration method.