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

Meeting held on 3 October 2018

(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; 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 21 & 22 February 2019, the record of which will be available in due course.

Record of the Gastrointestinal Subcommittee Meeting held on 3 October 2018

Contents

1. Record of previous minutes

1.1 The Subcommittee noted the minutes of the previous meeting that took place on 28 March 2017. The Subcommittee considered that the record was an accurate and true representation of that meeting.

1.2 The Subcommittee noted minutes of PTAC meetings that took place on 9 & 10 November 2017 and 3 & 4 May 2018.

1.3 The Subcommittee noted and disagreed with PTAC's minute on ustekinumab for the treatment of Crohn's disease. The Subcommittee considered that there was a lack of options for this patient group, especially given that vedolizumab was not available. The Subcommittee **recommended** that ustekinumab be listed for Crohn's disease, in patients where a TNF inhibitor has failed, with a high priority.

1.4 The Subcommittee noted and disagreed with PTAC's minute on adalimumab for the treatment of ulcerative colitis. Members noted that PTAC had considered the evidence quality to be limited, and members were comfortable with infliximab being the first biologic line as they considered it to be a better treatment than adalimumab. But the Subcommittee noted that vedolizumab was not available, and **recommended** that adalimumab be listed for treatment of ulcerative colitis as a second-line biologic treatment in patients who were secondary non-responders to infliximab with a high priority. The Subcommittee recommended funding adalimumab in secondary non-responders because it considered that patients who responded to one anti-TNF drug, but then developed antibodies to that drug, should respond to a second anti-TNF inhibitor.

2. Adalimumab and Infliximab – therapeutic drug monitoring

Application

2.1 The Subcommittee reviewed an application to amend the funding criteria for adalimumab and infliximab to incorporate a therapeutic drug monitoring algorithm that would require serum level testing to drug and/or antibody concentration, allow higher doses than are currently funded under some circumstances, and restrict access by limiting doses in other circumstances.

Recommendation

2.2 The Subcommittee **recommended** that the maximum doses set by renewal criteria for gastrointestinal indications for both infliximab and adalimumab be amended to allow higher maximum doses for patients who have undergone therapeutic drug monitoring and where a recent test indicated a higher dose would be beneficial.

2.3 The Subcommittee **recommended** that it would be acceptable to introduce restrictions to renewal criteria for gastrointestinal indications for both infliximab and adalimumab, where such restrictions require therapeutic drug monitoring to be performed and lower the maximum funded dose where test results show this can be done.

Discussion

2.4 The Subcommittee noted that therapeutic drug monitoring (TDM) was an approach to managing the dosage of medicines which involved regular patient testing and then, depending on the test results and a pre-set algorithm, raising or lowering the dose or stopping treatment altogether.

2.5 The Subcommittee noted that PHARMAC's renewal criteria for adalimumab and infliximab for gastrointestinal indications set a maximum funded dosage and this prevented use of TDM dosing adjustments as it did not allow for any increased doses. Members also noted that the maximum dose for infliximab was set some time ago and considered that the restrictions do not reflect international practices of flexible dosing on induction and maintenance.

2.6 The Subcommittee noted that there remained an unmet need for improved treatment of conditions such as ulcerative colitis and Crohn's disease.

2.7 The Subcommittee reviewed all evidence provided in the application. The Subcommittee also reviewed other guidance documents on therapeutic drug monitoring, such as Mitrev et al (Aliment Pharmacol Ther 2017 Dec;46(11-12):1037-53).

2.8 The Subcommittee considered a study by Barclay et al which reported a correlation between IBD disease control and trough concentrations of infliximab and adalimumab in a New Zealand IBD population (Barclay et al Int Med J 2018, not yet published).

2.9 The Subcommittee noted a paper by Khan et al which was a statement from the New Zealand Society of Gastroenterology (Khan et al, not yet published). This paper sets out recommended management approaches to take after measuring 6 thioguanine nucleotide and 6-mercaptopurine levels.

2.10 Members considered that there was a close correlation between TNF-inhibitor trough levels and disease activity. Members also considered that by keeping a dose within therapeutic levels, the patient is less likely to develop antibodies. Members considered that computer analysis suggests that the standard dose of infliximab (as recommended by its data sheet) does not reach the desired trough level (Wojciechowski et al AAPS J 2017 19:4;1136-47).

2.11 Members discussed the cost-effectiveness of the proposal. Members considered that incorporating TDM into the funding criteria of infliximab would likely increase the total amount of infliximab used, and estimated that the long-term median dose of infliximab would be 8-9 mg/kg/dose.

2.12 The Subcommittee discussed frequency of testing, and members considered that for both pharmaceuticals, testing could be after induction (after 3 months of use) and then yearly.

2.13 The Subcommittee noted that the test would be an additional cost, and estimated it to be about $80. However, members considered that the tests that would inform TDM are already a common part of treatment.

2.14 The Subcommittee considered that some amendment to the funding criteria would be appropriate to allow higher doses and so allow a TDM process to be done. The Subcommittee also considered it acceptable to introduce funding restrictions that require TDM and require dose reductions. However, the Subcommittee did not recommend particular new maximum doses, circumstances when that higher dose could be accessed, or under what circumstances a patient would be required to work to a lower maximum dose.

3. Budesonide capsules – Non-cirrhotic autoimmune hepatitis

Application

3.1 The Subcommittee reviewed a funding application to widen access for budesonide capsules for the treatment of non-cirrhotic automatic hepatitis.

Recommendation

3.2 The Subcommittee **recommended** that budesonide capsules be funded, with a medium priority, for the treatment of non-cirrhotic autoimmune hepatitis in adults, subject to the following restrictions:

> Special Authority for Subsidy
> Initial application from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:

1 Patient has autoimmune hepatitis; and
2 Patient does not have cirrhosis; and
3 Any of the following:
  3.1 Diabetes; or
  3.2 Cushingoid habitus; or
  3.3 Osteoporosis where there is significant risk of fracture; or
  3.4 Severe acne following treatment with conventional corticosteroid therapy; or
  3.5 History of severe psychiatric problems associated with corticosteroid treatment; or
  3.6 History of major mental illness (such as bipolar affective disorder) where the risk of conventional corticosteroid treatment causing relapse is considered to be high; or
  3.7 Relapse during pregnancy (where conventional corticosteroids are considered to be contraindicated).

Renewal application from any relevant practitioner. Approvals valid for 6 months where the treatment remains appropriate and the patient is benefitting from the treatment.

Discussion

3.3 The Subcommittee noted that autoimmune hepatitis is a severe condition in which nearly 50% of patients could die within 5 years if untreated. The Subcommittee noted that the standard treatment is with corticosteroids (usually prednisone) either alone or with azathioprine, and that this allows 80% of patients to achieve remission. The Subcommittee noted that steroid side effects are seen in 44% of patients, and treatment-ending side-effects in 12-29% of patients, and that this application related specifically to patients unable to take corticosteroids. The Subcommittee considered that mycophenolate mofetil was not a substitute for corticosteroids in such patients.

3.4 The Subcommittee noted the following studies of budesonide for autoimmune hepatitis which they considered relevant and key trials:

- Danielsson & Prytz Aliment Pharmacol Ther. 1994 Dec;8(6):585-90
- Manns et al Gastroenterology 2010 Oct;139(4):1198-206
- Snider & Potter Ann Pharmacother. 2011 Sep;45(9):1144-50
- Czaja Gut and Liver 2016 Mar;10(2):117-203
- Peiseler et al Clin. Gastro. & Hepat. 2018 Feb;16(2):260-7
- Alahmari et al Egypt. J. Hosp. Med. 2018 Apr;71(1):2226-31
- De Lemos-Bonotto et al Eur J Gastro & Hepat. 2018 Feb;30(2):212-216
- Woynarowski et al J Pediatr. 2013 Nov;163(5):1347-53

3.5 The Subcommittee noted that the evidence base included two randomised controlled trials against prednisone, systematic reviews and retrospective analyses, open-label studies, and literature reviews.

3.6 The Subcommittee noted, for example, that Danielsson & Prytz examined thirteen patients with autoimmune hepatitis in a single-arm, open label trial of oral budesonide capsules, and reported statistically significant decreases in surrogate measures (alanine aminotransferase and immunoglobulin) after 6 weeks and after

9 months.

3.7 The Subcommittee also noted, for example, Manns et al, which enrolled 208 patients and randomised them between budesonide and prednisone treatment to examine the primary endpoint of complete biochemical remission at last visit, among other secondary endpoints. The study found that the primary endpoint was achieved in 47% of patients taking budesonide, compared with 18% of patients taking prednisone after 6 months. However, no statistically significant difference was observed after 12 months.

3.8 The Subcommittee considered that the evidence was of sufficient quality to demonstrate that budesonide was an effective treatment of autoimmune hepatitis. The Subcommittee considered that overall budesonide was at least as effective as prednisone, and probably more effective, particularly noting the results of the Mann et al RCT. The Subcommittee also considered that there were less steroid side-effects. Members expected that benefits of taking budesonide would likely extend beyond the treatment period.

4. Budesonide CR (Cortiment) – ulcerative colitis

Application

4.1 The Subcommittee reviewed an application from Pharmaco (NZ) Ltd for the funding of budesonide CR 9 mg for the treatment of mild to moderate ulcerative colitis.

4.2 The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework.

Recommendation

4.3 The Subcommittee **recommended** budesonide CR 9 mg for the treatment of mild to moderate ulcerative colitis be funded with a medium priority, subject to the following initiation criteria:

Special Authority for Subsidy

Initial application – (ulcerative colitis) from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1. Patient has histologically confirmed left-sided or proctosigmoidal ulcerative colitis; and
2. Patient is aged 18 years or older; and
3. Patient has a Simple Clinical Colitis Activity Index (SCCAI) score of between 5 and 11; and
4. Patient has had an inadequate response following optimised therapy with 5-aminosalicylates; and
5. Any of the following:
    - 5.1. Diabetes; or
    - 5.2. Cushingoid habitus; or
    - 5.3. Osteoporosis where there is significant risk of fracture; or
    - 5.4. Severe acne following treatment with conventional corticosteroid therapy; or
    - 5.5. History of severe psychiatric problems associated with corticosteroid

treatment; or

5.6. History of major mental illness (such as bipolar affective disorder) where the risk of conventional corticosteroid treatment causing relapse is considered to be high; or

5.7. Relapse during pregnancy (where conventional corticosteroids are considered to be contraindicated)

6. Budesonide colonic release 9 mg tablets to be administered once daily for up to 8 weeks.

Renewal from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:

1. Treatment remains appropriate and the patient is benefiting from treatment; and
2. Budesonide colonic release 9 mg tablets to be administered once daily for up to 8 weeks; and
3. Patient can receive a maximum of two 8-week treatment cycles with budesonide colonic release 9 mg tablets within a 12-month period.

Discussion

4.4 The Subcommittee noted that in 2017 there were approximately 10,000 individuals in New Zealand with ulcerative colitis (UC), and that approximately two-thirds of these individuals would be expected to have mild or moderate disease.

4.5 The Subcommittee noted that the course of UC varies between individuals. The Subcommittee noted that more than 50% of patients experience initial high disease activity, more than 30% experience chronic relapsing disease, less than 10% experience chronic continuous UC, and approximately 1% experience later high activity.

4.6 The Subcommittee noted that a typical patient with mild-to-moderate UC would be treated initially with either oral or rectal 5-aminosalicylate (5-ASA) drugs. The Subcommittee noted that a hydrocortisone foam enema would be added to the treatment regimen for patients with distal disease who do not respond adequately to 5-ASA treatment.

4.7 The Subcommittee noted that patients with UC who do not respond to first-line treatment with 5-ASA drugs with or without a hydrocortisone foam enema would be treated with prednisone and/or azathioprine. The Subcommittee noted that patients not responding to these agents would be treated with immunomodulators and/or tumour necrosis factor (TNF) inhibitors.

4.8 The Subcommittee noted that up to 50% of the administered dose of a hydrocortisone foam enema may be absorbed, that the treatment has limited distribution, and that there can be poor compliance with an enema preparation.

4.9 The Subcommittee noted that there are concerns regarding the short- and long-term side effects associated with the use of systemically absorbed steroids such as prednisone, and that there are a number of patients for whom systemically absorbed steroids are contraindicated. The Subcommittee also noted that poor adherence or intolerance to steroids can result in the early use of

immunomodulators and/or TNF inhibitors.

4.10 The Subcommittee noted that budesonide colonic release (CR) 9 mg is an oral extended release tablet covered by a coating that dissolves in intestinal fluids with a pH greater than 7, allowing release throughout the colon.

4.11 The Subcommittee noted that budesonide is a glucocorticoid with low systemic bioavailability (approximately 10%) due to extensive first-pass metabolism in the liver.

4.12 The Subcommittee noted that the key clinical evidence for the use of budesonide CR 9 mg for the treatment of mild-to-moderate UC comes from three clinical trials: CORE I, CORE II, and CONTRIBUTE.

4.13 The Subcommittee noted that CORE I was a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial that investigated the efficacy of budesonide CR in 509 patients with active, mild-to-moderate UC (Sandborn et al. Gastroenterology. 2012;143:1218-1226). The Subcommittee noted that after 8 weeks of treatment, 17.9% of patients in the budesonide CR 9 mg group achieved a combined clinical and endoscopic remission (as defined by disease activity index), compared with 7.4% of patients in the placebo group (P = 0.0143); and 28.5% of patients in the budesonide CR 9 mg group achieved symptom resolution compared with 16.5% of patients in the placebo group (P = 0.0258). The Subcommittee noted that there were no significant differences in the proportion of patients achieving clinical improvement, endoscopic improvement, or histological healing between the treatment groups.

4.14 The Subcommittee noted that CORE II was a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial that compared the efficacy of budesonide CR with placebo in 410 patients with active, mild-to-moderate UC (Travis et al. Gut. 2014;63:433-41). The Subcommittee noted that after 8 weeks of treatment, 17.4% of patients in the budesonide CR 9 mg group achieved a combined clinical and endoscopic remission compared with 4.5% of patients in the placebo group (P = 0.0047); 16.5% of patients in the budesonide CR 9 mg group achieved histological healing compared with 6.7% of patients in the placebo group (P = 0.0361); and 23.9% of patients in the budesonide CR 9 mg group achieved symptom resolution compared with 11.2% of patients in the placebo group (P = 0.0220). The Subcommittee noted that there were no significant differences in the proportion of patients achieving clinical improvement or endoscopic improvement between the treatment groups.

4.15 The Subcommittee noted a pooled efficacy analysis of the CORE I and CORE II studies which demonstrated that the proportion of patients treated with budesonide CR 9 mg achieving combined clinical and endoscopic remission was greater than placebo in most subgroups analysed (Sandborn et al. Aliment Pharmacol Ther. 2015;41:409-418). The Subcommittee considered that the higher proportion of patients with proctosigmoiditis (23.5%) and left-sided disease (20.3%) who achieved a combined clinical and endoscopic remission with budesonide CR 9 mg compared with patients with extensive/pancolitis (9.4%), may reflect that a pH of 7 is only achieved towards the distal end of the colon.

4.16 The Subcommittee noted a pooled safety analysis of the CORE I and CORE II studies which demonstrated that the adverse event profile of budesonide CR 9 mg in the CORE I and CORE II trials was comparable to placebo (Lichtenstein et al. J Crohns Colitis. 2015;9:738-746). The Subcommittee noted that treatment with budesonide CR 9 mg resulted in a decrease in mean morning plasma cortisol concentrations.

4.17 The Subcommittee noted that CONTRIBUTE was a randomised, double-blind, placebo-controlled, phase 3 trial that investigated the safety and efficacy of budesonide CR 9 mg compared with placebo in 510 patients with mild-to-moderate UC who continued to receive oral mesalamine ≥2.4 g/day (Rubin et al. J Crohns Colitis. 2017;11:785-791). The Subcommittee noted that after 8 weeks of treatment, 13.0% of patients in the budesonide CR 9 mg group achieved a combined clinical and endoscopic remission compared with 7.5% of patients in the placebo group (P = 0.049); 20.0% of patients in the budesonide CR 9 mg group achieved endoscopic remission compared with 12.3% of patients in the placebo group (P = 0.025); and 27.0% of patients in the budesonide CR 9 mg group achieved histological healing compared with 17.5% of patients in the placebo group (P = 0.016). The Subcommittee noted that there were no significant differences in the proportion of patients achieving clinical remission between the treatment groups.

4.18 The Subcommittee noted that there were no significant differences in the proportion of patients achieving clinical improvement in CORE I, CORE II, or CONTRIBUTE, and considered that this is a critical endpoint for demonstrating an improvement in quality of life for patients with UC.

4.19 The Subcommittee considered that treatment with budesonide CR 9 mg may delay or prevent progression to treatment with immunomodulators or TNF inhibitors.

4.20 The Subcommittee considered that the standard treatment for patients experiencing a mild-to-moderate UC flare would be to double the dose of the patient's current 5-ASA drug, which is associated with increased cost.

4.21 The Subcommittee considered that there is a place in the UC treatment paradigm for an oral treatment for patients with left-sided or proctosigmoidal UC for whom systemically absorbed steroids are contraindicated and who have had an inadequate response following optimised therapy with 5-ASA drugs. The Subcommittee considered that there would be fewer than 3000 patients per year who would fit these criteria.

5. Multivitamin with trace elements – Bariatric surgery

Application

5.1 The Subcommittee reviewed a clinician application for the funding of a multivitamin with trace elements for patients who are being worked up for, or who have undergone bariatric surgery.

5.2 The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework.

Recommendation

5.3 The Subcommittee **recommended** that a multivitamin with trace elements for patients who are being worked up for, or who have undergone bariatric surgery be funded with a high priority, subject to the following criteria:

> Special Authority for Subsidy
> Initial application from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:
> Either:
> 1 Patient has undergone bariatric surgery; or
> 2 Patient is scheduled to undergo bariatric surgery.

Discussion

5.4 The Subcommittee noted that New Zealand has the third highest rate of adult obesity in the OECD, with approximately 1 in 3 adults having a body mass index of over 30 mg/kg2. The Subcommittee considered that obesity is a significant concern for Māori and Pacific peoples, with prevalence rates of 47% and 67% respectively.

5.5 The Subcommittee noted that a significant proportion of vitamins and essential elements are absorbed in the stomach, duodenum, and initial portion of the jejunum, which are the sections of the gastrointestinal tract bypassed with malabsorptive bariatric surgeries.

5.6 The Subcommittee considered that it is difficult to accurately estimate the number of patients who have undergone or will undergo bariatric surgery in New Zealand. The Subcommittee considered that approximately 1100 patients are likely to receive publicly funded bariatric surgery per year, that an unknown number will undergo privately funded bariatric surgery, and that there is a prevalent pool of between 5000 and 10,000 patients who have previously received bariatric surgery.

5.7 The Subcommittee noted that obesity is a known risk factor for nutrient deficiencies, even prior to bariatric surgery, and that micronutrient deficiencies worsen further following bariatric surgery (Stein et al. Aliment Pharmacol Ther. 2014;40:582-609).

5.8 The Subcommittee noted that while there is adequate evidence to demonstrate that patients who undergo bariatric surgery often experience nutrient deficiencies, there is very little evidence to indicate that supplementation improves patient outcomes. Members also considered that it is unlikely that there will ever been strong evidence in this area.

5.9 The Subcommittee noted the current NHS and Dietitians NZ Special Interest Group guidelines for specific micronutrient consideration for patients undergoing bariatric surgery. The Subcommittee noted that the recommended supplementation for a number of micronutrients is higher for patients undergoing malabsorptive bariatric

surgeries compared with patients undergoing gastric banding or sleeve gastrectomy.

5.10 The Subcommittee noted that the multivitamin currently funded in New Zealand without restriction, MVite, does not contain adequate micronutrients for use after bariatric surgery.

5.11 The Subcommittee noted that the application had listed a number of products with trace elements that could be appropriate, including Centrum 50+, Band Buddies Nutrichews, Clinicians MultiVit & Mineral Boost, and Celebrate Multivitamin (chewable). The Subcommittee considered that none of these products provide the levels of supplementation for micronutrients recommended by the Dietitians NZ Special Interest Group. The Subcommittee considered that if this proposal were to be progressed, then either a more complete supplement should be funded, or the above products would need additional supplementation.

5.12 The Subcommittee noted that a number of patients who have undergone bariatric surgery in New Zealand are likely to be receiving a funded multivitamin capsule containing vitamins A, D, E, and K (brand name Vitabdeck) under the Special Authority criteria for severe malabsorption syndrome. The Subcommittee considered that if an alternative and more complete supplement cannot be sourced, the Special Authority criteria for Vitabdeck could be widened to specifically include patients who are undergoing, or who have undergone bariatric surgery.

5.13 The Subcommittee noted that adherence to micronutrient supplementation is low among patients who have undergone bariatric surgery; however, the Subcommittee considered that it remains unclear whether this is due to the cost of supplements.

5.14 The Subcommittee noted that for the first three months following bariatric surgery there is a requirement for any supplement to be either in powder form or chewable.

5.15 The Subcommittee considered there is a sufficient unmet need for adequate micronutrient supplementation among patients who have undergone bariatric surgery to warrant funding a multivitamin with trace elements.

6. Prucalopride for chronic constipation

Application

6.1 The Subcommittee reviewed a funding application from the New Zealand Society of Gastroenterology for prucalopride for chronic slow-transit constipation.

Recommendation

6.2 The Subcommittee **recommended** that prucalopride be funded for patients with chronic slow-transit constipation with a medium priority, subject to the following criteria:

Initial application from a gastroenterologist or on the recommendation of a gastroenterologist. Approvals valid for 3 months for applications meeting the following criteria:

All of the following:

1 Patient is 18 years or older; and

2 Patient has chronic slow-transit constipation; and

3 Patient has tried two other laxatives, which have failed to provide adequate relief.

Renewal application from any relevant practitioner where the patient has had an increase in spontaneous complete bowel movements of at least 1 per week.

Discussion

6.3 The Subcommittee noted that severe constipation impacts quality of life as it causes symptoms including abdominal pain and bloating, and it can reduce a person's ability to perform usual activities. The Subcommittee noted that longer term complications can be serious, including fecal impaction, bowel perforations, and intestinal obstruction, and that fatalities have also occurred from unresolved constipation. Members considered that the quality of life reduction was comparable to moderate to severe Crohn's disease, or a symptomatic gastrointestinal ulcer.

6.4 The Subcommittee noted that most people with this condition have treatments available such as macrogol and lactulose, but there would be patients refractory to these treatments.

6.5 The Subcommittee noted that there were a number of trials of prucalopride in constipation including PRU-USA-11 (Camilleri et al N Engl J Med 2008;358:2344-54), PRU-INT-6 (Tack et al Gut 2009;58:357-365), PRU-USA-13 (Quiqley et al Aliment Pharmacol Ther 29, 315-318), and PRU-INT-12 (Müller-Lissner et al Neurogastroenterol Motil (2010) 22, 991-e255).

6.6 The Subcommittee considered that there was good quality evidence from randomised controlled trials that prucalopride provided better constipation relief than placebo. The Subcommittee considered that the outcomes measured in the trial, such as reaching at least 3 spontaneous complete bowel movements, were clinically significant outcomes, though also noted that such outcomes were achieved in notable numbers in placebo arms. The Subcommittee considered that the evidence showed prucalopride provided a modest, but clinically significant, benefit.

6.7 The Subcommittee expressed concern that prucalopride was less effective in the longer term, and noted the studies were not powered to detect more serious or life-threatening outcomes such as bowel perforation. Members considered that prucalopride would only improve quality of life, not length.

6.8 The Subcommittee noted that some adverse events were shown by the trials, but they were mostly only acute and wouldn't continue with long term use.

6.9 The Subcommittee considered that prucalopride would be used in combination with other agents, so funding it would not reduce use of any other medicine.

6.10 The Subcommittee discussed the diagnosis of slow-transit constipation and considered it was tricky, with different access to facilities around New Zealand. The Subcommittee considered that a gastroenterologist should be involved in the diagnosis of slow-transit constipation, either as the applicant or on their recommendation. Members considered that requiring gastroenterologist involvement could mean a barrier to access due to lack of capacity, but it was important to prevent misdiagnosis. The Subcommittee considered that it was not necessary to specify definitions of slow-transit constipation, such as the Rome III criteria, and it would be fine for any clinician to apply for a renewal.

6.11 However, members did consider that clear criteria were needed as there was a potential for scope creep. Members noted a number of other potential uses for prucalopride, including post-operative ileus after GI surgery, chronic intestinal pseudo-obstruction, GORD, functional dyspepsia, refractory gastroparesis, opioid-induced constipation, and IBS-C.

6.12 The Subcommittee considered that an improvement of at least one more spontaneous complete bowel movement was a good indicator of clinical success of prucalopride as it correlated with measures of quality of life in the clinical trials. Members also considered that prucalopride should be stopped if ineffective, and considered a 3 months initial trial would be appropriate.

6.13 The Subcommittee considered that it was difficult to estimate the number of patients that would receive prucalopride if it was funded as recommended, though noted that the group as defined would include opioid-induced constipation.

7. Tacrolimus suppository for rectal inflammation due to inflammatory bowel disorders

Application

7.1 The Subcommittee reviewed an application for the funding of tacrolimus suppositories for the treatment of moderate to severe rectal inflammation due to inflammatory bowel disorders (IBD) confirmed by endoscopy in patients who have failed oral and topical mesalazine and steroid preparations.

Recommendation

7.2 The Subcommittee **recommended** that tacrolimus suppositories be funded, without restriction, with a high priority.

Discussion

7.3 The Subcommittee considered that IBD and rectal inflammation cause considerable morbidity. The Subcommittee considered that proctitis was generally difficult to treat and that this patient group was one that had no current treatments options after using all available standard oral or rectal treatments (rectal and oral mesalazine, rectal steroids, and in some cases azathioprine).

7.4 The Subcommittee noted that the key clinical evidence of local tacrolimus came from three studies (Lawrance & Copeland 2008 Ailment Pharmacol Ther 28, 1214-1220; Lawrance et al 2017 Clin Gastro & Hepat 15, 1248-55; and van Dieren et al 2009 Inflamm Bowel Dis 15, 193-8). Members noted that these trials included a total of 47 patients and that only one of those trials used tacrolimus suppositories, and then only in 12 of its 19 patients; all other patients in these trials received either tacrolimus ointment, tacrolimus enema, or placebo. For example, the Lawrence et al 2017 study included 20 patients with resistant ulcerative proctitis. Of these, 11 patients received rectal tacrolimus ointment, with the rest receiving a placebo ointment. The primary outcome was met if a patient both reduced their Mayo score by at least 3 points and at least 30% from baseline and reduced rectal bleeding subscore by at least one point, all measured at 8 weeks. The study reported that 8 of the 11 tacrolimus patients met this outcome, compared with one out of 10 placebo patients.

7.5 The Subcommittee considered that there was limited data on the use of tacrolimus suppositories. Members noted that only one of the trials had a control arm and the trials each ran for 4-8 weeks. Members considered that this therapeutic area is unlikely to have large RCTs to produce good quality evidence.

7.6 The Subcommittee considered that clinicians would prescribe tacrolimus suppositories, but would likely try all other alternatives first. The Subcommittee considered that these standard options are rectal mesalazine, then oral mesalazine, then rectal steroids.

7.7 The Subcommittee discussed oral tacrolimus as an alternative. Members considered there was mixed evidence, and considered that a localised condition would benefit from localised treatment because it would give higher tissue concentrations at the site of disease, and would allow lower doses so reducing toxicity. Members considered that oral tacrolimus potentially has systemic side effects including hypertension and renal dysfunction, while local treatment has less potential for such side effects.

7.8 The Subcommittee noted that there is no Medsafe-registered tacrolimus suppository, and so if PHARMAC were to fund it, it would need to fund it as a compoundable form. Members considered that some centres would become skilled in preparing the suppositories. Members considered that it would be more convenient to administer a suppository than an ointment which would be administered into the rectum by a syringe.

7.9 The Subcommittee considered there could be a small reduction in the costs of other services if tacrolimus suppositories were funded.

7.10 The Subcommittee considered that there would be no need for funding criteria because the indication sought would be the only use for tacrolimus suppositories.

7.11 The Subcommittee estimated that the prevalence of people using tacrolimus suppositories could be 300 at any time, or perhaps could be around 5 patients per specialist.

7.12 The Subcommittee considered that while the scope and quality of the studies was limited, they did show efficacy, noting in particular the main study which was stopped as the trial organisers considered it was clear that the treatment was efficacious. The Subcommittee considered that there is significant morbidity and that medication used such as budesonide and other topical agents do not seem to be effective. Additionally, the Subcommittee considered tacrolimus suppositories might potentially reduce the need to escalate to biologics.