Record of the Gastrointestinal Advisory Committee Meeting held on 23 August 2022

This meeting was held virtually

Gastrointestinal Advisory Committee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) Specialist Advisory Committees 2021.

Note that this document is not necessarily a complete record of the Gastrointestinal Advisory **Committee meeting**; only the relevant portions of the meeting record relating to Gastrointestinal Advisory Committee discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

The Gastrointestinal Advisory Committee 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.

Pharmac Advisory Committees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Advisory Committee meeting will be reviewed by PTAC at an upcoming meeting.

Specialist Advisory Committees and PTAC may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

Pharmac is not bound to follow the recommendations made below. Applications are prioritised by Pharmac against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or Specialist Advisory Committees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

Table of Contents

1. Attendance

Present	Apologies
Alan Fraser (Chair)	Bruce King
Catherine Stedman	Simon Wynn Thomas
Jonathan Bishop	
Michael Schultz	
Murray Barclay	
Russell Walmsley	
Sandy Dawson	

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• Budesonide orodispersible tablets for the treatment of eosinophilic oesophagitis	Medium Priority
• Upadacitinib for the treatment of moderate to severe ulcerative colitis (UC) in individuals who have responded inadequately to either infliximab or adalimumab therapy	High Priority
• Macrogol (electrolyte-free) for the treatment of paediatric constipation	Medium Priority
• Prucalopride succinate for the treatment of chronic constipation	Medium Priority

3. The role of Specialist Advisory Committees and records of meetings

3.1. This meeting record of the Gastrointestinal Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and Specialist Advisory Committees 2021, available on the Pharmac website at https://pharmac.govt.nz/assets/2021-Specialist-Advisory-Committee-Terms-of-Reference.pdf. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

3.2. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

3.3. The Gastrointestinal Advisory Committee is a Specialist Advisory Committee of Pharmac. The Gastrointestinal Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Gastrointestinal Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for Gastrointestinal Therapeutic Group that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for Gastrointestinal Therapeutic Group that differ from the Gastrointestinal Advisory

Committee's, or Specialist Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'.

Pharmac considers the recommendations provided by both the Gastrointestinal Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for treatments for Gastrointestinal Therapeutic Group.

4. Pharmac update

4.1. The Committee noted an update from Pharmac with a summary of Pharmac's work in response to the Pharmac review, process improvements, the budget uplift, COVID vaccine transfer and COVID treatments.

5. Record of the previous Gastrointestinal Specialist Advisory Committee meetings

5.1. The Committee noted and accepted the record of its previous meetings held on 28 March 2017, 14 October 2020 and 16 August 2021.

5.2. With regard to the meetings held on 14 October and 16 August 2021, the Committee noted that these were specifically to:

5.2.1. Discuss the impact the possible introduction of a biosimilar adalimumab would have in the event of a Request for Proposals (RFP) for adalimumab; and

5.2.2. To discuss and provide feedback on the proposal to widen access to adalimumab and award Principal Supply Status to the citrate-free biosimilar brand of adalimumab (Amgevita), in advance of public consultation.

5.3. As part of its review of the previous records the Committee noted that funding of adalimumab to include the treatment of ulcerative colitis occurred in March 2022 as a result of the adalimumab commercial process in which Amgevita was awarded principal supply status. In addition, the Committee noted that the decision had also enabled Pharmac to make a number of changes to the Special Authority criteria for Amgevita, including the removal of dosing restrictions.

5.4. The Committee considered that the Special Authority criteria for adalimumab for the treatment of Crohn's disease should be widened further by lowering the CDAI threshold from 300 or greater to 220 or greater.

5.5. The Committee considered that there was an unmet health need for individuals who are between a CDAI count of 220 and 300 who are treated with repeated courses of steroids as there are no other funded alternatives.

5.6. The Committee noted that a CDAI count of 220 was used in the pivotal trials to define moderate to severe disease.

5.7. The Committee considered that treating from CDAI 220 would allow earlier treatment which could reduce possible damage to the bowel, limit adverse effects from steroids, improve an individual's quality of life and reduce hospitalisations. The Committee considered that if you allow earlier treatment that this could delay the development of fistulae and strictures. The Committee considered the New Zealand Society of Gastroenterology (NZSG) should be contacted to ask for more information on the health benefit that widening access could provide, particularly with regards to quantifying the impact on bowel damage and quality of life.

5.8. The Committee considered that if access was to be widened to allow treatment at CDAI 220 that this would be unlikely to result in a huge increase in numbers; approximately 10 to 20% increase could be expected. The Committee considered that many of those with CDAI of 220-300 would ultimately progress to more severe disease with CDAI>300 and be prescribed adalimumab.

5.9. The Committee considered that children have entry criteria of 30 which is more equivalent to a CDAI of 220; however, Members also considered that the health need of children with Crohn's disease was likely to be greater.

6. Previous recommendations and action points

6.1. The Committee noted its previous recommendation that the maximum funded dose for adalimumab should be amended to allow for higher doses.

6.2. The Committee noted that in March 2022, as a result of the request for proposals (RFP) commercial process in which Amgevita was awarded principal supply status, dosing restrictions had been removed from Amgevita, due to pricing achieved in the RFP. The Committee considered that this should also be applied to Humira.

6.3. The Committee considered that in individual cases where Amgevita cannot be tolerated, people who subsequently switch to Humira should be able to trial dose escalation of Humira to assess whether a clinical response can be achieved.

6.4. The Committee noted its previous recommendation that the maximum funded doses for gastrointestinal indications for infliximab be amended to allow higher maximum doses for individuals where therapeutic drug monitoring showed a higher dose would be beneficial. The Committee reiterated that this is still a priority for funding.

Budesonide orodispersible tablets for the treatment of eosinophilic oesophagitis

Application

6.5. The Advisory Committee reviewed an application from Dr Falk Pharma New Zealand Limited for budesonide orodispersible tablets (Jorveza) for the treatment of eosinophilic oesophagitis.

6.6. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

6.7. The Advisory Committee **recommended** that budesonide orodispersible tablets be listed with a **medium** priority for the treatment of individuals with eosinophilic oesophagitis, subject to the following Special Authority criteria:

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

1. The patient has difficult to treat eosinophilic oesophagitis and is at risk of developing secondary complications; and
2. Either:
   - 1.1 Patient has experienced non-response or loss of response to first line swallowed inhaled corticosteroids; or
   - 1.2 Treatment with swallowed inhaled corticosteroids has not been tolerated or is contraindicated.

Renewal application
Applications from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:

1. Both:
   - 1.1 Patient has experienced symptomatic improvement following an initial trial of oral budesonide; and
   - 1.2 Patient has experienced relapse following the withdrawal of oral budesonide.
     - 1.2.1 Patient has experienced signs of relapse following dose tapering; or
     - 1.2.2 Dose tapering of oral budesonide is clinically inappropriate

Discussion

Māori Impact Statement

6.8. The Committee noted the impact of budesonide orodispersible tablets on the treatment of eosinophilic oesophagitis. The Committee noted that no epidemiological evidence was identified relating to the impact of oral budesonide for the treatment of eosinophilic oesophagitis on Māori health outcomes or Hauora Arotahi (Māori Health Areas of Focus).

Background

6.9. The Advisory Committee noted that an application for budesonide oral viscous nebules for the treatment of eosinophilic oesophagitis (EoE) was reviewed by the Gastrointestinal Subcommittee in 2017 and by the Pharmacology and Therapeutics Advisory Committee (PTAC) in 2018.

6.10. At the time, the (then) Gastrointestinal Subcommittee recommended that budesonide 0.5 mg/mL nebules be listed on the Pharmaceutical Schedule for children with EoE for whom swallowed fluticasone is either intolerable or ineffective, with a high priority. The Subcommittee recommended that the application for funding of budesonide 0.5 mg/mL nebules for adults with EoE be declined, on the basis that adults did not appear to have the same difficulty using a fluticasone inhaler and coordinating their breathing with the dispensing button.

6.11. The Committee noted that there had been previous issues with supply of the budesonide respules to the New Zealand market, alongside pharmacy compounding issues for a pharmaceutical not registered or intended for use in this indication or administration method. Members previously considered that Pharmac should investigate if there is a supplier that would be willing to register a swallowed corticosteroid product in New Zealand for the EoE indication.

6.12. The Committee noted that PTAC reviewed the application in May 2018 and recommended that that budesonide 0.5 mg/mL nebules be listed with a medium priority for proven EoE with dysphagia in those whose disease is not responsive to first line corticosteroids, with applications to be made by a gastroenterologist or on the recommendation of a gastroenterologist.

6.13. The Committee noted that in making this recommendation, PTAC considered that there was sufficient evidence of clinical benefit to support the use of oral viscous budesonide for the treatment of eosinophilic oesophagitis in both children and adults and made no differentiation between the two groups, however PTAC did acknowledge the additional need of children, resulting from the difficulties with the oral use of inhaled fluticasone presentations in this population.

6.14. The Committee noted that Dr Falk Pharma New Zealand Limited had recently received Medsafe approval for its Jorveza brand of budesonide orally disintegrating tablets for the treatment of EoE in adults aged 18 and older. The Committee noted that Jorveza is listed on Australia's' Pharmaceutical Benefits Scheme (PBS).

Health Need

6.15. The Committee noted the comments made previously by PTAC and the Gastrointestinal Subcommittee's previous view regarding the significant health need of people with EoE, particularly in children, who often have difficulty using a fluticasone inhaler and coordinating their breathing with the dispensing button.

6.16. The Committee considered that, currently, children and adults with EoE are clinically managed in the same way, namely first-line treatment with proton pump inhibitors and, if this is not successful, a 6-food elimination diet for 8-12 weeks is usually tried for children, but the latter has limited acceptance in adolescence and adults. If proton pump inhibitor therapy and dietary treatment are ineffective individuals will typically receive swallowed inhaled corticosteroids (fluticasone) twice daily.

6.17. The Committee considered that swallowed inhaled fluticasone at higher doses is effective at achieving disease remission in many individuals, however, for many the method of delivery is unsuitable, as previously discussed. The Committee considered that there would be approximately 700 people with difficult to treat EoE for whom swallowed fluticasone is either ineffective or unsuitable. The Committee considered there to be a high unmet health need in this setting, with those affected being at risk of developing oesophageal strictures, dysphagia, and oesophageal perforation.

6.18. The Committee noted that there has been an increase in the number of this population group presenting to hospital with acute food bolus impactions requiring mechanical dilation. The Committee considered that some of this trend is likely attributable to an increasing prevalence of people with treatment refractory EoE.

Health Benefit

6.19. The Committee noted the comments made previously by PTAC and the Gastrointestinal Subcommittee's own views regarding the health benefit of budesonide oral viscous nebules in the treatment of EoE.

6.20. The Committee noted that budesonide and other swallowed topical corticosteroids reduce the recruitment of inflammatory cells to the oesophagus and subsequently, the fibrotic remodelling of the epithelial surface. The Committee noted that it had previously considered evidence that viscous topical budesonide was more effective at coating of the oesophagus compared with the swallowed nebulised corticosteroid which tend to show some diversion into the lungs (Nennstiel S, Schlag C. Treatment of eosinophlic esophagitis with swallowed topical corticosteroids. Gastroenterology. 2020 Sep 28;26(36):5395-5407. doi: 10.3748/wjg.v26.i36.5395).

6.21. The Committee noted that the primary data supporting the efficacy of budesonide orodispersible tablets for the treatment of people with EoE is available from three clinical studies of efficacy and safety:

- The pivotal Phase III study BUL-1/EEA, a double-blind, randomised, placebo-controlled study examining the efficacy of a 6-week twice-daily treatment with 1mg budesonide orodispersible tablets for patients with clinically- and histologically confirmed EoE who had previously trialled proton pump inhibitors (Lucendo AJ et al. Gastroenterology 2019;157 74-86). The primary end point for the study was clinico-histological remission at 6 weeks and the secondary end points were clinical, histological and endoscopic remission. 59 patients were allocated to the intervention arm and 29 to the placebo arm.

- The supportive BUU-2/EEA open label induction trial, which examined the efficacy of 6-week twice-daily treatment with 1mg budesonide orodispersible tablets in 181 patients with clinically- and histologically confirmed EoE. Patients who did not experience clinico-histological remission in BUL-1/EEA were offered a 6-week extension as a part of the BUU-2/EEA trial (Lucendo AJ et al. Gastroenterology 2019;157(1), 74-86)

- The pivotal Phase III study BUL-2/EER, which was a double-blind, randomised, placebo-controlled, maintenance of remission study comparing the efficacy and safety of twice-daily treatment with two different strengths of budesonide orodispersible tablets (1mg vs 0.5mg) in adults with EoE over 48-weeks (Straumann et al. Gastroenterology 2020; 159(5), 1672-1685). 68 patients were assigned to each of the budesonide 1mg twice-daily, 0.5mg twice-daily and placebo twice-daily arms.

6.22. The Committee noted that in BUL-1/EEA 57.6% (95% CI, 38.2 – 72.0%, P < .0001) of patients that received budesonide orodispersible tabs experienced clinico-histological remission at six-weeks, compared with 0% in the placebo group, and that this increased to 85% at 12-weeks as a part of the BUU-2/EEA extension study. The Committee noted that there was a marked increase in histological remission in patients receiving orodispersible budesonide compared with placebo at six weeks (93% vs 0%, P < 0.001) as well as endoscopic remission (61% vs 0%, P <0.0001). The Committee noted that while the evidence of clinical remission was more modest, owing to the complex nature of dysphagia, there was still a significant improvement in the proportion of patients experiencing resolution of dysphagia in patients receiving budesonide compared with placebo (59% vs 4%, P < 0.001).

6.23. The Committee noted that in the maintenance of remission study (BUL-2/EER) after 48-weekls 73.5% of patients receiving the 0.5mg budesonide orodispersible tabs twice-daily and 75% of patients receiving the 0.5mg budesonide orodispersible tabs twice-daily were in clinic-histological remission compared with 4% of patients in the placebo arm (P < 0.0001).

6.24. The Committee noted an evidence summary for inhaled fluticasone inhalers, budesonide suspensions and orodispersible tabs (Miehlke S, et al. Orodispersible budesonide tablets for the treatment of eosinophilic esophagitis: a review of the latest evidence. Therap Adv Gastroenterol. 2020 Jun 10;13:1756284820927282. doi: 10.1177/1756284820927282). The Committee considered that the benefits of the budesonide orodispersible tablets were similar to that of the compounded viscous suspensions.

6.25. The Committee considered that the most relevant evidence for the New Zealand treatment setting was a head-to-head trial comparing fluticasone inhaler vs budesonide oral suspension over 8-weeks (Dellon ES, Woosley JT, Arrington A, et al. Efficacy of budesonide vs fluticasone for initial treatment of eosinophilic esophagitis in a randomized controlled trial. Gastroenterology 2019; 157: 65–73). The Committee considered that both the inhaled fluticasone and budesonide oral suspension provide evidence of histological, endoscopic and symptom improvement post-treatment, however, noted that there were no statistically significant differences in endpoints between the agents.

6.26. The Committee noted that following an audit of practice into the treatment of paediatric EoE in New Zealand, that higher doses of swallowed fluticasone (ie 700micrograms twice-daily) have had reported stronger efficacy than lower doses.

6.27. The Committee noted a trial comparing a budesonide solution versus placebo in patients with EoE with dysphagia (Hirano I, et al. Budesonide Oral Suspension Improves Outcomes in Patients With Eosinophilic Esophagitis: Results from a Phase 3 Trial. Clin Gastroenterol Hepatol. 2022 Mar;20(3):525-534). The Committee noted that patients who received the budesonide oral solution received strong histological improvement but only a mild symptomatic improvement. The Committee noted that the manufacturer had withdrawn this product from the market.

6.28. The Committee noted that a common feature among the trials was the risk of a small number of individuals developing oropharyngeal and oesophageal candidiasis. The Committee considered that this would be expected in around 10-15% of those who are treated with swallowed corticosteroids and that this would likely limit maintenance treatment in these individuals.

6.29. The Committee noted there are several other treatments in other markets for the treatment of EoE including an orally disintegrating fluticasone tablet and biological therapies, including dupilumab, antolimab, and benralizumab

6.30. Overall, the Committee considered the evidence supporting the use of budesonide orodispersible tablets for the treatment of EoE to be strong and of high-quality, despite being limited to a small number of trials. The Committee considered that limited evidence comparing swallowed topical corticosteroids to nebulised steroidal solutions suggested there was little difference in clinical effectiveness.

Suitability

6.31. The Committee noted that the orodispersible tablet presentation of budesonide provides a suitability benefit over both funded (ie fluticasone inhalers) and unfunded (compounded viscous solutions) alternatives. In particular, the Committee considered that orodispersible tablets would provide an alternative for children or those with neuromuscular disabilities who find it difficult to coordinate the actuation of a nebuliser device with swallowing. The Committee noted that the tablets are not indicated in children and that smaller children may find it difficult to let the tablet dissolve in the mouth.

6.32. The Committee considered that adherence with the orodispersible tablets is likely to be significantly greater than with swallowed fluticasone due to these suitability advantages. The Committee considered that topical corticosteroids are also preferred to dietary interventions, particularly in children and young adults.

Cost and Savings

6.33. The Committee considered that given the relative cost of budesonide orodispersible tablets, it is appropriate for individuals to have trialled other funded alternatives such as swallowed fluticasone prior to trialling budesonide orodispersible tablets.

6.34. The Committee considered that the number of people with treatment refractory EoE was difficult to estimate given the increasing incidence of the condition. The Committee considered that there could be around 10 individuals per gastroenterologist within the country equating to approximately 700 people in total.

6.35. The Committee considered that it was difficult to know what proportion of these would be expected to receive maintenance therapy, however, most would be tapered off maintenance treatment and monitored for signs of relapse. The Committee considered that a 6-month initial approval period for budesonide orodispersible tablets would be appropriate.

Funding Criteria

6.36. The Committee noted that at its 2017 Gastrointestinal Subcommittee meeting, it was considered that it would be appropriate to require individuals to trial swallowed fluticasone (where appropriate) before being eligible to receive funding for the budesonide oral viscous nebules. The Committee considered that it was appropriate to similarly target funding for the budesonide orodispersible treatment to this same group.

Summary of Assessment

6.37. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for budesonide orodispersible tabs if it were to be funded in New Zealand for EoE. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Individuals with difficult to treat eosinophilic oesophagitis who have previously trialled swallowed fluticasone (aerosol inhaler presentation) and experienced it as ineffective or unsuitable.
Intervention	Budesonide orodispersible tablets 1mg or 0.5mg twice daily
Comparator(s) (NZ context)	Swallowed fluticasone (700 micrograms twice daily)
Outcome(s)	Histological improvement • Reduction in inflammatory infiltration of the oesophagus • Reduction in fibrotic remodelling of the oesophagus • Improvement in the integrity of epithelial junctures Improvement in symptoms: • Reduced pain when swallowing • Improved ability to swallow • Reduction in food bolus impactions • Quality of life improvements • Reduced risk of fibrosis, stricture or perforation
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)	

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

Tacrolimus for the treatment of rectal inflammation

Discussion

6.38. The Committee noted that Pharmac was seeking advice on the suitability of alternative tacrolimus products for the treatment of rectal inflammation due to inflammatory bowel disease.

6.39. The Committee noted that it had recommended that tacrolimus suppositories be funded for the treatment of rectal inflammation, without restriction, with a high priority. The Committee noted that PTAC had subsequently recommended the application be declined, based on the lack of a proprietary tacrolimus suppository product, and due to uncertainty around the quantity and quality of evidence for use of tacrolimus suppositories compared with other tacrolimus preparations and compared with other pharmaceuticals.

6.40. The Committee noted that Pharmac had, to date, been unable to source a proprietary tacrolimus suppository and was seeking advice on whether a 0.1% tacrolimus ointment, currently funded for facial eczema, would be a suitable alternative to tacrolimus suppositories.

6.41. The Committee considered that there is an unmet health need for people with severe proctitis when it is not desirable to remove the colon, or initiate treatment with a biologic agent due to the small amount of affected area, in some cases less than 5cm of colon.

6.42. The Committee considered that tacrolimus 0.1% ointment would not be a suitable alternative due to a lack of applicator for the product. Members considered that without an appropriate delivery device there would be no way for a patient to administer the treatment to the affected area.

6.43. Members noted that thioguanine tablets dispersed in mesalazine enemas are currently in clinical trials and could be a suitable alternative to explore in the future.

7. Therapeutic Group Review

Discussion

Therapeutic Group Summary

7.1. The Committee noted the annual net expenditure on the relevant subgroups of the Alimentary Tract and Metabolism therapeutic group from 2018 to 2022 and the projected expenditure for 2023 to 2025.

7.2. The Committee noted the key areas which have experienced expenditure growth over the past five years have been biologics for inflammatory bowel disease (IBD), minerals and antidiarrhoeals (primarily driven by the rectal and colonic anti-inflammatories medicines).

Antacids and Antiflatulants

7.3. The Committee noted that there are two antacids/antiflatulants listed; alginic acid sachets (Gaviscon infant), fully funded without restrictions, and sodium alginate liquid/tabs (Acidex/Gaviscon double strength) which is part funded.

7.4. The Committee noted that usage (numbers of prescriptions) for sodium alginate liquid had significantly increased from approximately 20,000 prescriptions in 2017 to approximately 55,000 prescriptions in 2022. The Committee considered that the increase in prescription numbers was likely due to a shift in clinical practice to wean people off proton pump inhibitors. Members considered that moving individuals from proton pump inhibitors to antacid liquid has a financial impact for them as antacids are not fully funded, and a fully funded antacid would therefore be useful.

7.5. The Committee considered that Mylanta would be an appropriate clinical alternative to Acidex.

7.6. The Committee noted that there had recently been supply issues with alginic acid sachets (Gaviscon infant) and considered that Pharmac should seek advice from paediatricians on appropriate alternatives.

Antidiarrhoeals and Intestinal Anti-inflammatory agents

7.7. The Committee noted that supply of prednisolone sodium rectal foam 20 mg per dose (brand name Essential Prednisolone) was secured by Pharmac as an alternative to hydrocortisone acetate 10% rectal foam (brand name Colifoam), due to supply issues with Colifoam. Members considered that once Colifoam was back in stock there would no longer be an unmet health need and Essential Prednisolone would no longer be required.

Mesalasine

7.8. The Committee noted that mesalasine is the major contributor to expenditure in this subgroup, and that Pharmac sought advice to consider possible commercial options for this market.

7.9. The Committee considered that all of the currently funded formulations are required. In addition, members highlighted that olsalasine and salazapyrin also remain essential treatment options for IBD.

7.10. The Committee considered that people who take mesalasine have a strong desire to reduce their tablet burden where possible and therefore high strength options are useful. In addition, the Committee considered that small tablet strengths are also required to help with titration and people who need to adjust their doses in gradual increments.

7.11. The Committee considered that the sachets are valued by individuals who have trouble swallowing tablets and small dose sachets would be useful for children.

7.12. The Committee considered that any commercial process would need to ensure that currently funded release profiles continued to be funded.

Local Preparations for Anal and Rectal Disorders

7.13. The Committee considered some people are unable to tolerate glyceryl trinitate 0.2% ointment (Rectogesic), for treatment of anal fissures, due to the adverse effect of headaches. The Committee noted that some community pharmacies compound diltiazem ointment as an alternative treatment and that funding a proprietary diltiazem ointment would be useful.

Antispasmodics and other agents altering Gut Motility

7.14. The Committee noted that Pharmac had received a funding application from a consumer for propantheline bromide 15 mg tablet (Pro-banthine), as an antispasmodic medication for the treatment of irritable bowel syndrome.

7.15. The Committee noted that hyoscine butylbromide and mebeverine were both currently funded as antispasmodics for the treatment of irritable bowel syndrome.

7.16. The Committee considered that propantheline did not provide any additional health benefit over and above the currently funded alternatives and did not consider there to be a clinical need for consideration of funding for propantheline bromide 15 mg tablet.

Antiulcerants

7.17. The Committee noted that in 2019 there was a global recall of ranitditine products and ranitidine was subsequently discontinued. The Committee noted that Pharmac had received clinical advice that this had resulted in an unmet health need for the prevention of allergic reactions to paclitaxel chemotherapy (in oncology). The Committee noted that Pharmac then secured supply of unapproved (by Medsafe) famotidine tablets.

7.18. The Committee considered that current use of famotidine tablets appears to be higher than what would be anticipated for those who are receiving chemotherapy with paclitaxel.

7.19. The Committee considered that it was likely that famotidine was also being prescribed to help wean people off proton pump inhibitors, and as an add on for those individuals who don't have complete resolution of symptoms from proton pump inhibitors. In addition, Members considered that H2 antagonists (eg famotidine), are recommended for use for people with chronic liver disease as proton pump inhibitors are avoided to minimise the risk of spontaneous bacterial peritonitis.

7.20. The Committee considered that primary care prescribers often use H2 antagonists to wean people off proton pump inhibitors that have been started 'over the counter' (purchased from a pharmacy, without prescription).

7.21. The Committee considered that famotidine tablets have also been helpful for children who do not like the taste of omeprazole liquid, and for some who experience constipation as an adverse effect from omeprazole.

7.22. The Committee considered that continuing funding of famotidine (or a similar H2 antagonist), would be important. In addition, Members considered that it would be useful to have another proton pump inhibitor funded.

Bile and Liver Therapy

7.23. The Committee noted that rifaximin was funded in 2014 via Special Authority for people with hepatic encephalopathy despite an adequate trial of lactulose; and that usage does not appear to have plateaued yet.

7.24. The Committee considered that the numbers involved and usage of rifaximin likely reflect the targeted population group, and that further increase was likely to occur over the next couple of years. Members considered that COVID-19 has likely contributed to growth in usage, as an increase in alcoholic liver disease appears to have occurred since the beginning of the COVID-19 pandemic.

7.25. The Committee considered that there is a clinical desire to use rifaximin for the treatment of small bowel overgrowth. Members considered that The New Zealand Society of Gastroenterology (NZSG) would be best placed to submit a funding application for this indication.

Digestives including Enzymes

7.26. The Committee considered there had been significant growth in prescription volume and resultant expenditure for pancreatic enzymes.

7.27. The Committee considered pancreatic enzymes are used to treat pancreatic insufficiency in a range of conditions including cystic fibrosis. Members considered it could also be prescribed for chronic diarrhoea and to assist with weight gain for elderly people where there is pancreatic insufficiency.

7.28. The Committee considered it is possible that up until recently people have been undertreated. However, the Committee noted, from the data provided from Pharmac, that approximately one third of all people receiving pancreatic enzymes were aged 70 or over, and considered that this seemed overly high.

7.29. The Committee considered that dieticians can prescribe this treatment now and this could be contributing to the significant growth in prescription volume. The Committee suggested that Pharmac should do some analysis on the prescriber type to work out if dieticians are the majority of prescribers, and then seek advice from the Special Foods Advisory Committee.

Laxatives

7.30. The Committee noted that usage of laxatives continues to grow. Members considered that increased use would be providing associated health benefits and were encouraged that treatment of constipation in the community setting is increasing. The Committee considered that use is likely predominantly in residential care homes where people do not receive sufficient fibre in their diets.

7.31. The Committee considered that psyllium husk is only useful in mild constipation, and that people who use it commonly experience bloating and stop taking it, so it was unsurprising that use of macrogol with electrolytes (Molaxole) use was greater.

7.32. The Committee considered that despite the number of funded laxatives available there remained an unmet health need for some people in the community for those whose constipation is not adequately treated with laxatives and require oral bowel cleansing preparations (eg Picosalax) once or twice a week.

7.33. The Committee considered that docusate sodium with sennosides should be moved under the stimulants section of the Schedule as it more appropriately reflects its main mode of action.

Methylnaltrexone bromide

7.34. The Committee noted that the Analgesics Advisory Committee had recommended that methylnaltrexone bromide for the treatment of opioid induced constipation, subject to Special Authority criteria, be funded with a **medium** priority

7.35. The Committee considered that gastroenterologists typically do not treat this cohort of people but considered that it could be used in a potentially large group of post-operative patients concomitantly prescribed opioids. For this reason, the Committee considered that it would be important to ensure that the funding criteria adequately targeted the group most likely to benefit.

Hospital Bowel-Cleansing Preparations

7.36. The Committee noted that there were a number of bowel-cleansing preparations listed on the HML and that Pharmac was seeking advice on whether it could rationalise bowel preparations to ensure only essential or clinically preferred products are listed.

7.37. The Committee considered that at least two and preferably three bowel-cleansing preparations are needed. Members considered that if Pharmac were to run any commercial process that could result in a change of preparations that a significant amount of hospital resource would be required to implement changes to protocols, patient information and nursing information leaflets. This could be time consuming, and that any changes to the range of funded products should be made infrequently.

7.38. Members considered that there is clinical variance between hospitals with bowel-cleaning procedures and that this would be very difficult to standardise.

Vitamins and Minerals

7.39. The Committee noted that Pharmac had received a funding application to remove the specialist restrictions for ferric carboxymaltose in patients with a serum ferritin of 20mcg/L and CRP>5. The Committee noted that this had been referred to the Haematology Advisory Committee for further advice. With regards to Inflammatory Bowel Disease-related anaemia, the Committee considered that the request to widen access would be in line with international guidelines.

7.40. The Committee noted that ferrous fumarate and ferrous sulphate were the funded oral iron preparations currently. The Committee considered that it could be worth exploring other oral iron preparations (such as iron polymaltose) for those that are intolerant of both ferrous fumarate and ferrous sulphate.

7.41. The Committee considered that a tablet or capsule formulation of magnesium, preferably a chelate would be useful for people with short bowel syndrome.

Horizon Scanning

7.42. The Committee noted that Pharmac was aware of upadacitinib, rizankizumab, guselkumab and tofacitinib for IBD. Members highlighted that there were likely other selective janus kinase (JAK) inhibitors and anti-interleukin agents on the horizon.

Named Patient Pharmaceutical Application (NPPA) review

7.43. The Committee noted that there had been several NPPAs for colesevalam and that if Pharmac would like specific advice on this it could be discussed at the next meeting.

7.44. The Committee noted that there had been several NPPAs for prucalopride and that Pharmac had received a Schedule funding application, that was being discussed at this meeting as a separate paper.

7.45. The Committee noted that there had been NPPAs for teduglutide and considered that there is an unmet health need for people with short bowel syndrome. The Committee noted that the Rare Disorders Subcommittee had initially recommended that the funding application be declined. The Committee noted that since the recommendation more evidence had been received and that it would be considered by the Rare Disorders Advisory Committee at its next meeting.

8. Upadacitinib for the second-line biologic treatment of moderate to severe ulcerative colitis

Application

8.1. The Advisory Committee reviewed the supplier application for upadacitinib for the second-line treatment of moderate to severe ulcerative colitis.

8.2. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

8.3. The Advisory Committee **recommended** that upadacitinib for the second-line biologic treatment of moderate to severe ulcerative colitis be listed with a **high** priority within the context of treatments of gastrointestinal disease subject to the following Special Authority criteria:

> **Initial application — (ulcerative colitis – second-line)**
> Applications only from a gastroenterologist or relevant practitioner on the recommendation of a gastroenterologist. Approvals valid for 4 months.
> All of the following:
> 1. Patient has histologically confirmed ulcerative colitis; and
> 2. Patient has a Simple Clinical Colitis Activity Index (SCCAI) of $\geq$ 4 or a Mayo endoscopic sub-score of 2-3; and
> 3. Patient is 16 to 75 years of age; and
> 4. Patient has tried but had received an inadequate response to, or has experienced intolerable side effects from, prior treatment with infliximab and/or adalimumab therapy; and
> 5. Surgery (or further surgery) is considered clinically inappropriate; and
> 6. Upadacitinib to be administered at a dose not greater than 45mg daily
>
> **Renewal — (ulcerative colitis – second-line)**
> Applications only from a gastroenterologist or relevant practitioner on the recommendation of a gastroenterologist. Approvals valid for 6 months.
> All of the following:
> 1. The SCCAI score has reduced by 2 points or more from the SCCAI score when the patient was initiated on upadacitinib and the benefit of continuing treatment outweighs the risks
> 2. Upadacitinib to be administered at a dose not greater than 30mg daily

8.4. In making this recommendation, the Committee noted:

8.4.1. the high health need of individuals living with ulcerative colitis, and the high burden of disease on their family, whānau, and caregivers;

8.4.2. the lower, but rapidly increasing, prevalence of Māori compared to non-Māori presenting with ulcerative colitis in New Zealand;

8.4.3. the evidence of effect and improved outcomes for individuals treated with upadacitinib, including lowered incidence of hospitalisation; and

8.4.4. the favourable suitability of upadacitinib as an orally administered treatment without the need for regular travel and infusion which decreases the cost for both those receiving treatment and healthcare providers/infusion centres.

Discussion

Māori Impact Statement

8.5. The Committee discussed the impact of funding upadacitinib on Māori health areas of focus and Māori health outcomes. The Committee noted that a study from Lakes DHB in 2022 reported that there had been an 8-fold increase in IBD diagnoses in Māori between the 2011–2015 and 2016–2020 periods, though incidence remains significantly lower than that of non-Māori (Qiu et al. N Z Med J. 2022;135:99-105).

8.6. The Committee considered that the incidence of Māori presenting with ulcerative colitis/IBD is potentially under-represented in secondary care due to factors such as delays in diagnosis, inequities throughout health services including delays to see a GP, lack of accessibility to healthcare services, or lower rates for referral to and having a colonoscopy.

8.7. The Committee considered that an orally administered treatment would contribute meaningfully to improving equity of access to treatment, as it would be more easily available and suitable for people living rurally (including Māori who live rurally), or who cannot travel to infusion centres. The Committee also considered that an oral option is likely to increase treatment adherence and acceptability.

Health Need

8.8. The Committee noted that the health needs of people with ulcerative colitis (UC) are high, and that impacts of treatment failure or UC flares are significant for those affected and can be socially isolating and affect relationships and the ability to work. The Committee noted that according to the American College of Gastroenterology moderate to severe UC is defined by patients: usually having six or more stools per day, frequently experiencing blood in their stool, often feeling bowel urgency, having a lower haemoglobin than normal, and Mayo endoscopy scores of two to three (Rubin et al. Am J Gastroenterol. 2019;114:384-413).

8.9. The Committee noted that disease activity refers to a cross-sectional assessment of inflammatory impact on an individual's symptoms, endoscopy findings, histology, and biomarkers at a point in time, whereas severity refers to the longitudinal and historical factors that provide a complete picture of the overall disease burden since the patient's diagnosis. The Committee noted that many factors contribute to disease severity scores, including presence of mucosal lesions, impacts of UC on daily activity, experience with biologic treatment, recent hospitalisations, and recent steroid use. The Committee noted that although some of these scores reflect disease activity, these factors are the primary markers to predict a patient's UC activity in the near future. The Committee considered that disease activity and severity are both necessary to determine the correct treatment pathway for each individual.

8.10. The Committee noted that there have been no significant new medicines funded for inflammatory bowel disease (IBD; includes Crohn's disease and ulcerative colitis) since adalimumab was funded in 2006. The Committee noted that there are approximately 20,000 people in New Zealand affected by IBD, and that approximately 40% of these people suffer from UC.

8.11. The Committee noted that the incidence of IBD is increasing globally in both industrialized and newly industrializing countries (Kaplan & Ng SC. Gastroenterology. 2017;152:313-21.e2), and that the same trend is occurring in New Zealand. The Committee noted that a study from Lakes DHB in 2022 reported that there had been an 8-fold increase in in IBD diagnoses in Māori between the 2011–2015 and 2016–2020 periods, though incidence remains significantly lower

than that of non-Māori (Qiu et al. N Z Med J. 2022;135:99-105). The Committee considered that factors contributing to the increase in prevalence amongst the Māori population is not yet known.

8.12. The Committee considered that the incidence of Māori presenting with ulcerative colitis/IBD may be under-represented in secondary care due to factors such as delays in diagnosis, inequities throughout health services including delays to see a GP, lack of accessibility to healthcare services, or lower rates for referral to and having a colonoscopy. The Committee considered that due to the highly symptomatic nature of UC, it may be unlikely that those affected would go undiagnosed for long periods of time. The Committee noted that there is no IBD registry in New Zealand, and thus any epidemiological data and information on the incidence of UC in New Zealand may not be representative of the entire population.

8.13. The Committee noted that current treatment options for those with moderate to severe UC in New Zealand includes 5-aminosalicylic acid (5-ASA) and/or steroids in the first instance, followed by immunomodulators (eg thiopurines with or without steroids) if necessary, followed by surgery. The Committee noted that if an individual has not received sufficient benefit from treatment, if side-effects are intolerable, and surgery is not considered to be a clinically appropriate treatment course, they would be treated with anti-tumour necrosis factor (TNF) agent infliximab or adalimumab. The Committee considered that approximately 50% of people would receive infliximab first-line, and 50% would receive adalimumab. The Committee noted that if treatment with anti-TNF agents is no longer appropriate or effective, they do not have other funded treatment options. The Committee noted that it has been estimated that approximately 10–30% of those treated with anti-TNF agents will experience primary non-response (failure of induction therapy) while secondary loss of response occurs in approximately 23–46% patients by 12 months (Khan et al. N Z Med J.2019;132:46-62).

8.14. The Committee noted that both ustekinumab and vedolizumab have been previously considered by PTAC and the Gastrointestinal Advisory Committee in the second line setting for treatment of UC and noted that both agents had received positive recommendations. The Committee noted that currently neither of these agents are funded in this setting.

8.15. The Committee noted that although many people develop antidrug antibodies to anti-TNF treatments, clinicians persist with anti-TNF treatment at high doses due to a lack of funded alternatives. The Committee noted that people often have repeated courses of steroids which have long term negative effects, and that ongoing morbidity is high for many individuals. The Committee noted that treatment with corticosteroids should be used as a bridge to further therapy, and not a long-term treatment modality. The Committee also noted that individuals experience increasing hospital admissions due to treatment failure, and that the rates of surgery are now similar to the rates observed before the funding of anti-TNF treatments. The Committee noted that post-surgical morbidity is high for those living with UC who often need stomas and experience diarrhoea, urgency, inability to work, and high caregiver burden.

Health Benefit

8.16. The Committee noted that upadacitinib is an oral, selective, reversible inhibitor of Janus Kinase 1 (JAK-1) which is important in inflammatory cytokine signalling. The Committee noted that the 15 and 30 mg formulation of upadacitinib is Medsafe approved for rheumatoid arthritis, atopic dermatitis, psoriatic arthritis, and ankylosing spondylitis. The Committee noted that a submission for use in the

treatment of UC has been lodged with Medsafe for use in UC, and 45 mg tablet strength. The Committee noted that JAK-1 inhibitors have a rapid onset of effect compared to anti-TNF agents

8.17. The Committee noted that the recommended dose of upadacitinib for UC is 45 mg once daily for eight to 16 weeks as induction, then 15 or 30 mg once daily based on clinical presentation, with no maximum treatment duration. The Committee noted that the 15 mg daily dosing would be most appropriate for those with a lower burden of disease or who are of a more advanced age.

8.18. The Committee noted that the application was for second-line treatment following failure of, or intolerable side effects from, anti-TNF agents infliximab and/or adalimumab. The Committee noted that for inidividuals for whom upadacitinib is not effective, surgical management would be considered where appropriate.

8.19. The Committee noted the published results from three upadacitinib UC trials where upadacitinib treatment was compared with placebo (Danese et al. Lancet. 2022;399:2113-28), which included two replicate eight-week induction studies (U-ACHIEVE induction [UC1] and U-ACCOMPLISH [UC2] with 45 mg upadacitinib versus placebo) and a single 52-week maintenance study for those who responded in the induction phase (U-ACHIEVE maintenance [UC3] with 30 or 15 mg upadacitinib versus placebo). The Committee noted that the participants in the trials had moderate to severe ulcerative colitis (adapted Mayo score 5–9; endoscopic sub score 2 or 3), were between 16 and 75 years of age, and that many had received previous treatment with 5-ASA (68%), steroids (40%), immunomodulators (1-2%) and biologics (~50%).

8.20. The Committee noted that in UC1, 26% of patients in the upadacitinib arm experienced clinical remission (as per the adapted Mayo score) compared to 5% in the placebo group (adjusted treatment difference 21.6%; 95% CI 15.8 to 27.4). The Committee also noted that endoscopic improvement was seen in 36% of upadacitinib treated patients versus 7% of placebo treated patients, with endoscopic remission reported as 14% and 1%, respectively. The Committee noted that a clinical response (as per the adapted Mayo score) was reported in 73% of upadacitinib patients versus 27% of placebo treated patients, with histological-endoscopic mucosal improvement seen in 30% versus 6%, respectively. The Committee also noted that mucosal healing was reported in 11% of the upadacitinib treated group versus 1% in the placebo group.

8.21. The Committee noted that in UC2, 44% of patients in the upadacitinib arm experienced clinical remission (as per the adapted Mayo score) compared to 4% in the placebo group (adjusted treatment difference 35.1%; 95% CI 28.6 to 41.6). The Committee also noted that endoscopic improvement was seen in 44% of upadacitinib treated patients versus 8% of placebo treated patients, with endoscopic remission reported as 18% and 2%, respectively. The Committee noted that a clinical response (as per the adapted Mayo score) was reported in 74% of upadacitinib patients versus 25% of placebo treated patients, with histological-endoscopic mucosal improvement seen in 36% versus 6%, respectively. The Committee also noted that mucosal healing was reported in 13% of the upadacitinib treated group versus 2% in the placebo group.

8.22. The Committee noted that in the UC3 study, 42% of patients in the upadacitinib 15 mg group and 52% of patients in the 30 mg group experienced clinical remission (as per adapted Mayo score) compared to 12% in the placebo group (adjusted treatment difference 30.7% [95% CI 21.7 to 39.8] and 39.0% [95% CI 29.7 to 48.2]

for 15 mg and 30 mg, respectively). The Committee also noted that 49% of the 15 mg group and 62% of the 30 mg group were reported to have endoscopic improvement, compared to 14% in the placebo group. The Committee noted that maintenance of clinical remission (as per adapted Mayo score) was reported in 57% of the 15 mg group and 68% of the 30 mg group compared to 22% in the placebo group.

8.23. The Committee noted that corticosteroid-free clinical remission was reported in 57% of the 15 mg group and 68% in the 30 mg group, compared to 22% in placebo treated patients. The Committee also noted that maintenance of endoscopic improvement was reported in 62% of the 15 mg group and 70% of the 30 mg group, compared to 19% in the placebo group. The Committee noted that endoscopic remission was reported in 24% of the 15 mg group and 26% of the 30 mg group compared to 6% in the placebo group. The Committee noted that mucosal healing was reported in 18% of the 15 mg group and 19% of the 30 mg group, compared to 5% in the placebo group.

8.24. The Committee noted that adverse events reported in the trial were generally non-severe and occurred in low rates. The Committee noted small increases in the incidence of hepatic disorder, neutropenia, lymphopenia and CPK elevation in the upadacitinib groups versus the placebo groups in the UC1 and UC2 trials. The Committee also noted a slight increase in the rates of herpes zoster, neutropenia and CPK elevation in the UC3 trial.

8.25. The Committee considered the strength and quality of the evidence to be high, and that there is high relevance to the New Zealand population concerned. The Committee considered that while the placebo population in the maintenance trial had previously received upadacitinib, this was unlikely to impact the week 52 response rates due to the short half-life of upadacitinib (especially in comparison to biologics such as ustekinumab).

8.26. The Committee noted that evidence for upadacitinib in the treatment of moderate/severe UC is not available beyond 52 weeks. The Committee considered that safety data relating to the use of upadacitinib beyond 52 weeks should not be different to that of other indications, which have longer-term data available.

8.27. The Committee noted an unpublished network meta-analysis provided by the supplier that indirectly compared upadacitinib, vedolizumab, and ustekinumab at week 6-10 of induction and 52-60 weeks of maintenance compared to placebo. The Committee noted that upadacitinib possibly performed better than the other two agents regarding clinical remission, clinical response, and mucosal healing, but such signals were substantially limited by the comparisons being only indirect.

8.28. The Committee noted that treatment with upadacitinib statistically significantly reduced the rates of UC-related hospitalisations in the UC1 and UC3 trials. The Committee also noted that rates of UC-related operations were not significantly reduced with upadacitinib treatment, but considered that statistical significance was unlikely to be achieved given the small number of operations occurring in the trial and that longer follow-up will be required to show whether a difference materialises. The Committee also considered that funding a treatment that contributes to a decrease in hospitalisations would reduce the resource burden in hospitals.

8.29. The Committee noted that treatment sequencing with regard to biologic treatment is difficult, as most biologic treatments do not have head-to-head published trial data. The Committee noted that the surface under the cumulative ranking (SUCRA) score

is a tool used in network meta-analysis to compare agents indirectly, with a score of 1 being the best possible outcome. The Committee noted that for biologic naïve patients, infliximab has been reported as having the highest SUCRA ranking for UC (SUCRA score 0.95 for clinical remission), while tofacitinib and ustekinumab have the highest SUCRA scores (SUCRA score 0.87 for both agents for clinical remission) for UC patients previously exposed to anti-TNF agents (infliximab/adalimumab; Singh et al. Clin Gastroenterol Hepatol. 2020;18:2179-91). The Committee noted that vedolizumab was reported as having the lowest risk of infection (SUCRA score 0.81). The Committee noted that adalimumab was the lowest ranked treatment for anti-TNF exposed patients. The Committee noted that this network meta-analysis was published prior to publication of trial results for upadacitinib for UC.

8.30. The Committee considered that the sequencing/order of treatment is not as important as the availability of treatment, and that each line of treatment would likely reduce the treatment gap further (ie provide additional benefit to those patients with an unmet health need). The Committee noted that patient preference studies have reported that UC patients are more concerned about complications of their disease (such as increased risk of colon cancer or the possible need for an ostomy) than they are about possible side-effects of treatments (Thompson et al. Inflamm Bowel Dis. 2016;22:940-7). The Committee also noted that patients are more likely to accept significant mortality risks to avoid surgery or ostomy (Bewtra et al. Inflamm Bowel Dis. 2014;20:103-14).

Suitability

8.31. The Committee noted that upadacitinib is an oral therapy that can be self-administered at home. The Committee considered that funding of upadacitinib would reduce the burden on infusion centres and would be easy to manage in both community and hospital settings.

Costs and Savings

8.32. The Committee considered that in a situation in which both vedolizumab and upadacitinib were funded, that it would be likely that upadacitinib would be used before vedolizumab for the majority of affected individuals, due to suitability and evidence of benefit. The Committee also considered, however, that vedolizumab would still have a relatively large market share due to the favourable safety profile. The Committee considered that vedolizumab would particularly be used in those who are elderly or who have a higher risk of complications or infection. The Committee considered that usage of vedolizumab in these groups would also occur if vedolizumab and ustekinumab (but not upadacitinib) were funded.

8.33. The Committee considered that in a situation where vedolizumab, ustekinumab, and upadacitinib were all funded for UC that most individualts would receive upadacitinib following treatment with anti-TNF agents, followed by ustekinumab or vedolizumab. The Committee again noted the favourable safety profile of vedolizumab, and also prescriber familiarity with vedolizumab, and considered that vedolizumab would still be considered beneficial owing to its improved safety.

8.34. The Committee considered that treating the elderly with anti-TNF agents poses some risks in terms of safety. The Committee considered that approximately 30% of people would be treated with vedolizumab in the first-line setting if it were available.

8.35. The Committee considered that it was unclear how many people would receive the 15mg maintenance dose of upadacitinib, and how many would receive the 30mg maintenance dose. The Committee also considered that it was unclear what factors

influence who benefits most from each dosing regimen. The Committee considered that elderly individuals or those with moderate disease may be maintained on the 15mg dose.

Funding Criteria

8.36. The Committee considered that the population group who would benefit most from funding of upadacitinib is those with moderate/severe UC who have experienced treatment failure (primary or secondary non-response) with infliximab and/or adalimumab. The Committee noted that if an individual experiences remission with infliximab or adalimumab and secondary treatment failure is due to anti-drug antibodies, then a second anti-TNF treatment would typically be trialled before moving them to upadacitinib or another biologic treatment.

8.37. The Committee considered that it would be appropriate to use either the Simple Clinical Colitis Activity Index (SCCAI) of > 4 or a Mayo endoscopic sub-score of 2-3 to define eligibility for upadacitinib. The Committee considered that endoscopy is generally more accessible than 5-10 years ago, and access to endoscopies is less of a barrier to diagnosis and treatment, though this varies between centres.

8.38. The Committee noted that there is no safety or efficacy data relating to the use of upadacitinib for treatment of UC in the paediatric setting. The Committee noted that there is some data for the use of vedolizumab in this setting.

Summary for Assessment

8.39. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for upadacitinib if it were to be funded in New Zealand for the second-line biologic treatment of ulcerative colitis. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with moderate to severe UC who have received inadequate benefit from at least one prior biologic
Intervention	Upadacitinib, at a dose of: - 45mg daily for the induction period (8-16 weeks) - 15mg daily for maintenance for individuals with less extensive disease, and 30mg daily for maintenance in individuals with more severe disease In the absence of alternative evidence, assume 50% of individuals receive the 15mg maintenance dose, and 50% receive the 30mg maintenance dose
Comparator(s)	When used as a second-line biologic: adalimumab or infliximab (50% adalimumab, 50% infliximab)
Outcome(s)	Based on U-ACHIEVE and U-ACCOMPLISH, superior rates of clinical remission and response vs placebo - Improved clinical remission associated with superior quality of life and lower need for hospitalisation and other health resource utilisation Based on indirect comparisons vs other biologics for UC, assume higher rates of clinical remission and response vs a second-line anti-TNF
Table definitions: **P**opulation, the target population for the pharmaceutical; **I**ntervention, details of the intervention pharmaceutical;	

Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care);
Outcomes, details the key therapeutic outcome(s) and source of outcome data.

9. Macrogol (electrolyte-free or flavourless) for the treatment of paediatric constipation

Application

9.1. The Advisory Committee reviewed the Pharmac-initiated application for macrogol (electrolyte-free or flavourless) for the treatment of paediatric constipation.

9.2. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

9.3. The Advisory Committee **recommended** that macrogol (electrolyte-free or flavourless) for the treatment of paediatric constipation be listed with a **medium** priority within the context of treatment of gastrointestinal disease, subject to the following endorsement:

> **MACROGOL (ELECTROLYTE-FREE)**
> Only prescribed when patient is a child and macrogol with electrolytes has previously been trialled and is unsuitable due to poor palatability and the prescription is endorsed accordingly.

9.4. In making this recommendation, the Committee considered:

- The high unmet health need for a pleasant tasting, low dose volume, osmotic laxative product to treat constipation
- The suitability benefit of electrolyte-free or flavourless macrogol due to its improved palatability, thereby providing a health benefit through increased adherence

Discussion

Māori Impact Statement

9.5. The Committee noted the impact of macrogol (electrolyte-free or flavourless) for the treatment of paediatric constipation. The Committee noted that no epidemiological evidence was identified relating to the impact of macrogol (electrolyte-free or flavourless) for the treatment of paediatric constipation on Māori health outcomes or Hauora Arotahi (Māori Health Areas of Focus). The Committee anticipated that the impact on Māori may be slightly greater given the increased likelihood that this population may have reduced access to care.

Background

9.6. The Committee noted that the proposal for electrolyte-free macrogol for the treatment of paediatric constipation was initiated following the Therapeutic Group Review at the Gastrointestinal Subcommittee in April 2012. At this time, the Subcommittee recommended that a half-dose preparation of macrogol 3350 or a preparation more palatable for children be funded, noting that the palatability issue for children with this product is more related to the electrolyte components rather than the flavouring. The Committee noted that this application was also reviewed and recommended for funding with no priority at the following clinical advice

meetings: PTAC Aug 2012, Gastrointestinal Subcommittee May 2014, and PTAC Nov 2014.

9.7. The Committee noted that at the Gastrointestinal Subcommittee March 2017 meeting macrogol (electrolyte-free or flavourless) was recommended for funding with a high priority. It was noted that, at this time, the Subcommittee considered that it was important for children, particularly those with developmental disorders and the very young, to have access to a tasteless formulation such as the electrolyte-free macrogol 3350. The Subcommittee members considered that the taste of the macrogol 3350 to be a barrier to use in those children, as even mixing it with juice did not disguise the taste. The Subcommittee also considered that it would be appropriate to require children to trial the standard macrogol 3350 before being eligible for the electrolyte-free formulation. The Committee noted that this high priority recommendation was supported by PTAC at the PTAC Nov 2017.

Health Need

9.8. The Committee noted the comments made previously by PTAC and the Gastrointestinal Subcommittee regarding the unmet clinical need for a low dose volume, pleasant tasting New Zealand registered product to treat constipation.

9.9. The Committee noted that constipation is defined variably, but involves infrequent, difficult, painful, or incomplete evacuation of hard stools. The Committee noted that constipation is common among children, accounting for an estimated 3-5% of all visits to paediatricians. The Committee noted that estimates of the true prevalence of constipation vary between 1-30%, even when uniform criteria are used, with the peak prevalence being during the pre-school years in most reports (van den Berg et al. Am J Gastroenterol. 2006;101:2401). The Committee considered that other groups that may be disproportionally impacted by paediatric constipation would include those with neurological disabilities and developmental delay. The Committee noted that this proposal aligns with the government health priority to improve child wellbeing and to strengthen primary health care.

9.10. The Committee considered that macrogol (electrolyte-free or flavourless) is not a direct alternative to sodium picosulfate, and therefore that Pharmac's recent decision to fund sodium picosulfate does not fulfil the unmet health need. The Committee considered that osmotic laxatives should be used as first-line therapy for constipation before introducing a stimulant laxative such as sodium picosulfate. The Committee considered macrogol to be the most effective osmotic laxative available in the paediatric setting, and that it was reasonable that children first trial macrogol with electrolytes. The Committee considered that current treatment is likely to include lactulose.

Suitability

9.11. The Committee noted that electrolyte-free or flavourless macrogol provides a suitability benefit over macrogol with electrolytes due to its improved palatability for children, thereby improving adherence to treatment. The Committee noted comments from the Gastrointestinal Subcommittee in the 2017 meeting that it was important for children, particularly those with developmental disorders and the very young, to have access to a tasteless formulation such as the electrolyte-free macrogol 3350. The Committee noted that the taste of the macrogol 3350 with electrolytes may affect uptake in children as even mixing it with juice did not disguise the taste.

Cost and Savings

9.12. The Committee considered that, if macrogol were to be funded, there are likely to be cost offsets to the health sector from successful treatment of constipation and avoidance of stimulant laxatives, including reduced GP and hospital outpatient visits.

9.13. The Committee noted that it is assumed that 30% of children would switch from macrogol 3350 with potassium chloride, sodium bicarbonate, and sodium chloride to electrolyte-free macrogol; and 15% would switch from lactulose. The Committee noted that the proportion of those affected unable to tolerate regular macrogol is 15-30%, based on expert advice obtained in May 2018, and that uptake would be 50% in year 1, increasing to 100% in year 5.

Funding Criteria

9.14. The Committee noted that in the 2017 Gastrointestinal Subcommittee clinical advice meeting, it was considered that it would be appropriate to require children to trial macrogol 3350 with electrolytes before being eligible to receive funding for the electrolyte-free formulation. The Committee considered that this requirement be incorporated into the proposed funding criteria.

Summary of Assessment

9.15. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for macrogol (electrolyte-free or flavourless) if it were to be funded in New Zealand for paediatric constipation. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Children with constipation who have previously trialled macrogol with electrolytes and found it unsuitable due to palatability.
Intervention	Macrogol (electrolyte-free): 0.5 to 1 sachet per day
Comparator(s) (NZ context)	Lactulose
Outcome(s)	Improvement in constipation compared with lactulose.

Table definitions:

Population: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

10. Prucalopride for the treatment of slow-transit constipation

Application

10.1. The Advisory Committee re-reviewed the application for prucalopride for the treatment of slow-transit constipation

10.2. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

10.3. The Advisory Committee **agreed** with its previous recommendation, that prucalopride be funded for individuals with chronic, slow-transit constipation with a **medium** priority, subject to the following criteria:

> Initial application from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Treatment has been recommended by a gastroenterologist; and
> 2. Outlet obstruction (anismus) has been excluded or treated; and
> 3. Patient has chronic slow-transit constipation; and
> 4. 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.

10.4. In making this recommendation the Advisory Committee considered the significant unmet health need for people with treatment refractory, slow-transit constipation and the evidence that prucalopride is a safe and effective treatment in this setting.

10.5. The Advisory Committee considered that it was appropriate for initial applications to be restricted to gastroenterologists to ensure that treatment is targeted to those with slow-transit constipation rather than other types of constipation.

Discussion

Background

10.6. The Advisory Committee noted an application for prucalopride succinate was considered by the (then) Gastrointestinal Subcommittee in October 2018 and again by PTAC in May 2019. The Subcommittee recommended that prucalopride be funded for patients with chronic slow-transit constipation with a medium priority, subject to eligibility criteria. In making this recommendation the Subcommittee noted the impact that severe constipation has on quality of life and the good quality evidence from randomised controlled trials that prucalopride provided better constipation relief than placebo.

10.7. At that meeting 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.

10.8. The Advisory Committee noted that PTAC recommended that the application for prucalopride for the treatment of chronic slow-transit constipation be deferred pending advice from the Gastroenterology Subcommittee regarding how to define the population with the highest need and those mostly likely to benefit, and the evidence for the use of prucalopride in this population.

10.9. The Advisory Committee noted that PTAC considered this was potentially a very large group of people, some of whom might have a serious health need, and noted that the evidence suggested that prucalopride has a modest effect. The Advisory Committee noted that PTAC considered that requiring a gastroenterologist be involved in the Special Authority was a considerable access barrier given the common nature of the condition and the limited number of gastroenterologists.

Health Need

10.10. The Advisory Committee noted the comments previously made by the Gastrointestinal Subcommittee and PTAC regarding the significant health need of individuals with treatment refractory slow-transit constipation. The Advisory Committee noted that this unmet health remains and that severe constipation impacts quality of life and can lead to serious complication if left untreated.

10.11. The Advisory Committee noted that while most people with this condition have treatments available such as macrogol and lactulose, there would be individuals whose constipation is refractory to these treatments.

Health Benefit

10.12. The Advisory Committee noted the comments previously made by the Gastrointestinal Subcommittee regarding the health benefit of prucalopride succinate in the treatment of constipation. The Advisory Committee considered that there was good quality evidence from randomised controlled trials that prucalopride provided a modest, but clinically significant, benefit over placebo in terms of constipation relief.

10.13. The Advisory Committee noted that prucalopride is a selective, high-affinity 5-HT4 receptor agonist approved by Medsafe for the treatment of chronic constipation in adults in whom laxatives have failed to provide adequate relief.

10.14. The Advisory Committee noted that PTAC had concerns however, regarding the evidence of benefit in the targeted group, noting the absence of head-to-head trials comparing prucalopride with other laxatives for the treatment of slow-transit constipation. The Advisory Committee considered that it was unlikely that there would be any emerging clinical trial evidence directly comparing the respective laxative agents and considered that indirect evidence was likely the best available data to guide decision making.

10.15. The Advisory Committee noted that in a systematic review and meta-analysis of the comparative efficacy of laxative treatments in the treatment of chronic idiopathic constipations, that all agents were effective at inducing spontaneous complete bowel motions compared with placebo and that there was no statistically significant difference in efficacy between agents (Nelson et al. Gut 2017;66:1611-22).

10.16. The Advisory Committee noted that there had been concerns regarding the safety of previous affinity 5-HT4 receptor agonists due to their cardiovascular side-effects but that due to the high-affinity binding of newer generation agents such as prucalopride, this was no longer a concern (Hong et al. Ther Clin Risk Manag. 2021; 17: 601–15; Gilsenan et al. Drug Safety (2019) 42:1179-90).

10.17. The Advisory Committee considered that it was appropriate to retain the requirement that a gastroenterologist should be involved in the diagnosis of slow-transit constipation, either as the applicant or on their recommendation. While Members considered that requiring gastroenterologist involvement could mean a barrier to access due to lack of capacity, they considered that it was important to prevent misdiagnosis and it was an important way to limit use outside the intended population. The Committee considered that it wasn't possible to describe clinical circumstances, for diagnosing slow-transit constipation in funding criteria, that would avoid the need for a gastroenterologist. The Committee considered that the majority of individuals who appear to have slow-transit constipation have anismus (outlet obstruction) and require biofeedback as the main intervention. The Committee considered it was important to ensure that treatment with prucalopride

was targeted to those individuals who have had anismus excluded. The Advisory Committee considered that the other criteria remained appropriate in this context.

Suitability

10.18. The Advisory Committee noted that prucalopride is a single tablet taken once daily and that this may make it more suitable for some patients than other treatments.

Costs and Savings

10.19. The Advisory Committee noted that prucalopride would be used alongside other laxative agents and would constitute additional pharmaceutical expenditure.

10.20. The Advisory Committee noted a cost-effectiveness analysis on prucalopride for the treatment of chronic constipation conducted in the Netherlands (Nuijten MJ, Dubois DJ, Joseph A, Annemans L. Cost-effectiveness of prucalopride in the treatment of chronic constipation in the Netherlands. Front Pharmacol. 2015 Apr 14;6:67). The Advisory Committee considered that prucalopride appeared to be a cost-effective intervention compared with continuation of standard of care treatment.

Summary of Assessment

10.21. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for prucalopride if it were to be funded in New Zealand for individuals with slow-transit constipation. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with treatment refractory slow-transit constipation.
Intervention	Prucalopride 1-2 mg once daily
Comparator(s) (NZ context)	Currently listed laxatives, in particular macrogol 3350
Outcome(s)	Improvement in constipation compared with currently listed agents.
Table definitions: **P**opulation: the target population for the pharmaceutical; **I**ntervention: details of the intervention pharmaceutical; **C**omparator: details the therapy(s) that the target population would receive currently (status quo – including best supportive care); **O**utcomes: details the key therapeutic outcome(s) and source of outcome data.	