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

Meeting held on 28 March 2017

(minutes for web publishing)

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Note that this document is not necessarily a complete record of the Gastrointestinal Subcommittee meeting; only the relevant portions of the minutes relating to Gastrointestinal Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Gastrointestinal Subcommittee may:

(a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes were reviewed by PTAC at its meeting on 9 & 10 November 2017, the record of which will be available in due course.
1 Macrogol Correspondence and Clozapine Coroner’s Report

Recommendation

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

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

Discussion

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

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

Macrogol 3350 for patients treated with clozapine

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

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

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

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

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

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

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

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


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

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

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

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

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

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

Macrogol 3350 for the treatment of constipation in all patients

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

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

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

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


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

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

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

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

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

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