Analgesic Subcommittee of PTAC
Meeting held 1 March 2016

(minutes for web publishing)

The Analgesic Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

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

The Analgesic 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 5 & 6 May 2016, a record of which will be available in due course.

Record of the Analgesics Subcommittee of PTAC meeting held at PHARMAC on 1 March 2016

1. Matters arising

Tramadol oral solution

1.1. The Subcommittee noted that as a result of safety concerns (i.e. potential for dosing errors) in children prescribed concentrated tramadol oral drops 100 mg/ml, the Paediatric Compounding Pharmacists group created a standardised formulation for tramadol oral liquid 10 mg/ml compounded using the 50 mg capsules. Using this formula, tramadol 10 mg/ml has been available fully funded in the community since 2014.

1.2. The Subcommittee noted two reports of recent paediatric medication errors, where children had been administered a significant overdose of tramadol oral drops. Members noted in both cases, the availability of both the 10 mg/ml and 100 mg/ml formulations was considered to be a significant contributing factor to the prescribing/dispensing errors.

1.3. The Subcommittee noted anecdotal reports that some pharmacists have been reluctant to compound the tramadol 10 mg/ml oral solution, possibly due to time constraints, despite the oral drops 100 mg per ml not being funded in the community setting.

1.4. The Subcommittee considered that the availability of both 10 mg/ml and 100 mg/ml formulations in DHB hospitals and the community presents a significant safety concern. Members noted that due to their high concentration, tramadol 100 mg/ml formulations have also raised safety concerns internationally, including a reported fatal overdose in two year old child in Australia, prompting a Therapeutics Goods Administration (TGA) review.

1.5. The Subcommittee **recommended** PHARMAC investigate funding a proprietary product of tramadol 10 mg/ml, as this would be preferable to a compounded formulation for access reasons. Members noted that this product would require Medsafe registration.

1.6. The Subcommittee considered that, provided a 10 mg/ml formulation of tramadol was available in hospitals and funded in the community, there was no clinical need for the 100mg/ml oral tramadol drops to remain available.

1.7. The Subcommittee **recommended** PHARMAC delist tramadol oral drops 100 mg/ml from the HML for safety reasons. The Subcommittee considered that this delisting should occur once a tramadol 10 mg/ml formulation is widely available either through pharmacy compounding or the funding of a proprietary product.

1.8. The Subcommittee noted the review of funded anaesthetics, analgesics, antinausea and vertigo agents provided by PHARMAC staff.

1.9. The Subcommittee noted that paracetamol remained the highest item of expenditure and were surprised at the amount of paracetamol with codeine still being prescribed given the low-codeine dose contained within the formulation.

1.10. The Subcommittee noted the low usage of isoflurane nationally. Members considered sevoflurane was the current preferred treatment option and had equivalent cardio-

protective effects to isoflurane. The Subcommittee considered there was no ongoing clinical need for isoflurane to remain listed on the Hospital Medicines List (HML).

1.11. The Subcommittee considered that the HML restrictions on the current listing of methoxyflurane remained appropriate.

1.12. The Subcommittee considered that any community listing for methoxyflurane would require clinical training and education beyond the practical aspects of using the device. Members considered a BPAC NZ article could provide appropriate information. Members further considered training would likely need to include some detail on contraindications, recognising deepening sedation levels, and early warning signs of malignant hyperthermia. The Subcommittee considered that it would be appropriate for the supplier to provide the necessary training.

1.13. Members considered that the use of methoxyflurane in the community could reduce visits to the hospital for minor surgical procedures.

2. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) for Osteoarthritis (OA)

Recommendation

2.1. The Subcommittee **recommended** that topical diclofenac 1% be funded with a low priority for mild to moderate osteoarthritis of the hand and knee.

2.2. The Subcommittee **recommended** that Special Authority (SA) criteria on initial application be limited to 12 weeks treatment, and that the SA be renewed only if a clinical benefit of topical treatment is demonstrated and that adjunctive treatment with oral NSAIDs has not been required.

Discussion

2.3. The Subcommittee noted that in May 2015, PTAC had considered topical NSAIDs for OA. Members noted that PTAC had recommended funding topical NSAIDs with a low priority. Members also noted that PTAC sought advice from the Analgesic Subcommittee of PTAC on appropriate SA criteria for funding topical NSAIDs.

2.4. The Subcommittee considered that the evidence was of weak strength but moderate quality. Members noted that the evidence supporting the use of topical NSAIDs in OA was for hands and knees only. The evidence primarily focussed on diclofenac and the longest trials were for a duration of only 12 weeks which is relatively short when considering a long-term disease.

2.5. The Subcommittee noted various topical NSAIDs are available internationally including diclofenac, ibuprofen, ketoprofen, piroxicam and felbinac. The Subcommittee considered the evidence of efficacy was only sufficient in strength to make a recommendation on topical diclofenac 1% gel.

2.6. The Subcommittee noted a 2013 article by Singleton et al (N Z Med J. 2013;126:23-30). reviewing OA in the Māori population. Members noted that although Māori had a lower prevalence of OA, they developed symptoms at an earlier age and had worse joint replacement post-operative outcomes than non-Māori.

2.7. The Subcommittee noted the Cochrane reviews of topical NSAIDs for acute and chronic musculoskeletal pain in adults (Derry et al. Cochrane Database Syst Rev. 2015;6:CD007402; Derry et al. Cochrane Database Syst Rev. 2012;9:CD007400) reported that topical NSAIDs can provide effective levels of pain relief when compared to placebo. Members noted topical diclofenac 1% is equivalent to that of oral NSAIDs in knee and hand osteoarthritis only.

2.8. The Subcommittee noted the Lin et al (BMJ 2004;329:324) meta-analysis reporting topical NSAIDs to be superior to oral NSAIDs only in the first two weeks of treatment, after which time there was no evidence of an efficacy benefit over placebo.

2.9. The Subcommittee noted the Deng et al (Clin Rheumatol 2015;Aug 5 [Epub ahead of print]) meta-analysis of nine randomised controlled trials examining topical diclofenac 1-1.5% presentations, and a diclofenac patch for osteoarthritis. The Subcommittee noted that topical diclofenac appeared to provide effective pain relief (standard mean differences (SMD) = 0.40; 95 % confidence interval (CI) 0.19 to 0.62; P = 0.0003) and function improvement (SMD = 0.23; 95 % CI 0.03 to 0.43; P = 0.03) when compared to the control group. Members noted topical diclofenac had a higher incidence of adverse events such as dry skin, rash, dermatitis, neck pain, and withdrawal. The trials were all short term (four were 12 weeks, and the remaining five trials were for 2, 3, 4, 6, or 8 weeks).

2.10. The Subcommittee noted the results of a paper by Baraf et al (Drugs Aging. 2011;28:27-40). Key efficacy outcomes were Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, and physical function (0-68) subscales, global rating of disease (GRD; 100-mm visual analogue scale) and pain on movement (POM; 100-mm VAS). Of 976 patients overall, among patients aged 25-64 years (n=602), the improvement from baseline to week 12 was greater for diclofenac 1% gel versus placebo for WOMAC pain (-5.8 vs -4.7, p = 0.007), WOMAC physical function (-17.9 vs -14.2, p = 0.002), GRD (-29.5 vs -23.8, p = 0.01) and POM (-37.3 vs -29.0, p < 0.001). The efficacy of diclofenac 1% gel did not differ significantly between patients aged 25-64 years and ≥65 years. The authors concluded that diclofenac 1% gel was effective and generally well-tolerated in patients aged 25-64 and those aged ≥65 years who have been diagnosed with knee osteoarthritis.

2.11. The Subcommittee noted that there were multiple international guidelines on topical NSAIDs for OA from the European League Against Rheumatism (EULAR), the American College of Rheumatology (ACR), the National Institute for Health and Care Excellence (NICE), the American Association of Orthopaedic Surgeons (AAOS), and the Osteoarthritis Research Society International (OARSI), which have all recommended the use of topical NSAIDs in the management of hand and knee OA.

2.12. The Subcommittee noted two trials by Peniston (Phys Sportsmed. 2011;39:31-8; Clin Interv Aging. 2012;7:517-23) which provided some evidence of safety up to 12 months of use but these were of limited quality.

2.13. Members noted the efficacy of topical NSAIDs may be partially attributed to the placebo effect of the hands-on care involved with the application of a topical presentation.

2.14. The Subcommittee noted that systemic absorption of the topical preparation is likely to be low. The Subcommittee considered it plausible that the lower systemic absorption associated with topical administration of NSAIDs is likely to lead to a lower

incidence of gastrointestinal, cardiac and renal adverse effects, however considered the long-term safety data to be inadequate to conclusively support this theory.

2.15. The Subcommittee noted that alternative treatments for OA were most likely to be oral NSAIDs and intraarticular corticosteroids, but also included opioid and non-opioid analgesics, possibly in combination with an oral NSAID. The Subcommittee considered that any treatment that would delay a patient taking oral NSAIDs would provide benefit, by lessening the gastrointestinal, renal and cardiovascular complications associated with oral NSAID use.

2.16. Members considered that topical NSAIDs would likely be taken with paracetamol, and would potentially replace oral NSAIDs, tramadol, and other analgesic agents including codeine and dihydrocodeine. The Subcommittee considered there were no significant barriers to accessing current treatments.

2.17. The Subcommittee noted that standard dosing of topical diclofenac 1% in the trials was 4 g four times per day. The Subcommittee considered that it would be difficult for patients to measure out 4 g without a dose-dispenser, which was not available in New Zealand.

2.18. The Subcommittee considered that topical diclofenac 1% could be restricted by Special Authority to those with mild to moderate hand or knee osteoarthritis in patients not currently prescribed an oral NSAID, with a maximum initial treatment duration of 12 weeks. The Subcommittee considered SA renewals should only be approved if a clinical benefit (i.e pain relief and/or functional improvement) of topical treatment is demonstrated without adjunctive treatment with oral NSAIDs.

2.19. The Subcommittee considered that the patient group with hand and knee OA may be potentially large, up to tens of thousands of people, and this could incur a significant fiscal risk.

3. Serotonin ($5HT_3$) receptor antagonists

Recommendation

3.1. The Subcommittee **recommended** that the granisetron injection be listed on the Pharmaceutical Schedule as an additional longer-acting option to ondansetron injection, due to its lower cost and possible superior efficacy when compared with tropisetron, with a high priority

3.2. The Subcommittee **recommended** that PHARMAC seek advice from its Cancer Treatments Subcommittee of PTAC (CaTSoP) regarding the ongoing need for tropisetron injection for the prevention of nausea and vomiting induced by cytotoxic therapy should granisetron be listed as a longer-acting alternative to ondansetron injection.

Discussion

3.3. The Subcommittee noted that a bid was received for granisetron injection 1 mg per ml, 1ml in the 2014/15 Invitation to Tender (ITT). Members noted PHARMAC staff sought advice on the clinical need for granisetron (or another product) as an additional injectable $5HT_3$-receptor antagonist in order to resolve the tender line item.

3.4. The Subcommittee noted a double-blind controlled study by Metaxari et al (J Anesth. 2011;25:356-62) comparing the antiemetic efficacy of granisetron, ondansetron or tropisetron on the incidence and intensity of post-operative nausea and vomiting (PONV) in 254 randomised female patients undergoing thyroidectomy. Nausea and vomiting were evaluated at five points in time, as during the first hour in the post-anaesthesia care units and at 6, 12, 18, and 24 hours postoperatively. Nausea intensity was measured using a visual analogue scale score (0–10). Patients in the placebo group displayed a high incidence of PONV. The administration of granisetron reduced significantly the incidence of nausea at 6, 12, and 18 hours and vomiting at 6 and 12 hours. Ondansetron significantly reduced the incidence of nausea and vomiting only at 6 hours postoperatively. The administration of tropisetron did not affect the incidence of PONV compared with placebo. The Subcommittee considered that this trial provides evidence for the longer duration of action of granisetron compared with ondansetron and the possibility of granisetron being superior to tropisetron for PONV.

3.5. The Subcommittee noted a review by Gan (CNS Drugs 2005;19:225-238) comparing the pharmacological profiles of dolasetron, granisetron, ondansetron and tropisetron, and the clinical implications of differences in their profiles. The Subcommittee noted that pharmacokinetic and pharmacodynamics characteristics vary between the various $5HT_3$ receptor antagonists. The Subcommittee noted that CYP2D6 is not involved in the metabolism of granisetron, which may present a theoretical advantage in those individuals who are considered ultrarapid metabolisers due to genetic polymorphisms of CYP2D6.

3.6. The Subcommittee noted meta-analyses by del Giglio et al (Cancer. 2000;89:2301-8), Jordan et al (Support Care Cancer. 2007;15:1023-33) and a Cochrane review by Billio et al (Cochrane Database Syst Rev. 2010:CD006272) have concluded that both ondansetron and granisetron have similar antiemetic efficacy for the prophylaxis of chemotherapy-induced nausea and vomiting.

3.7. The Subcommittee considered that there was limited evidence of dose equivalence between the $5HT_3$ receptor antagonists, however for comparison purposes 1 mg granisetron injection could be considered equivalent to 16-32 mg of ondansetron injection administered in divided doses.

3.8. The Subcommittee considered that $5HT_3$ receptor antagonists with longer durations of action may be useful where a reduced dosing frequency is desirable or in instance of delayed emesis.

3.9. The Subcommittee **recommended** that PHARMAC fund at least two $5HT_3$ receptor antagonist injections, including ondansetron for a short half-life option and granisetron or tropisetron for a longer half-life option.

3.10. The Subcommittee noted that, based on price received in the tender, granisetron injection was a considerably less expensive option than tropisetron injection.

3.11. The Subcommittee considered that generally the $5HT_3$ receptor antagonists ondansetron, granisetron and tropisetron provided the same or similar therapeutic effects. Members further considered there was some evidence that granisetron injection was more effective than tropisetron injection for PONV. The Subcommittee considered that it would be preferable for the longer acting half-life option to be granisetron.

3.12. The Subcommittee considered that if granisetron was to be listed on the Hospital Medicines List (HML), there would be no ongoing clinical need for tropisetron injection.

3.13. The Subcommittee **recommended** that PHARMAC seek advice from oncologists, including paediatric oncologists, on their preferred treatments and any clinical reasons for continuing to fund tropisetron.