Analgesic Subcommittee of PTAC
Meeting held 24 September 2013

(minutes for web publishing)

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 13 & 14 February 2014

Record of the Analgesic Subcommittee of PTAC meeting held at PHARMAC on 24 September 2013

1 Therapeutic group review

Lignocaine 2.5% with prilocaine 2.5% (EMLA)

1.1 The Subcommittee noted that lignocaine 2.5% with prilocaine 2.5% (EMLA) cream is currently restricted by Special Authority to use in children with chronic medical conditions requiring frequent injections or venepuncture, and that PTAC had recommended that the Special Authority criteria be widened to include its use in "painful procedures" and to remove the age restriction, with a high priority. The Subcommittee noted that PHARMAC staff were seeking advice around potential uses of EMLA if the Special Authority were amended in this way (or removed altogether).

1.2 The Subcommittee noted that EMLA cream is indicated for topical analgesia of the skin in connection with needle insertion and superficial surgical procedures such as split skin grafting, of leg ulcers to facilitate mechanical cleansing/debridement, and of the genital mucosa/skin (e.g. prior to superficial surgical procedures or infiltration anaesthesia).

1.3 The Subcommittee considered that there was a high risk of extensive off-label use of EMLA cream if the access was widened under Special Authority to include "painful procedures", for example in non-medical procedures such as bikini waxing. The Subcommittee considered that if the Special Authority was removed altogether there was an even greater risk around off-label and potentially inappropriate use.. Members noted that there was a risk of toxicity from EMLA cream if it was spread over large areas of the body.

1.4 The Subcommittee noted that EMLA cream was relatively expensive. The Subcommittee considered that the greatest area of unmet clinical need was adults receiving frequent injections and, therefore, **recommended** that the age restriction be removed from the Special Authority for EMLA cream be removed, with a high priority. The Subcommittee further **recommended** that the indication criteria for EMLA cream not be amended because of the financial risk associated with off-label prescribing.

1.5 The Subcommittee considered that access to EMLA patches would be useful in patients receiving frequent injections and that the patches were much less likely than the cream to be used off-label if there were no restrictions in place. The Subcommittee **recommended** that PHARMAC staff investigate the possibility of listing EMLA patches in Section B of the Pharmaceutical Schedule, without Special Authority restrictions.

Tramadol oral drops

1.6 The Subcommittee noted that tramadol oral drops 100 mg per ml were listed on the HML but not on Section B of the Pharmaceutical Schedule and that PHARMAC staff were seeking the Subcommittee's advice on the possibility of listing it in Section B.

1.7 The Subcommittee considered that there was an unmet clinical need for tramadol oral drops, for paediatric use and in adults who cannot swallow tablets, where stronger pain relief than paracetamol was required (e.g. post-operatively). Members considered that it would also be useful where slower titration was needed than was afforded by the available tablet and capsule strengths.

1.8 The Subcommittee considered that the main funded alternative was morphine oral liquid, which is a stronger opioid and carries a greater risk of abuse and diversion.

1.9 The Subcommittee considered that typical doses of tramadol oral drops would be 50–100 mg in adults, and 1–2 mg per kg in children, every 6 hours. Members considered that the duration of perioperative use would be approximately 5–10 days, but tramadol oral drops could be used for longer in patients with chronic or cancer-related pain.

1.10 The Subcommittee **recommended** that tramadol oral drops be listed in Section B of the Pharmaceutical Schedule, with a high priority. The Subcommittee considered that it would be reasonable to restrict tramadol oral drops to patients who cannot swallow tablets, depending on price.

1.11 The Subcommittee considered that there was a risk that tramadol could be used inappropriately as an alternative to paracetamol oral liquid in children, which was a potential concern because of the lower seizure threshold with tramadol. Therefore, the Subcommittee **recommended** that if tramadol oral drops were listed in Section B of the Pharmaceutical Schedule the listing should be accompanied by education around its appropriate use.

Sugammadex

1.12 The Subcommittee noted that during consultation on the inclusion of sugammadex on the HML, PHARMAC had received a request to include "severe neuromuscular degenerative disease where the use of neuromuscular blockade is required" as a permitted indication, and that PHARMAC staff were seeking the Subcommittee's view on this request.

1.13 The Subcommittee noted that suxamethonium was considered 'contraindicated or undesirable' in patients with severe neuromuscular disease because of excessive potassium release which has the potential to cause fatal cardiac events. The Subcommittee considered that despite this, patients would not meet the current criteria for sugammadex because such patients would not be undergoing a rapid sequence induction – however, they would still require sugammadex because of the use of a long-acting, non-depolarising muscle relaxant.

1.14 The Subcommittee **recommended** that "severe neuromuscular degenerative disease where the use of neuromuscular blockade is required" should be added to

the HML restrictions and that if this was included the number of additional patients would be low, in the region of 50 per year.

2 Glycopyrronium injections for noisy breathing in patients near death (death rattle)

Application

2.1 The Subcommittee considered information provided by PHARMAC staff in relation to requests to fund glycopyrronium bromide injection 0.2 mg per ml for use in controlling oral secretions in order to reduce noisy breathing in patients near death ('death rattle').

Recommendation

2.2 The Subcommittee **recommended** that glycopyrronium bromide injection 0.2 mg per ml be listed in Section B of the Pharmaceutical Schedule, without restrictions, only if it was cost-neutral to hyoscine injections.

Discussion

2.3 The Subcommittee noted that glycopyrronium bromide is an anticholinergic agent indicated for use in anaesthesia and the treatment of peptic ulcer. Members noted that glycopyrronium bromide was unlikely to be widely used in the peptic ulcer indication.

2.4 The Subcommittee noted that cause of noisy breathing in patients near death (NBIPND) is presumed to result from accumulation of respiratory secretions and that it occurs in between 23% and 97% of patients near death.

2.5 The Subcommittee considered that NBIPND has a high emotional impact on family members and caregivers but the impact on the patient is unknown as invariably the patient is unconscious. Similarly, the impact of anticholinergic side effects on the patient is unknown.

2.6 The Subcommittee noted that there are two formulations of hyoscine injection that are funded and can be used in the management of NBIPND: hyoscine hydrobromide inj 400 mcg per ml, 1 ml (typical dosing 0.4 mg stat & prn or 1.2 mg per 24 hours continuous subcutaneous infusion [csci]) and hyoscine N-butylbromide inj 20 mg per ml, 1 ml (typical dosing 20 mg stat & prn or 60 mg per 24 hours csci). The Subcommittee considered that hyoscine N-butylbromide is often preferred over hyoscine hydrobromide as it is less lipophilic than hyoscine hydrobromide and less likely to cross the blood brain barrier and, therefore, in theory is less likely to cause delirium and paradoxical agitation.

2.7 The Subcommittee considered that, if funded, typical dosing of glycopyrronium bromide in NBIPND would be 0.2 mg stat & prn or 0.8 mg per 24 hours csci.

2.8 The Subcommittee noted several publications relating to use of glycopyrronium bromide in palliative care settings (Black et al. Palliative Care Med 2001;15:329-336; Bennett et al, Palliative Med 2002;16:369-74; Hugel et al. J Palliative Med

2006;9:279-84; Hughes et al. Palliative Med 2000;14:221-222; Lawry et al. Br J Community Nursing 2005;10:421-426; Likar et al. Wien Klin Wchenschr 2008;120:679-83 [abstract only]; Murtagh et al. Palliative Med 2002;16:449-50), as well as a Cochrane Review of interventions for NBIPND (Wee et al. Cochrane Database of Systematic Reviews 2008;1:Art. No: CD005177).

2.9 The Subcommittee noted that the studies of glycopyrronium bromide use were mostly small cohort studies, audits or retrospective chart reviews, and considered that the evidence for glycopyrronium bromide in NBIPND was somewhat equivocal.

2.10 The Subcommittee noted that the authors of the Cochrane Review concluded that there is no evidence that any intervention (pharmacological or non-pharmacological) is superior to placebo in the management of NBIPND, noting that there is a need for well-designed placebo-controlled prospective studies.

2.11 The Subcommittee noted that there was no evidence to suggest that glycopyrronium bromide would be effective in cases where hyoscine was ineffective (or vice versa) and it was likely that, if both glycopyrronium and hyoscine were available, treatment would be stopped altogether if the first agent tried was not successful. The Subcommittee considered that the availability of glycopyrronium bromide would be unlikely to grow the NBIPND treatment market or to extend the treatment time.

2.12 The Subcommittee considered that there was no particular unmet clinical need for glycopyrronium bromide and noted that there was a lack of compelling evidence for its use; however, there did not appear to be any reason not to list it in Section B if it was no more expensive than the currently funded options.

3 Zoledronic acid

3.1 The Subcommittee noted that zoledronic acid 4 mg in 5 ml (Zometa) is listed on the HML, restricted to the treatment of hypercalcaemia of malignancy, and is not listed in Section B of the Pharmaceutical Schedule. The Subcommittee noted that PHARMAC had received requests to widen HML access to include prevention of skeletal related events (SREs) in patients with bone metastases (including in the absence of hypercalcaemia) and to list this formulation of zoledronic acid in Section B of the Pharmaceutical Schedule. The Subcommittee noted that PHARMAC staff were seeking the Subcommittee's view on these requests, given that some of the requests had come from the palliative care community.

3.2 The Subcommittee noted that many hospices cannot access DHB-funded pharmaceuticals listed on the HML, even where dispensing into the community is permitted by the HML rules, because this requires a DHB hospital doctor to write the prescription, which is not an option or not practical in many instances. For this reason, a Section B listing would be required to ensure consistency of access by hospices.

3.3 The Subcommittee noted that, in the context of malignancies, bisphosphonates have three key effects:

- reduction in serum calcium concentrations
- prevention of SREs in patients with bone metastases
- reduction of pain in patients with bone metastases (including in the absence of fractures and hypercalcaemia)

3.4 The Subcommittee noted that it had not had the opportunity to review all the relevant studies – of which there were many, including several meta-analyses – and **recommended** that a full review should be conducted by PTAC and/or the Cancer Treatments Subcommittee of PTAC. The Subcommittee considered that there appeared to be a significant publication selection bias in reporting of bisphosphonate trials, with members understanding that many trials remain unpublished due to negative results.

3.5 However, the Subcommittee considered that, in general, zoledronic acid appeared to provide similar efficacy to pamidronate (which is listed on the HML and in Section B of the Pharmaceutical Schedule without restrictions), with similar side effects, in the prevention of SREs and reducing hypercalcaemia, with the key difference being that the infusion time for zoledronic acid is shorter (15 minutes versus approximately 90 minutes for pamidronate). The Subcommittee considered that the cost and time associated with each infusion should be included in PHARMAC's analyses.

3.6 The Subcommittee considered that the shorter infusion time would be of benefit in DHB hospitals as it would free up resources to treat more patients in a given timeframe, although members considered that the longer infusion time for pamidronate was unlikely to be a significant barrier to accessing treatment if a bisphosphonate was required. The Subcommittee considered that the difference in infusion times was less likely to be an issue in hospices.

3.7 The Subcommittee noted that with respect to reduction of SREs, there appeared to be good evidence for pamidronate in some malignancies (e.g. breast cancer and multiple myeloma) but not in others (e.g. prostate cancer). The Subcommittee considered that there was some evidence for zoledronic acid in prostate cancer.

3.8 The Subcommittee noted that the effects in reducing SREs were not apparent until 6-12 months after treatment, so there did not appear to be any benefit in giving bisphosphonates to patients with a prognosis of less than 6 months to live.

3.9 The Subcommittee considered that a cost-utility analysis should be undertaken based on the evidence of effect for the specific type of cancer given the differing benefits of pamidronate and zoledronic acid.

3.10 The Subcommittee considered that it would not be appropriate to restrict zoledronic acid to patients demonstrating pamidronate-resistant hypercalcaemia, as resistance to pamidronate in this setting could be indicative of disease progression rather than pamidronate resistance in some patients. The Subcommittee noted that it was not aware of good evidence that zoledronic acid would provide benefit in pamidronate-resistant disease, although it is often used in this setting.