

**August 2005 PTAC Meeting**

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**“Minute”** means that part of the record of a PTAC or Sub-committee meeting (including meetings by teleconference and recommendations made by other means of communication) that contains a recommendation to accept or decline an application for a new investment or a clinical proposal to widen access and related discussion.”

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## Insulin detemir (Levemir)

The Committee reviewed an application from Novo Nordisk to list insulin detemir on the Pharmaceutical Schedule.

The Committee reviewed the studies that had been provided in the submission for the use of insulin detemir in patients with diabetes. It noted that the clinical studies compared insulin detemir with neutral protamine hagedorn (NPH), known as insulin isophane in New Zealand. Five studies were conducted in patients with type 1 diabetes and one in patients with type 2 diabetes. The Committee noted that the studies were all multicentre, randomised, open-label controlled trials of four to six months duration in patients on basal-bolus regimens. It considered that the studies were of satisfactory quality but that there was insufficient long-term data, particularly regarding safety. Of note, these studies excluded patients with severe hypoglycaemia.

The Committee noted that there were no direct comparisons of insulin detemir with insulin glargine. It reviewed the meta-analysis provided, which indirectly compared insulin detemir with insulin glargine and considered that based on this evidence, insulin detemir and insulin glargine appeared to have similar therapeutic effects.

The Committee considered that evidence of improved control (measured by HbA1c) and reduced hypoglycaemic episodes (particularly severe hypoglycaemia) would be required to demonstrate a significant advance in insulin treatment. Members noted that insulin detemir was associated with less variability than isophane, as assessed by the coefficient of variation (CV) for the glucose infusion rate in euglycaemic clamp conditions and fasting blood glucose levels. The Committee noted that a meta-analysis of the five studies in patients with type 1 diabetes demonstrated that insulin detemir was similar to insulin isophane in terms of glycaemic control measured by HbA1c but statistically significantly superior in terms of reduction in fasting plasma glucose, all hypoglycaemic events and nocturnal hypoglycaemic events. Members noted that in the five studies, insulin detemir was associated with a relative risk reduction in nocturnal hypoglycaemic events of 5-50% compared with isophane, with three of the five studies demonstrating statistically significant reductions in favour of detemir. The Committee considered that the clinical studies demonstrated no significant adverse event concerns with insulin detemir.

The Committee considered that insulin detemir would be used as a replacement for insulin isophane or other long-acting insulin. It considered that the average daily dose would be higher than insulin isophane and that it would most likely be administered by twice daily dosing. The Committee considered that there was no additional risk, in terms of significant adverse events, associated with insulin detemir compared with insulin isophane. However, they considered that there were modest benefits over insulin isophane in terms of reduced hypoglycaemic events, particularly nocturnal hypoglycaemic events.

The Committee considered that insulin detemir would be of most benefit in particular patient groups, including patients with type 1 diabetes who have frequent hypoglycaemic episodes with existing insulin preparations.

The Committee **recommended** that insulin detemir should be listed on the Pharmaceutical Schedule, with Special Authority criteria 1 and 2 as follows:

1. Treatment of patients with type 1 diabetes receiving an intensive regimen (injections at least three times a day) of an intermediate or long acting insulin in combination with a rapid acting insulin analogue for at least three months who have experienced more

than one unexplained severe hypoglycaemic episode in the previous 12 months (severe defined as requiring the assistance of another person).

2. Treatment of patients with type 1 diabetes receiving an intensive regimen (injections at least three times a day) of an intermediate or long acting insulin in combination with a rapid acting insulin analogue for at least three months who have experienced unexplained symptomatic nocturnal hypoglycaemia, biochemically documented at <3.0 mmol/L, more than once a month despite optimal management.

Reapplication after one year:

Patient is continuing to derive benefit due to reduced hypoglycaemic events whilst maintaining similar or better glycaemic control.

The Committee considered that insulin detemir should be funded under these criteria with a moderate to high priority.

The decision criteria relevant to the assessment of this application include: *(i) the health needs of all eligible people within New Zealand; (ii) the particular health needs of Maori and Pacific peoples; (iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) the clinical benefits and risks of pharmaceuticals; (v) the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical; and (viii) the Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.*

## **Leuprorelin**

The Committee considered an application from Mayne Pharma requesting the listing of Eligard (leuprorelin acetate 1, 3, 4, and 6 month sub-cutaneous depot injections). It noted that Mayne had stated in its proposal that the unique delivery system (Atrigel), as well as the availability of two longer-acting depot formulations, four and six month depots, differentiates Eligard from Lucrin Depot (leuprorelin acetate).

The Committee considered that all four preparations of Eligard are efficacious in suppressing testosterone production in patients with advanced prostate cancer, with an acceptable safety profile. It considered that the formulation of Eligard was similar to that of Lucrin Depot in that they both contain the same active chemical, but have different delivery systems.

The Committee noted that Eligard is indicated for prostate cancer, but not endometriosis or precocious puberty. The Committee also noted that Eligard is contraindicated for women who are breastfeeding, pregnant or intending to become pregnant, and in paediatric patients. Therefore, the Committee concluded that Eligard could not be used as a replacement for Lucrin Depot on the Pharmaceutical Schedule, as patients with endometriosis and precocious puberty would not be adequately catered for.

In considering potential cost savings with the longer-acting depot formulations of Eligard, the Committee noted that regardless of whether the depot is given monthly, 3-, 4- or 6-monthly, most urologists would see their patients 6-monthly after the first six months, with primary care reviewing the patients and providing the injection (at no cost, or a very low cost) in between. Hence the predicted cost savings from the manufacturer were overestimated.

## Levetiracetam (Keppra)

The Committee considered the proposal from UCB Pharma for the listing of levetiracetam (Keppra) on the Pharmaceutical Schedule. The Committee noted that the application was of good quality, and contained good evidence of efficacy. Members noted that the studies tended to be short-term only, with relatively wide confidence intervals. Members also noted that trials tended to be populated with patients where onset of epilepsy began in childhood, but that its only registered indication in New Zealand is for patients aged 16 years and over.

The Committee noted that levetiracetam is registered as an add-on therapy for the treatment of partial seizures, while many other of the newer antiepileptic agents were also indicated for the treatment of generalised seizures. Members noted that the Special Authority criteria for the other newer antiepileptic agents already allow for dual therapy. The Committee noted that follow-up data out to 60 weeks indicated that levetiracetam is relatively ineffective as monotherapy.

The Committee noted UCB Pharma's claim that levetiracetam would mainly replace lamotrigine, which may be a potential advantage, given the risk of Stevens-Johnson syndrome with lamotrigine. It noted that 2 g of levetiracetam was less expensive than 300 mg lamotrigine. The Committee considered that, as levetiracetam could also be used in combination with lamotrigine, the projected cost savings may not accrue.

The Committee considered that there were difficulties in comparing levetiracetam with other new antiepileptic agents, as there appear to be no head-to-head trials, and only indirect meta-analyses were available. Members noted comments in the application that levetiracetam could be more efficacious than gabapentin and lamotrigine, with an improved safety profile.

The Committee noted that there are no long-term safety data for levetiracetam available, although it had a good short-term safety profile, and the side-effects of other antiepileptic agents tend to occur early after initiation. The Committee noted that dose titration is not required with levetiracetam.

Members noted anecdotal evidence of patients who continue to have frequent seizures despite current therapy, and for whom levetiracetam may provide a benefit.

The Committee considered that the prescribing criteria for levetiracetam would be broadly similar to those applying to the newer antiepileptic agents, although noted the differences in the registered indications.

The Committee **recommended** listing levetiracetam in the Pharmaceutical Schedule as an adjunctive agent for the treatment of partial seizures, and gave a high priority to this recommendation.

The particularly relevant decision criteria are: (i) *The health needs of all eligible people within New Zealand;* (iii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* and (iv) *The clinical benefits and risks of pharmaceuticals.*

## **Budesonide/eformoterol (Symbicort) – widening access**

The Chair of PTAC left the room for the duration of the discussion regarding Symbicort and the Deputy Chair chaired this part of the discussion.

The Committee considered the proposal from AstraZeneca for an amendment to the Special Authority criteria for Symbicort (budesonide with eformoterol), noting that it had reviewed a similar application from AstraZeneca in May 2004, at which time the Committee had recommended declining the application.

The Committee noted that the application from AstraZeneca contained no new clinical evidence, but relied on a cost-based argument.

Members noted that there was some evidence that a single inhaler may increase compliance, which could result in improved outcomes, but that this evidence was limited. Members noted overseas data showing that combination inhalers had a higher repeat pick-up rate than individual inhalers.

The Committee considered that the cost comparison between combination and concomitant inhalers was difficult to assess without a constant dose of inhaled corticosteroid and long-acting beta agonist. Members noted that AstraZeneca had varied the dose of LABA between combination and concomitant inhalers in its cost analysis.

Members noted that one benefit of combination inhalers is that it would reduce the risk of using a long-acting beta agonist without an inhaled corticosteroid, but also considered that there is a disadvantage with combination inhalers in that patients cannot have the dose of one chemical titrated without also altering the dose of the other.

The Committee was concerned about the possible over-use of long-acting beta agonists in mild asthma that might result from a further de-restriction of combination inhalers.

The Committee **recommended** that access to Symbicort be widened; it recommended that, unless the proposal to increase access to Symbicort was at least cost-neutral, then a low priority should be given to the proposal. The particularly relevant decision criteria are: (vi) *the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any change to the Pharmaceutical Schedule.*