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PHARMAC responds on long-acting insulin analogues

A Special Series article in August by Dr Jeremy Krebs discussed the timing of funding of long-acting insulin analogues in glycaemic control in diabetes (http://www.nzma.org.nz/journal/118-1221/1641/). We respond to three issues raised by Dr Krebs: process; availability of long-acting insulin analogues internationally; and cost-effectiveness.

Timeframes and PHARMAC's processes

PHARMAC aims to ensure fair allocation of funding across competing new medicines, and must ensure appropriate targeting of medicines to get best value for money. For this reason, our processes for assessing new pharmaceutical funding applications are necessarily diligent. PHARMAC's process involves both expert clinical review, negotiation with suppliers, consultation with the health sector, and then decision by PHARMAC's Board. The process is described in the Attachment to this letter (at the end).

For insulin glargine, the most significant delays have been caused elsewhere. Insulin glargine has been registered for use in New Zealand since June 2001, following first application to Medsafe for registration in May 1999—some two years earlier. Insulin glargine was then registered for three years before the supplier applied to PHARMAC for funding in July 2004.

We have had the application to list insulin glargine for little over a year, during which time:

- The Pharmacology and Therapeutics Advisory Committee (PTAC)[1] or its Diabetes subcommittee (one of eleven expert subcommittees) have reviewed the application four times—as part of obtaining satisfactory expert clinical advice (including information gaps). PTAC originally recommended a low priority for listing insulin glargine for the patient population proposed; hence PTAC referred the application to its Diabetes subcommittee to develop appropriate targeting criteria.
- The application has also undergone further economic evaluation, at PTAC's request (PTAC had concerns with the original cost utility analysis (CUA) submitted by the supplier).
- In response to an application from another supplier for insulin detemir (another long-acting insulin analogue), PHARMAC's economic evaluations and the Diabetes subcommittee have also this month looked at long-acting insulin analogues as a whole.

The next steps will be for PHARMAC to negotiate with the suppliers of both insulin glargine and insulin detemir for a commercial arrangement to list one or both long acting insulin analogues; any agreed proposal(s) would then be consulted on and considered by PHARMAC's Board. Any proposals for the listing of any long-acting

insulin analogues would be subject to the standard decision criteria that all proposals are weighed against, and prioritised alongside competing new medicines at the time.

Timelines for the applications to PHARMAC for long acting insulin analogues are detailed in the Attachment to this letter (at the end). Available relevant minutes of PTAC and Diabetes subcommittee meetings are also included in the Attachment.

Long-acting insulin analogues are not funded in Australia nor recommended for funding in Canada

Neither insulin glargine nor insulin detemir is funded in Australia. The New Zealand application for insulin glargine coincided with an application to the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia. The Pharmaceutical Benefits Advisory Committee (PBAC) has since already rejected insulin glargine and deferred a decision for insulin detemir:

- PBAC has decided twice not to recommend the listing of insulin glargine, in November 2004 and then July 2005, citing an uncertain and only modest extent of clinical benefit over existing treatments and unfavourable albeit uncertain cost effectiveness (http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacrec-nov04-neg2, http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacrec-jul05-neg2#insu).[2] Insulin glargine's supplier disagreed with the decisions and was said to be considering its position regarding any future course of action, posting a press release on its website (http://www.pharma.aventis.com.au/corporate/media/pr/2005/0508011antus/050801lantus.htm).
- In July 2005 PBAC also deferred an application to list insulin detemir, given that the supplier had made a precondition that there be a PBAC recommendation to list insulin glargine—a precondition that PBAC rejected (http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacrec-jul05-defer). According to the PBAC website, insulin detemir's supplier is considering its position regarding any future course of action.

The Canadian Expert Drug Advisory Committee (CEDAC) (https://www.ccohta.ca/CDR/cdr_pdf/cdr_submissions/Complete/cdr_complete_Lantus_2005Sept28.pdf) has recently recommended that insulin glargine not be listed, citing *inter alia* no significant differences in 21 open-label RCTs between insulin glargine and NPH (or ultralente) insulin in the incidence of severe symptomatic hypoglycaemia. CEDAC also did not feel that the claimed differences in clinically important outcomes in favour of insulin glargine over NPH insulin justified the three-fold difference in cost.

Cost-effectiveness

Long-acting insulin analogues aim to achieve at least as good glycaemic control as insulin isophane (insulin NPH) while reducing the frequency and severity of hypoglycaemic episodes. At PTAC's request, PHARMAC staff performed a preliminary[3] CUA, based on the supplier's original submission to PTAC for insulin glargine.[4] Depending largely on the impact of fear of further hypoglycaemic episodes,

PHARMAC estimated a wide range of cost/QALY values for insulin glargine treatment, ranging between $17-18,000/QALY and $3.1-3.3 million/QALY.[5]

Guidance from the UK National Institute of Clinical Excellence (NICE) on the use of long-acting insulin analogues[6] was informed by a comprehensive systematic review and analysis by ScHARR[7] (http://www.ncchta.org/fullmono/mon845.pdf). This analysis showed, similarly to PHARMAC's CUA, a wide range of cost-utility values, again driven by the degree of anxiety/fear of further severe hypoglycaemia and this fear's effects on quality of life.[8] The ScHARR authors commented that the supplier's submission's claimed base case was based on the most favourable of a number of analyses. They also concluded that further research was needed that on the quality of life issues associated with the fear of hypoglycaemia, and also the economic impact of balancing HbA1c control and the incidence of hypoglycaemia achieved in practice.

PHARMAC has since estimated a $34,500 to $58,000/QALY range for long acting insulin analogues for the key group recommended by the Diabetes subcommittee – being Type 1 diabetes patients using intensive insulin regimes who had had an unexplained severe hypoglycaemic episode in the previous 12 months.[9]

The PHARMAC Board will use the above ranges of cost-effectiveness estimates, alongside clinical advice from PTAC and the Diabetes subcommittee and consultation feedback, when deciding whether to fund long-acting insulin analogues and if so under what access arrangements.

Conflict of interest: Scott Metcalfe is externally contracted to work with PHARMAC for public health advice. Jackie Evans and Peter Moodie declare no conflicts.

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Footnotes and references:

1. http://www.pharmac.govt.nz/ptac.asp The volume of applications received by PHARMAC and considered by PTAC is considerable. During 2005 PTAC will have undertaken 51 reviews of new and revised applications etc. PTAC agendas are full and submissions are extensive; agenda papers typically weigh 20 to 25 kg. PTAC recommend moderate to high priority for funding in one quarter of cases, the rest being lower priority, declines, deferrals, or referrals to subcommittees. Further details are in the Attachment to this letter (at the end).
2. While agreeing that there are patients who will potentially benefit from fewer treatment-related hypoglycaemic events with insulin glargine (compared with insulin NPH), PBAC considered that insulin glargine's absolute reductions in the different types of hypoglycaemic events were small, and that insulin glargine does not totally remove the risk of hypoglycaemic

events. PBAC also rejected claims of cost-effectiveness, stating that the absolute differences in hypoglycaemic event rates used in the economic model submitted were higher than those observed in the clinical trials, and that the model's utility values were poorly justified.

3. PHARMAC undertakes four levels of economic analysis: very rapid, preliminary, indicative, and detailed. Preliminary analyses typically are rapid assessments using data derived mostly opportunistically, not systematically, typically with 1-2 weeks FTE input. Preliminary analyses are based on the broad principles used by PHARMAC for pharmacoeconomic evaluations as described by the Recommended Methods to Derive Clinical Inputs for Proposals to PHARMAC (http://www.pharmac.govt.nz/pdf/62465.pdf) and PHARMAC's Prescription for Pharmacoeconomics (http://www.pharmac.govt.nz/pharmo_economic.asp). These principles include: the systematic identification, synthesis and presentation of relevant clinical input data; the use of overall health sector costs and direct patient costs when measuring effects on costs overall; measuring QALY gains; discounting both costs and QALY gains according to PHARMAC's current discount rate [8% from 1 July 2005, 10% before then]; and the use of univariate and multivariate sensitivity analyses.

4. The supplier's submission included efficacy data from a meta-analysis of both published and unpublished data for insulin glargine in type 1 and type 2 diabetes, with 0.31 severe hypoglycaemic events per patient year. PHARMAC in turn estimated a 8%-21% risk of hospitalisation for each severe hypoglycaemic episode, hence 0.02-0.07 hospitalisations for severe hypoglycaemic episodes per patient year. PHARMAC used ScHARR's (http://www.ncchta.org/fullmono/mon845.pdf) value for the loss of quality-of-life due to severe hypoglycaemic episodes themselves (0.15 over 4 days) and a range of values for the associated fear of further severe hypoglycaemic episodes.

5. Under the most cost-effective scenario ($17-18,000/QALY), the fear of further hypoglycaemic episodes was assumed to be both high (loss in quality of life (i.e. disutility) of 17%) and pervasively continual. The 17% disutility derived from the Erasmus disability weight for mild/moderate generalised anxiety disorder. (Stouthard MEA, Essink-Bot M, Bonsel GJ, Barendregt PGN, et al. Disability weights for diseases in the Netherlands. Rotterdam: Department of Public Health, Erasmus University, 1997.)

   Using a New Zealand-based EQ-5D disutility score for mild/moderate anxiety/depression (11112) of 0.296 would have given lower cost/QALYs. (See Devlin N, Hansen P, Kind P, Williams A. Logical inconsistencies in survey respondents' health state valuations – a methodological challenge for estimating social tariffs. Health Economics 2003;12(7):529-544.)

   Under the least cost-effective scenario ($3.1-3.3 million/QALY), the fear of further hypoglycaemic episodes was assumed to be lower-grade (0.5% disutility) and lasting three months after each episode. The 0.5% disutility derived from a patient-based survey commissioned by Aventis using the EQ-5D, used and cited by the ScHARR analysis (Warren E, Weatherley-Jones E, Chilcott J, Beverley C. Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. Health Technol Assess. 2004 Nov;8(45):iii, 1-57.)

   Assuming a high disutility from fear (but not continual disutility, rather lasting for three months) gave a cost /QALY of $210-220,000.

   The cost-effectiveness estimates that assumed the fear of further hypoglycaemia to be both high and continual imply a significant loss in quality of life – with continual anxiety and moderate effects on the ability to perform usual activities (work, recreation, etc). Using such values means that the fear of hypoglycaemia is counted as being worse than the event itself (both day-to-day and as it affects year-long quality of life). It is consistent with the impact of severe hypoglycaemia on some patients and their families – where, for instance, following hospitalisations for severe hypoglycaemia and knowledge of others who have suffered perhaps crippling consequences, patients or parents consistently test frequently during the day and then at night, and diabetes control and the fear of hypoglycaemia in an individual dominate family life.

6. National Institute for Clinical Excellence. Guidance on the use of long-acting insulin analogues for the treatment of diabetes: insulin glargine. Technical appraisal guidance 2002; No 53. http://www.nice.org.uk/pdf/53_Insulin_analogues_full_guidance.pdf

7. Warren E, Weatherley-Jones E, Chilcott J, Beverley C. Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. Health Technol Assess. 2004 Nov;8(45):iii, 1-57. http://www.ncchta.org/fullmono/mon845.pdf Also see http://www.nice.org.uk/pdf/Insulin_Analogues.pdf, with revisions to original model (lower prices, higher disutilities, higher hype costs) at http://www.nice.org.uk/pdf/Final_report_addendum_insulin.pdf

8. The ScHARR analysis used by NICE examined both HbA1c improvements and reducing the risk of hypoglycaemia, giving a range of £3,500 to £72,000. However, these values understate the cost/QALYs in New Zealand, due to both currency conversion, and then the price of insulin isophane (NPH) in New Zealand being half of that of the UK, yet the insulin glargine price proposed for New Zealand being 34% higher than the UK.

9. In general insulin detemir is expected to have similar effectiveness as insulin glargine. Note however that insulin detemir's supplier has claimed additional clinical benefit and greater convenience to patients with insulin detemir over insulin isophane (NPH) and insulin glargine, in terms of improved glycaemic control and corresponding reduction in hypoglycaemic events, and an improved delivery system (FlexPen). Prices for the two products differ, hence PHARMAC's cost/QALY estimates range according to the products' prices. The $34,500-$58,000/QALY range (for Type 1 diabetes patients using intensive insulin regimes with unexplained severe hypoglycaemic episode in the previous 12 months) uses the high but not continuous fear scenario; this analysis did not attempt to account for the other claimed differences in efficacy and ease of use.

Attachment to 'PHARMAC responds on long-acting insulin analogues': further details

1. PHARMAC's processes

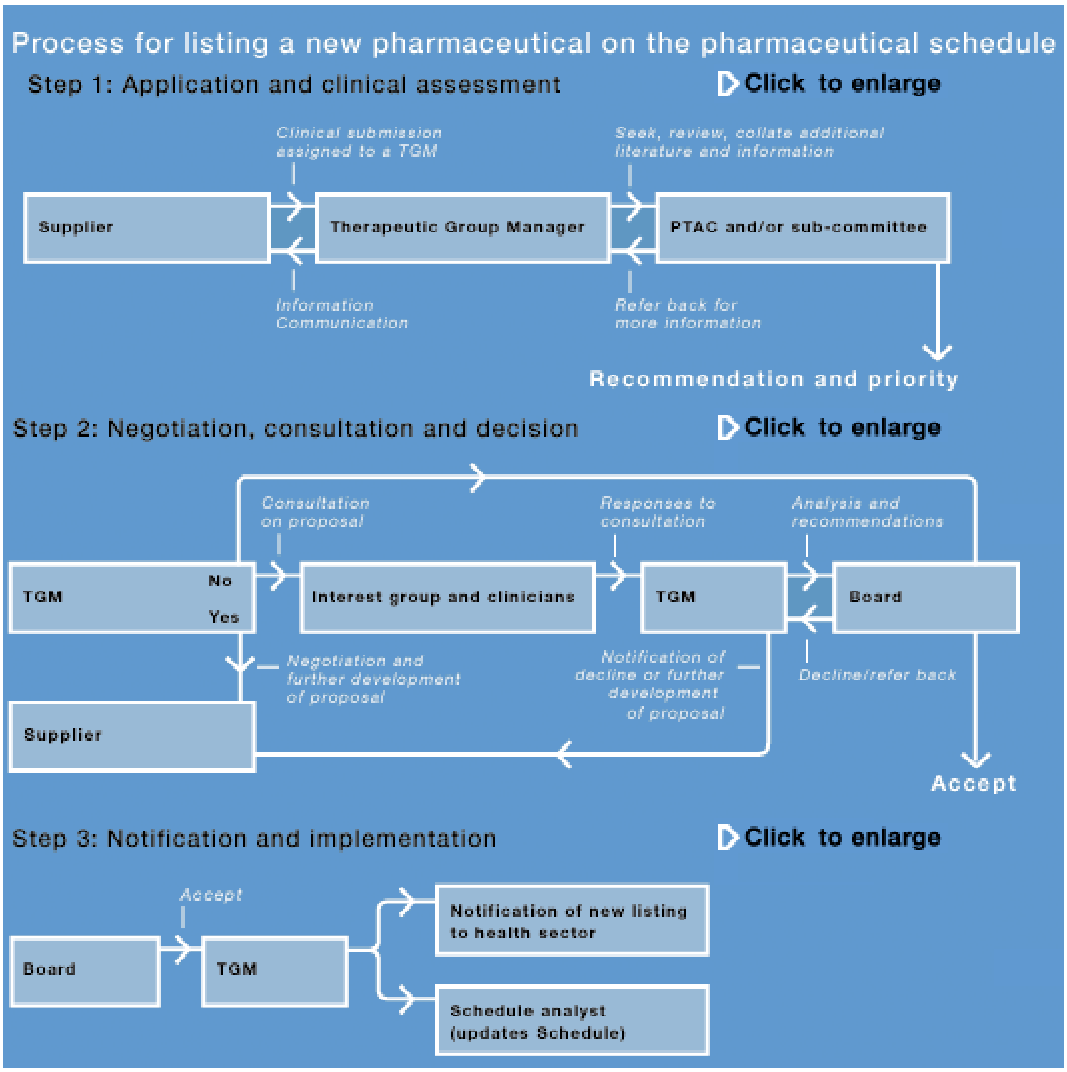
PHARMAC's process for assessing new pharmaceutical funding applications (http://www.pharmac.govt.nz/funding_applications.asp) is well established and involves both expert clinical review, negotiation with suppliers, consultation with the health sector, and then decision by PHARMAC's Board:

- Once a new funding application has been received from a supplier, PHARMAC staff seek and collate more information for the application to be considered by the Pharmacology and Therapeutics Advisory Committee (PTAC);

- Following its consideration, PTAC either refers the application back to PHARMAC for further information or analysis, refers it on to one of its eleven expert subcommittees, or recommends whether PHARMAC funds the medicine and at what priority;

- If PTAC makes a recommendation for funding, PHARMAC then negotiates with the supplier to reach a provisional agreement on the terms and conditions of listing, including subsidy;

- PHARMAC then consults with the health sector on the proposal, takes this feedback into account, and submits the proposal (with any revisions) to the PHARMAC Board for a final decision.



2. PTAC

The volume of applications received by PHARMAC and considered by PTAC (http://www.pharmac.govt.nz/ptac.asp) is considerable. PTAC received 27 applications during 2004, and has received 25 this year so far. PTAC often reviews applications more than once (pending further information), usually reviewing at least ten applications each meeting. PTAC has eleven expert subcommittees that provide clinical evaluations in specialist areas.

PTAC meets four times each year, and during 2005 PTAC will have undertaken 51 reviews of new and revised applications etc. These numbers do not include applications sent directly to subcommittees and later ratified by PTAC – particularly many cancer drugs.

PTAC makes recommendations for moderate to high priority for funding in one quarter of cases, the rest being lower priority, declines, deferrals, or referrals to subcommittees.

PTAC agendas are full and submissions are extensive; agenda papers typically weigh 20 to 25 kg.

In turn, PHARMAC's budget has meant listing or extending access to 25 medicines in 2004/05, and decisions made since July 2005 affect 23 medicines costing an expected $9.9 million this financial year ($36 million by 2007/08).

3. Timelines with applications for long acting insulin analogues

As part of obtaining satisfactory expert clinical advice, the application for insulin glargine was referred by PTAC to its Diabetes subcommittee. This is a normal process that aims to ensure objective decisions.

Timelines are as follows:

- Insulin glargine has been registered for use in New Zealand since June 2001, following first application for registration in May 1999 – some two years earlier.

- The supplier first applied to PHARMAC for funding in July 2004 – three years after registration.

- The application was considered by the PTAC in August 2004, which at that stage recommended a low priority for listing insulin glargine for the wider patient population proposed. PTAC considered that the evidence presented by the supplier demonstrated only modest improvements in HbA1c and hypoglycaemic episodes, and that insulin glargine would best benefit particular patient groups – particularly Type 1 diabetes with frequent hypoglycaemic episodes from existing insulin preparations.

  PTAC requested PHARMAC undertake its own cost utility analysis (CUA) (PTAC had concerns with the CUA submitted by the supplier), and referred the application to its Diabetes subcommittee to develop appropriate targeting criteria; PTAC members considered the low priority recommendation might change if the Diabetes subcommittee could identify an appropriate target population and if there was a satisfactory CUA.

- PTAC's Diabetes subcommittee considered insulin glargine at its next meeting in May 2005. The subcommittee recommended a high priority for funding for certain patients with severe or nocturnal hypoglycaemia (described in Jeremy Kreb's article http://www.nzma.org.nz/journal/118-1221/1641/). PHARMAC's preliminary CUA for insulin glargine was part of the evidence considered by the subcommittee.

- In July 2005 an application from another supplier was received for another long-acting insulin analogue, insulin detemir, to be funded

- PTAC accepted the Diabetes subcommittee's May 2005 recommendation for insulin glargine when it next met in August 2005. At the same time PTAC considered insulin detemir, including PHARMAC's CUA for insulin glargine (where it was noted that cost/QALYs for insulin detemir may differ from insulin glargine). PTAC recommended insulin detemir be listed for the same patient groups recommended for high priority for insulin glargine.

- Given the application for another long-acting insulin antagonist (insulin detemir), advice was sought from the Diabetes subcommittee comparing the two products. The Diabetes subcommittee met again in October 2005, considering (amongst other material) adaptations to PHARMAC's CUA for insulin glargine specific to patients with previous severe hypoglycaemia, and a CUA for insulin detemir for those patients.

PHARMAC is now negotiating with the suppliers of both insulin glargine and insulin detemir for a commercial arrangement to list one or both long acting insulin analogues; any agreed proposal(s) would then be considered by PHARMAC's Board. Any proposals for the listing of any long-acting insulin analogues would then be subject to the standard decision criteria that all proposals are weighed against, alongside competing investment opportunities at the time.

4. Relevant portions of PTAC and Diabetes subcommittee minutes

Record of the Pharmacology and Therapeutics Advisory Committee Meeting held on 19 August 2004 (http://www.pharmac.govt.nz/latest_PTAC_minutes.asp)

Insulin glargine (Lantus)

The Committee reviewed an application from Aventis to list insulin glargine on the Pharmaceutical Schedule.

The Committee reviewed the studies that had been provided in the submission for the use of this product in patients with type I and type II diabetes. Members noted that the trials were predominantly open-label in design due to the difficulty in blinding participants to the clarity difference between isophane insulin and insulin glargine. They considered that the majority of the trials had adequate sample sizes and treatment duration.

The Committee considered that, to represent a significant advance in insulin treatment, evidence of improved control (measured by HbA1c) and reduced hypoglycaemic episodes (particularly severe hypoglycaemia), as well as simplification in treatment schedules, would be required. Members noted that insulin glargine should provide physiological benefits over existing insulin preparations; however, they considered that the evidence demonstrated only a modest improvement in HbA1c and hypoglycaemic episodes.

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

The Committee reviewed the cost-effectiveness study provided by the supplier and considered that the modelling used was not appropriate for standard clinical practice. The Committee therefore disagreed with some of the assumptions in the analysis and recommended that PHARMAC conduct its own cost-utility analysis.

Members considered that the Diabetes Sub-committee of PTAC should review the application and that the Sub-committee be asked to recommend appropriate targeting criteria.

The Committee **recommended** that insulin glargine be listed on the Pharmaceutical Schedule, but should also be referred to the Diabetes Sub-committee of PTAC. In view of the high price and modest clinical benefit of insulin glargine compared with currently available insulins the Committee gave a low priority to listing. However, members considered that this recommendation might change if the Diabetes Sub-committee could identify an appropriate target population and if there were a satisfactory CUA.

> The decision criteria relevant to the assessment of this application include: (i) the health needs of all eligible people within New Zealand, as diabetes is a major health problem in New Zealand; (ii) the particular health needs of Maori and Pacific peoples, due to the higher prevalence of diabetes in these populations; (iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things, as current insulin regimes are far from ideal; (iv) the clinical benefits and risks of pharmaceuticals, as insulin glargine has some clinical advantages over currently available insulins; (vi) the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule in view of the high price of insulin glargine; 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, as diabetes is a priority for health funding.

Minutes of the Diabetes subcommittee's 17 May 2005 and PTAC's 17-18 august 2005 meetings have yet to undergo full public release. Draft minutes of the Diabetes subcommittee's 10 October 2005 meeting await ratification by the subcommittee.