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PHARMAC's response on gemcitabine and transparency

In this issue of the Journal, Dr Andrew Simpson (*What's happening in PHARMAC—where do all the submissions go? On the trail of gemcitabine.* URL: http://www.nzma.org.nz/journal/118-1225/1733) discusses the clarity of PHARMAC's process for the funding of new medicines for cancer, in particular that of gemcitabine for advanced bladder cancer.

We respond in terms of PHARMAC's timeframes and processes; transparency and consultation; the role of cost-effectiveness for the process and that of gemcitabine; and progress to date.

New process for hospital-administered cancer treatments

For hospital-administered cancer treatments, PHARMAC currently assesses applications on behalf of district health boards (DHBs). Following that assessment, if national agreement is reached on funding, then PHARMAC will seek a contract with the supplier for the product, before consulting on a proposal and seeking the approval of the PHARMAC Board. PHARMAC also consults before declining applications.

One objective of the cancer control strategy action plan is to improve national consistency in access to cancer treatments. Hence it is important that all DHBs agree to any funding proposal. At present this requires an agreement from all 21 DHBs at the national CEO meeting, held four times each year. PHARMAC and the DHBs are currently streamlining this decision-making process.[1]

PHARMAC receives about 30 applications for funding each year.[2] The Pharmacology and Therapeutics Advisory Committee (PTAC) makes a recommendation about the relative priority of each application—when not referring applications to its expert subcommittees, or deferring pending further information. In general, about 20% of applications have been given high priority, 20% moderate priority, 30% low priority or fund only if cost-neutral, and for 30% PTAC has recommended they be declined.[2] This priority rating is used both to inform PHARMAC on the use of analyst resources in conducting technology assessments and in prioritising spending.

Few cancer drug applications under the new process have been recommended as high priority, but progress has been good for those that have:

- 20 applications for cancer drugs have moved through the process since 2002 (18 in the last two years). Four applications have progressed to funding, with a number of other proposals either being considered by the Board or shortly to be consulted on.
- Advisory committees (the Cancer Treatments Sub-committee of PTAC (CaTSoP) and/or PTAC itself) have given a high priority to six applications. CaTSoP/PTAC have recommended that eight applications be declined.
- Of the six applications given a high priority, four have been funded already, and one is currently being negotiated with a supplier. The other application was reviewed very recently (September 2005).

Transparency

Transparency can be difficult in the face of commercial sensitivity. Pharmaceutical companies have consistently insisted that their applications remain confidential. There have been times when disclosure of PTAC minutes has been resisted by a company and they have been released only as the result of an Official Information Act request.[3]

Likewise the results and component assumptions of PHARMAC's economic analyses have not generally been widely disseminated. Indeed, in order to satisfy the industry, those analyses undertaken by PHARMAC on behalf on DHB hospitals have had to be made available via a secure website (the Hospital Pharmaceutical Assessment Database (HPAD) website).

The HPAD website (http://www.pharmac.govt.nz/hpad/) has a number of economic analyses, available to DHB staff.

We acknowledge that the table of new funding applications on the PHARMAC website (http://www.pharmac.govt.nz/new_funding_applications.asp) has not included gemcitabine. PHARMAC apologises for this oversight, and will make sure that the few applications not sponsored primarily by suppliers are included.

Consultation

PHARMAC has an established consultation process for proposed changes to the Pharmaceutical Schedule, scheduled around PHARMAC's monthly Board meetings and printing deadlines. PHARMAC consults (and is required to consult) with relevant clinical and patient groups[5–7] to ensure it has all the information before making a decision.

In the case of technology assessments, PHARMAC has four levels of economic analysis: very rapid, preliminary, indicative, and detailed, with increasing external involvement. Naturally, the more detailed the analysis and the greater the consultation and discussion sought, the longer it takes to complete the assessment stage of PHARMAC's process.

Use of economic analysis at PHARMAC

Economic analyses such as cost-utility analysis (CUA) help PHARMAC to prioritise funding where there is a constrained budget. They form only a part of the reason why funding might ultimately be approved, or declined. Cost-effectiveness is but one of PHARMAC's nine formal decision criteria (http://www.pharmac.govt.nz/pharmaceutical_schedule_update.asp).[8]

Because PHARMAC works in the pragmatic public policy/purchasing environment and analytical capacity is finite, there are inevitable trade-offs between precision and timeliness. The level (extent and depth) of analysis does vary according to circumstances; more definitive analysis may occur in future, according to need, competing priorities and available resources.

PHARMAC's CUA for gemcitabine was a preliminary analysis (see the above taxonomy). Preliminary analyses typically are interim assessments using opportunistic data, and the results generated by preliminary analyses area reasonably rapid, aiming to inform decision-making within time constraints.[9]

Further details on the role of economic analysis at PHARMAC can be found at http://www.nzma.org.nz/journal/116-1170/362/

The preliminary CUA for gemcitabine

At times the overall results of CUAs are highly sensitive to the inputs, for instance the utility estimates and the cost of treatment. PHARMAC relies on publicly available information for its CUAs.

In the case of gemcitabine, utility values generated by the supplier (Eli Lilly) and published in the UK gave a cost/QALY of about $30,000. By contrast, using the comprehensive disability weights used by the Australian Burden of Disease Study (http://www.aihw.gov.au/publications/health/bdia.html)[10] (viz. the Global Burden of Diseases Study[11] and Netherlands[12] disability weights) gave poorer results at around $800,000/QALY. The CUA report that Dr Simpson refers to was an early draft version released to the supplier under the Official Information Act, and included both of these estimates.

PHARMAC stands behind its preliminary CUA, which noted that the >$800,000/QALY figure was imprecise, with sensitivity analyses giving a wide range of values. The PHARMAC preliminary analysis and that of the supplier[13] used different methodologies and hence are difficult to compare.[14] The text of the PHARMAC CUA was careful to acknowledge these differences, and stated quite clearly that the QALY gain aspect of the preliminary NZ analysis were not particularly robust. The supplier's UK-based estimates of QALY gain were included in the PHARMAC analysis, and results based on the UK QALY data were explicitly included in the analysis' conclusion. PHARMAC's preliminary analysis concluded:

"Given the…imprecision of the cost-utility estimates, it cannot be said at this stage whether or not gemcitabine should be listed for the proposed indication. It may warrant additional assessment of quality of life gains (including further local clinical input) and potential for reducing the cost of the medication. More efficacy data as they become available would also be valuable. Nevertheless, at the current price, the cost per QALY is likely to be above $33,000 per QALY gained."

A copy of the full PHARMAC preliminary CUA[15] is available at the corresponding position of the full text version: http://www.nzma.org.nz/journal/118-1225/1741

Progress to date

Both the Cancer Treatments Sub-committee of PTAC (CaTSoP) and PTAC have given gemcitabine for advanced bladder cancer a moderate priority.

PHARMAC staff presented a recommendation to the DHB chief executive officers (CEOs) at the end of August on the funding of gemcitabine. PHARMAC is now actively in discussions with the supplier, and hopes to be in a position to consult on a proposal in early 2006.

The progress of individual applications is fluid. PHARMAC is happy to provide updates at any time as to where applications have progressed. For clinicians and others wanting to know the status of applications, PHARMAC can be contacted directly (contact details are on PHARMAC's website http://www.pharmac.govt.nz/).

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Conflict of interest: Scott Metcalfe is externally contracted to work with PHARMAC for public health advice. Steffan Crausaz declares no conflicts.

Endnotes and references:

1. PHARMAC and the DHBs are currently streamlining the decision-making process, by agreeing a national budget each year for hospital cancer treatments (including baseline funding for existing treatments and funding for new investments) that will be managed by PHARMAC. This will require a consistent national dataset on current usage before this process can occur. It is currently proposed that the streamlined process start from 1 July 2007.
2. Applications considered by PTAC during 2004 and 2005 to date.
3. Historically the pharmaceutical industry has lobbied for greater transparency in PHARMAC's processes. However, when PHARMAC has consulted on making changes – such as publishing PTAC minutes as soon as signed off by the committee, or publishing hospital pharmaceutical assessments directly and openly on the PHARMAC website – the pharmaceutical industry has argued against such publication, citing right of review as a reason.
4. HPAD analyses are undertaken for DHB hospitals as part of the Hospital Pharmaceutical Assessment Process (HPAP). HPAP was established in 2002 as part of the National Hospital Pharmaceutical Strategy, to reduce duplication of work and increase discussion on the costs and benefits of new pharmaceuticals by distributing hospital pharmaceutical assessments nationally. These assessments are distributed to DHBs as confidential documents, which is at the request of and agreement with the pharmaceutical industry. PHARMAC has recently undertaken a review of the HPAP; feedback from DHBs who responded indicated that many considered that the HPAP had improved transparency, facilitated review and improved the consistency and quality of assessments. Further information on the purpose of HPAP and PHARMAC's role in the distribution of discussion documents can be found on the PHARMAC website – www.pharmac.govt.nz/hospital_strategy.asp
5. New Zealand Public Health and Disability Act 2000, Section 49 Pharmac to consult in implementing objectives and carrying out functions
6. PHARMAC. Operating policies and procedures of the Pharmaceutical Management Agency ("PHARMAC"), 2nd 0edition. January 2001. http://www.pharmac.govt.nz/pdf/opps.pdf Section 4.2 Consultation.
7. PHARMAC. Operating policies and procedures of the Pharmaceutical Management Agency ("PHARMAC"), 2nd edition. January 2001. http://www.pharmac.govt.nz/pdf/opps.pdf Section 3.3.3 "PHARMAC will carry out appropriate consultation on the classification of pharmaceuticals into therapeutic sub-groups and its application of reference pricing in respect of a particular sub-group."
8. PHARMAC. Operating policies and procedures of the Pharmaceutical Management Agency ("PHARMAC"), 2nd edition. January 2001. http://www.pharmac.govt.nz/pdf/opps.pdf Section 2.2 Decision Criteria

9. Taxonomy of economic analyses undertaken by PHARMAC

Type	Description
Detailed	Detailed and systematic identification and synthesis of effectiveness, natural history, QoL and cost data. Follows Prescription for Pharmacoeconomic Analysis. Follows policies of Recommended Methods to Derive Clinical Inputs for Proposals to PHARMAC. Reviewed internally (PTAC for clinical assumptions, PHARMAC) and externally. 3-6 months FTE input.
Indicative	Interim assessment using opportunistic data but more detailed than preliminary CUA. Follows Prescription for Pharmacoeconomic Analysis. Largely follows policies of Recommended Methods to Derive Clinical Inputs for Proposals to PHARMAC. Typically reviewed internally (PTAC for clinical assumptions, PHARMAC). 4-6 weeks FTE input. Includes remodelling of supplier analyses.
Preliminary	Rapid assessment using largely opportunistic data. 1-2 weeks FTE input.
Rapid	First cut assessment using opportunistic data, 1-2 days FTE input. Includes supplier analyses not yet evaluated by PHARMAC staff.

Preliminary analyses are based on the 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/61396.pdf) and PHARMAC's Prescription for Pharmacoeconomics (available online at http://www.pharmac.govt.nz/pharmo_economic.asp). These principles include: 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%]; use of univariate and multivariate sensitivity analyses; and the systematic identification, synthesis and presentation of relevant clinical input data.

Note however that with preliminary analyses that many data are derived opportunistically, not systematically.

10. Mathers C, Vos T, Stevenson C. The burden of disease and injury in Australia. Australian Institute of Health and Welfare. Canberra: AIHW, 1999. http://www.aihw.gov.au/publications/health/bdia.html

11. Murray CJL, Lopez AD (eds). The global burden of disease: a comprehensive assessment of mortality and disability from disease, injuries, and risk factors in 1990 and projected to 2020. Harvard School of Public Health on behalf of the World Health Organisation and the World Bank. Boston: Harvard University Press, 1996.

12. 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.

13. Robinson P, von der Maase H, Bhalla S, et al. Cost-utility of the GC versus MVAC regimens for the treatment of locally advanced or metastatic bladder cancer. Expert Rev Pharmacoeconomics Outcomes Res 2004; 4: 27-38.

14. In the M-TAG/Eli Lilly analysis (Robinson et al 2004), oncology healthcare professionals were surveyed to estimate difference in quality of life between the treatment arms. The survey used willingness-to-trade-time (WTTT) as the primary measure (in weeks), reflecting the degree to which clinicians would be willing to trade reductions in life expectancy with improvements in toxicity during treatment. The total estimated WTTT included the following adverse events: febrile neutropenia requiring hospitalisation or neutropenic sepsis; alopecia (hair loss); mucositis; diarrhoea; weight loss. This gave a WTTT of 25.4 weeks, which equated to 0.13 QALYs gain (over life expectancy). However, actual utility values for each treatment arm were not derived (or at least not reported in the Robinson et al 2004 paper).

15. Extending access to gemcitabine in the Pharmaceutical Schedule for patients with advanced bladder cancer. PHARMAC Technology Assessment Report No. 66, August 2005. Official

Information Act (OIA) version withholding confidential information (author's and reviewers' names and gemcitabine price information, under sections 9(2)(a) and 9(2)(b) of the OIA).