

Can we deny patients expensive drugs?

Karen I Kaye, Executive Officer, NSW Therapeutic Advisory Group; Christine Y Lu, PhD student; and Richard O Day, Professor of Clinical Pharmacology, School of Medical Sciences, University of New South Wales, and Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Sydney

Key words: cost of drugs, Pharmaceutical Benefits Scheme.

(Aust Prescr 2006;29:146–8)

A key principle of Australia's National Medicines Policy is that 'essential' medicines should be available for all patients who need them, at a price they and society can afford.¹ Decisions about which medicines will be nationally subsidised through the Pharmaceutical Benefits Scheme (PBS) are made by the Pharmaceutical Benefits Advisory Committee (PBAC) on the grounds of comparative safety and efficacy, as well as cost-effectiveness. These decisions challenge us all – patients, carers, the wider community, prescribers, government and the pharmaceutical industry.

Limits on public subsidy are increasingly inevitable. Negative decisions concerning expensive medicines are often contentious, providing material for the more sensationalist media. The impression is reinforced that the PBS is a government mechanism for limiting expenditure, rather than enabling equitable access to cost-effective medicines based on careful evaluation of evidence. Can we better balance an individual's right to optimal care and society's expectation of effective and efficient health services within the constraints of the health budget?

In this issue...

Dominic Barnes tells us it can take many years to develop a new drug. Drug companies aim to recover the cost of development during the period of patent protection. However, Paul Kubler questions whether strategies to extend this protection act against the policy of access to affordable medicines.

The affordability of highly specialised drugs is a particular problem in hospital practice. Karen Kaye, Cindy Lu and Ric Day ask how we can balance limited budgets with unlimited expectations for treatment.

Nick Pavlakis says that highly specialised drugs may improve the outcomes for patients with renal cancer. Drugs that alter the immune response inevitably have adverse effects, including accelerating periodontal disease, which Ivan Darby tells us can present as gingival bleeding.

For prescribers, whose duty and inclination is to provide optimal care for patients, denial of subsidised access in some circumstances raises clinical and ethical dilemmas. Australia's Quality Use of Medicines (QUM) framework can help. This means selecting the best treatment options for each patient (including using no medicines), choosing the most appropriate and cost-effective medicines, and using medicines safely and effectively with careful individualisation of regimens.

Restrictions on PBS access are increasingly applied, often because cost-effectiveness ('value for money') is only demonstrated in subsets of patients, such as those with more severe manifestations of disease. Patients with less severe disease may therefore be denied subsidised access to an effective medicine. The ethical dilemma here is to balance individual needs against the greater common good – to maximise the use of scarce resources for society and have everyone accept the decision as fair. Vested interests can encourage an expectation that treatment should be subsidised irrespective of cost. For example, intense lobbying led the government to subsidise trastuzumab (Herceptin) by creating a special program. This was outside the normal PBS mechanisms because the PBAC had advised against including trastuzumab in the PBS. Such decisions will inevitably fuel future lobbying efforts for other expensive drugs. If successful, they will no doubt benefit some individual patients, but may not represent best value for society and may undermine the PBAC process of evaluating cost-effectiveness.

Anomalies in the subsidies of drugs can undermine confidence in the system. In some cases, specific patient groups have different levels of access. For example, a drug that is not listed on the PBS may be subsidised for treatment of veterans. In other cases, a drug with proven efficacy may not be subsidised because data to support its cost-effectiveness have not been submitted to the PBAC. The cost of submitting an application for extension of indications or for an uncommon condition may not make economic sense to the drug company, particularly if the drug's patent is about to expire.

Evidence from small studies indicates that some tumour necrosis factor inhibitors, which are expensive biological drugs, are effective in patients with arthritis associated with Crohn's

disease. However, it is unlikely that a PBS submission will be made for this indication. Is it ethical that this patient group be denied access because of the rarity of their condition?

One option might be for the PBAC to specifically request submissions for 'essential' medicines for particular indications and consider ways to encourage such submissions. In the absence of a submission, an acceptable approach may be for the PBS to subsidise the use of these medicines for an indication after conventional therapies have proven ineffective, with an explicit requirement that an objective and subsequent clinically significant response would determine ongoing treatment subsidy. The financial risk to society would be small and patients with rare diseases would not be markedly disadvantaged or advantaged.

Sometimes patients needing expensive drugs are referred to a public hospital. Decision-making in hospitals allows more flexibility in prescribing, but unless the argument for using a drug is sound, and the evidence for efficacy and cost-effectiveness is rigorously evaluated in a consistent manner, our national system is undermined. This practice, unless carefully and responsibly undertaken, shifts costs from one sector of the health system to another. Hospital budgets are capped and the money spent on an expensive drug will not be available to treat other patients who may be equally or more deserving. A more consistent and equitable approach to the provision of expensive medicines to patients across all healthcare settings is worthy of exploration.^{2,3,4}

Self-funding by patients is an option for registered, non-subsidised medicines. This option can be extremely challenging, particularly when patients and their families use their life savings to purchase a medicine. The patient has a right to be informed about such options, including the costs and why the medicine is not subsidised.⁵ The clinician's role is critical in helping the patient come to a reasonable decision given the circumstances and the evidence for drug effectiveness and safety. It is important that the clinician's advice is not biased by competing interests. Information about PBAC decisions (regarding treatment subsidies) is helpful for patients who are considering paying for drugs. Efforts by the PBAC to communicate this information as public summary documents are very welcome.⁶

The concept of a 'worthwhile' response to treatment needs to be discussed explicitly with patients and their carers. There should be agreement about what constitutes an acceptable response before starting treatment, regardless of whether treatment is subsidised or not. The Cochrane Collaboration provides summaries for consumers that can sometimes assist.⁷ Prescribers and patients have an obligation, both clinically and ethically, to monitor the effects of all medicines and be prepared to withdraw therapy if there is an inadequate response.

Clinicians have a responsibility to provide optimal care but to

do so within the limits of our system (that is, without 'bending the law'), so that equity of access for all patients is preserved.^{8,9} This balancing act is at times morally difficult. It would be made easier if the excessive manipulations of vested interests were not tolerated.

We want a health system that is transparent, accountable, and able to respond to both individual and societal needs. Demand for expensive drugs (and other therapies) will continue and funding for them will continue to be limited. Inevitably some patients will be denied access to some treatments. This will be better accepted if the community is educated and involved in open dialogue about priorities and values, and has confidence that the system is just – not only for access to medicines, but for all health services. This will require a continuing commitment to transparency by government¹⁰ and the pharmaceutical industry, a willingness to consider continued improvements to the system, and a commitment by clinicians and consumers to work within the system.

The authors gratefully acknowledge guidance from members of the High Cost Drugs Working Group of the NSW Therapeutic Advisory Group.

References

1. Australian Government Department of Health and Ageing. National Medicines Policy. Canberra: Commonwealth of Australia; 1999.
2. Shenfield G. Cost containment and equity of access. *Aust Prescr* 1995;18(Suppl 1):11-12.
3. NSW Therapeutic Advisory Group. Off-label use of registered medicines and use of medicines under the personal importation scheme in NSW public hospitals: a discussion paper. Sydney: NSWTAG; 2003. <http://www.nswtag.org.au> [cited 2006 Nov 8]
4. NSW Therapeutic Advisory Group. Hospital Formulary Submission Template: A decision tool for drug and therapeutics committees. Sydney: NSWTAG; 2006. <http://www.nswtag.org.au> [cited 2006 Nov 8]
5. Jefford M, Savulescu J, Thomson J, Schofield P, Mileshekin L, Agalinos E, et al. Medical paternalism and expensive unsubsidised drugs. *BMJ* 2005;331:1075-7.
6. Department of Health and Ageing. Public summary documents. <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/public-summary-documents> [cited 2006 Nov 8]
7. The Cochrane Collaboration. <http://www.cochrane.org> [cited 2006 Nov 8]
8. McKneally MF, Dickens BM, Meslin EM, Singer PA. Bioethics for clinicians: 13. Resource allocation. *CMAJ* 1997;157:163-7.
9. Nisselle P. Signing the script. *Aust Prescr* 2004;27:108-9.
10. Lu CY, Williams KM, Day RO. Accessing health outcome data on high-cost medicines in Australia. *Med J Aust* 2006;184:411-3.

Professor Day is a member of the advisory boards to sponsors for adalimumab, infliximab and anakinra in Australia. He has

also been contracted to undertake clinical trials of etanercept, infliximab, adalimumab and anakinra. Recompense for these activities is placed in audited hospital trust funds for use in the research activities of the Clinical Pharmacology Department, St Vincent's Hospital, Sydney.

Christine Lu was supported by an Australian National Health and Medical Research Council postgraduate research scholarship (Grant No. 351040).

NSW Therapeutic Advisory Group is an initiative of NSW clinical pharmacologists and pharmacists, funded by the NSW Department of Health.

Evergreening prescription products – riding the wave of patent extension

Paul Kubler, Clinical Pharmacologist/Rheumatologist, Royal Brisbane and Women's Hospital, Brisbane

Key words: evergreening, patent, perindopril.

(*Aust Prescr* 2006;29:148–9)

Evergreening is a strategy to extend the effective duration of a product's patent. Drug patent evergreening refers to filing 'new use' patent claims for a 'known' drug on the grounds of a change in formulation or method of administration rather than an alteration in the active chemical entity. Typically, these claims are made late in the life of the original patent. When successful, evergreening can delay the entry of generic products into the market while the originator company maintains the commercial advantage of a familiar, established brand. Multinational pharmaceutical companies have used evergreening to sustain the profitability of their 'blockbuster' (high sales volume) drugs for as long as possible.¹ Australia is not immune from this practice.

'New' drugs have been developed which are single isomers of well-established chiral compounds.² Examples include esomeprazole (omeprazole) and escitalopram (citalopram). Despite the promise of potential benefits such as improved safety or enhanced efficacy because of different pharmacokinetic and pharmacodynamic properties, there is little evidence to suggest that these isomers offer clinically meaningful advantages.

Another evergreening strategy involves changing the pharmacokinetic properties of the drug. The creation of 'long-acting' or 'modified-release' formulations on the basis of altered absorption characteristics and/or extended plasma concentrations after administration is appealing, particularly if it helps patient compliance. However, there is often no significant benefit in terms of clinical efficacy or adverse events. In some cases (such as zolpidem for insomnia) the proposal appears to be counter-intuitive because the purpose of the drug is to create a short-term effect.

The recent regulatory approval of an alternative formulation of the 'blockbuster' ACE inhibitor, perindopril, has highlighted the issue of drug patent evergreening in Australia. The previous formulation contained perindopril erbumine in 2, 4 and 8 mg tablets. The new formulation contains an alternative salt, perindopril arginine, in different dose formulations of 2.5, 5 and 10 mg. According to an unreferenced statement from the manufacturer, the principal reason for the change is that the perindopril arginine formulation has improved stability which makes it 'better suited to the extremes of the Australian climate'. The new formulation offers no additional therapeutic benefit, however some problems with the changeover may arise. Compliance may be compromised by patient uncertainty about their therapy if prescribed and dispensed tablets in a 'higher' strength with different packaging without adequate counselling about the changes to the product. Busy general practitioners and pharmacists will be left with this burden of additional explanation.

Prescribing figures suggest that this 'salt change' may help the manufacturer maintain a significant commercial benefit. Perindopril erbumine was the seventh most prescribed pharmaceutical benefit in 2005–06 with over three million prescriptions (see page 167). Prescribing figures for general practitioners in August 2006 show that the new formulation (PBS-listed that month) entered in seventeenth place. This equates to an initial uptake of approximately 70% of the prescribing of the old formulation.³

There is an intriguing anomaly in the approved product information for the new formulation. Like its predecessor, the 'new' document contains pivotal clinical data from the EUROPA trial which used the original formulation, that is, 2, 4 and 8 mg doses of perindopril erbumine.⁴ However, the new document portrays the original clinical data as dosing with 2.5, 5 and 10 mg