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New drugs: weighing up the risks and benefits

Our first impressions of new drugs are often of improvements over older drugs in efficacy and safety.

This *NPS News* discusses principles for putting promised improvements in context, and gives practical examples of applying these principles when deciding whether to prescribe new drugs.

Increasing transparency about new drugs — a positive trend

Access to information about medicines was the theme of the recent NPS summit *Informing judgements about medicines*. Safe and effective use of medicines depends on this access. Worldwide, official bodies (including our own Pharmaceutical Benefits Advisory Committee — the PBAC) are revealing more details of their assessment of drug safety and efficacy; this includes publishing the data that underpin these assessments, which were previously kept confidential.

Increasing openness not only allows closer scrutiny of official decision making, it also allows providers of independent information to make better-informed appraisals of the benefits and harms of new medicines. Greater disclosure by the PBAC and the pharmaceutical industry have meant that *NPS RADAR* reviews have been able to provide detailed explanations of new PBS listings since November 2003.

Health professionals, do you need information about new drugs?

NPS
National Prescribing Service Limited

TAiS
Therapeutic Advice & Information Service
1300 138 677

When to prescribe new drugs

In the early stages of a drug's marketed life, evaluating the place in therapy — that is, deciding which specific patients it might benefit — must be done with limited evidence. Registration of a new drug by the TGA or listing on the PBS is only one piece of the puzzle. In a presentation at the NPS summit, Prof Les Toop (Dept of General Practice, University of Otago, New Zealand) highlighted the principles that prescribers should apply when considering new drugs:

A prescriber's primary responsibility is to act as a patient advocate. Every prescribing decision should be informed by joint consideration [by prescriber and patient] of benefits and risks. The marketing of new medicines is typified by the presentation of partial and unbalanced information.

The sad fact is that perhaps 80–90% of new medicines don't actually offer much in the way of therapeutic gain. Information on short-term efficacy almost always precedes information on long-term safety. We need a cautionary approach; that sometimes means saying 'hang on, we don't need to explore this new medicine quite yet, for you'.

The discovery of unknown adverse effects after registration is a risk for any new drug because pre-registration clinical trials typically involve only a relatively small number of people for a short duration of treatment. It is worth noting that a study of new drugs introduced in the US between 1975 and 1999 found that 10% had serious adverse effects that only emerged after approval.¹ In the period 1998–2004, US post-marketing surveillance identified serious adverse drug reactions a median 3 years after approval², while about 40% of safety withdrawals in Canada 1963–2004 were within 3 years of registration.³

The challenge of assessing and communicating risk

How did the rofecoxib story unfold?

The time line (opposite) contains a sample of the pieces of evidence, competing opinions and regulatory actions that made up the context for the prescribing of rofecoxib (Vioxx). Along the way, safety concerns were raised repeatedly, but their significance was uncertain.

The response by regulators to these concerns was largely an untold story at the time — investigation and debate went on behind the scenes for close to 5 years. Some of this is now on public record.

The sustained volume of rofecoxib prescribing suggests that when the initial evidence of short-term efficacy and safety is well-received, subsequent signs of a safety problem make less of an impression on prescribers.

At the time of registration, it was established that rofecoxib had similar efficacy to that of older NSAIDs, and there was some evidence of improved gastrointestinal safety in short-term use. The VIGOR trial⁴, which confirmed a gastrointestinal safety benefit for rofecoxib but revealed the first substantial evidence of a cardiovascular safety problem, was published almost 18 months after rofecoxib was registered in Australia.

Who was prescribed rofecoxib?

While debate about the interpretation of the VIGOR trial went on without clear resolution, the small and conditional nature of the observed safety advantage was not widely appreciated.

The VIGOR trial established rofecoxib's improved gastrointestinal safety over naproxen in a population at high risk for gastrointestinal events, but with relatively few cardiovascular risk factors. In this group, to avoid one perforation, ulcer or bleed 41 patients needed to be treated with rofecoxib rather than naproxen, while there was one additional serious cardiovascular event for every 100 patients treated with rofecoxib.⁵

It was suggested early on that COX-2 selective NSAIDs had the greatest potential benefit for patients at particular risk of gastrointestinal complications; however, recommendations to restrict their use to high-risk patients or second-line therapy were viewed by some as cost control rather than a way to achieve the best balance of benefits and harms. A clinical audit of Queensland GPs published in 2002 showed that many rofecoxib and celecoxib prescriptions were being written for patients under age 70 (63%); NSAID-naive patients (24%); patients with no prior history of peptic ulcer disease (83%); and patients taking low-dose aspirin, likely to be at high cardiovascular risk and unlikely to experience any benefit in gastrointestinal safety (23%).⁶

New drugs in practice: New on the PBS

Comparative efficacy is rarely known

Ciclesonide (Alvesco) is an inhaled corticosteroid that was listed on the PBS in August 2005. As an addition to an established therapeutic class, it may prove over time to offer an incremental improvement over existing therapy. For the moment, the available evidence establishes that it is of similar efficacy to that of other corticosteroids but offers little other comparative information.⁸ The PBS listing of ciclesonide was on the basis that it is dose-for-dose equivalent to fluticasone.

Approach new drugs with caution

Caution implies that we reserve our judgement about new drugs until the evidence of their efficacy and safety is as convincing as for more established agents. Because it is a pro-drug, ciclesonide might be expected to have fewer local effects in the mouth and throat than other inhaled corticosteroids;

however, this has not been established in an appropriate clinical trial.⁸ For the moment there is no compelling evidence for preferring ciclesonide over other agents on the grounds of safety.⁸ So far the adverse-effect profile of ciclesonide resembles that of other inhaled corticosteroids.

Weigh up the benefits and harms for the individual patient

When new drugs are introduced there is rarely enough evidence to justify first-line use. Initially they can best find a use as backup agents or in specific groups of patients in whom the benefits clearly outweigh the harms. For example, patients who have experienced dysphonia or oropharyngeal candidiasis with other inhaled corticosteroids might benefit from a trial of ciclesonide if a review of correct inhaler technique does not resolve the problem.

Rofecoxib — how the story unfolded

1999

May

Evidence

Pre-registration safety assessment on a total of 5435 patients exposed to rofecoxib (1396 for 6 months or more) shows a pattern of adverse events similar to that for other NSAIDs.

US FDA New Drug Application

August

Opinion

'... how would it be possible to prescribe a drug with known gastric side-effects when another, equally efficacious, which did not show this type of toxicity, was readily available?'

Flower, *Rheumatology* 38, pp.693–6

October

Regulatory actions

TGA approves rofecoxib with indication for symptomatic treatment of osteoarthritis (rheumatoid arthritis was added in January 2002).

2000

April

Behind the scenes

Preliminary VIGOR report forwarded to TGA.

October

Opinion

'... rofecoxib show[s] significantly lower incidences of gastrotoxicity ... than non-selective NSAIDs ... COX-2 inhibitors would be cost effective in high risk patients ...'

Brooks and Day, *Med J Aust* 173, pp.433–6

November

Evidence

VIGOR trial published. The published data show that risk of myocardial infarction in the rofecoxib arm is 0.4%, but 0.1% in the naproxen arm. The authors suggest that naproxen may protect against thrombosis.

Bombadier et al, *NEJM* 343, pp.1520–8

2001

February

Regulatory actions

PBS listing (restricted benefit): Treatment of chronic osteoarthritis with an inflammatory component.

May

Opinion

'In response to news and analyst reports ... Merck & Co, Inc. today reconfirmed the favorable cardiovascular safety profile of Vioxx(R) (rofecoxib) ...'

Merck US press release

July

Opinion

'Cox II selective inhibitors ... should be used ... only in patients who may be at "high risk" of developing serious gastrointestinal adverse effects ... In all patients with cardiovascular disease ... they should not therefore be prescribed routinely in preference to standard NSAIDs.'

UK NICE *Technology Appraisal Guidance No 27*

August

Opinion

'Our findings suggest a potential increase in cardiovascular event rates for the presently available COX-2 inhibitors ... [We] urge caution in prescribing these agents to patients at risk for cardiovascular morbidity.'

Mukherjee et al, *JAMA* 286, pp.954–9

September

Behind the scenes

'You have engaged in a promotional campaign for Vioxx that minimizes the potentially serious cardiovascular findings that were observed in the ... VIGOR study, and thus, misrepresents the safety profile for Vioxx.'

US FDA letter to Merck

November

Regulatory actions

TGA revises the rofecoxib PI 'Precautions. Cardiovascular effects ... Doctors should assess the importance of these data [VIGOR results] for an individual patient at risk for cardiovascular thromboembolic events, if considering long-term therapy ...'⁵

2002

September

Behind the Scenes

ADRAC begins a review of the safety of COX-2 selective NSAIDs.

October

Evidence

Cohort study of Tennessee Medicaid patients finds a 93% increase in risk of serious coronary heart disease in new users of high-dose (50mg/day) rofecoxib.

Ray et al, *Lancet* 360, pp.1071–3

2003

February

Evidence

Cohort study in Canada finds no increase in risk of myocardial infarction among users of rofecoxib, but no reduced risk with naproxen.

Mamdani et al, *Arch Intern Med* 163, pp.481–6

October

Regulatory actions

ADRAC bulletin on rofecoxib, celecoxib and cardiovascular risk. Warns of risk that appears greater with rofecoxib than celecoxib, and that cardiovascular risk should be evaluated before prescribing.

2004

September

Evidence

APPROVe study halted early because of an excess of one thrombotic event for every 139 patient-years of treatment with rofecoxib.⁷

September

Regulatory actions

World-wide withdrawal of rofecoxib.

Abbreviations

ADRAC = Adverse Drug Reactions Advisory Committee (Australia)

FDA = Food and Drug Administration (USA)

NICE = National Institute for Clinical Excellence (UK)

TGA = Therapeutic Goods Administration (Australia)

Monthly PBS Prescriptions

300 000
200 000
100 000

1999

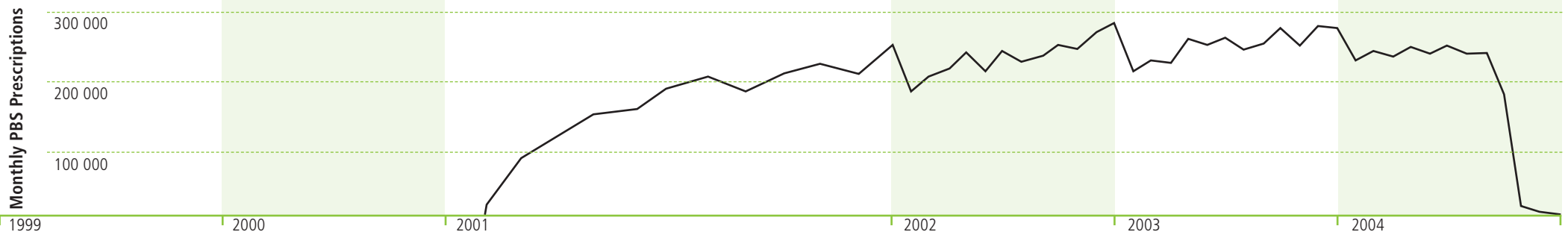
2000

2001

2002

2003

2004



New drugs in practice: Down-scheduling

New is not always better

Fluconazole (Diflucan One) as a single 150 mg oral dose for the treatment of vaginal candidiasis has been **pharmacist only** since January 2004, and patients may now ask for it by name more frequently. Although the oral route may be more convenient than the topical, no significant differences in efficacy have been shown between oral systemic and intravaginal antifungal treatment.⁹ Topical antifungals are first-line treatment¹⁰, and oral fluconazole is indicated when topical therapy has failed.¹¹

Choose the most suitable and safe, old or new

From a consumer perspective the choice between oral or topical therapy may be a matter of preference; however, it is important to consider the individual patient when assessing the balance of benefits and harms of any drug. Oral fluconazole is preferred if there is hypersensitivity to topical products. On the other hand, topical antifungals have established safety in pregnancy (ADEC Category A).¹⁰ Systemic fluconazole also has more potential interactions (e.g. with warfarin or drugs that prolong the QT interval).¹⁰

Documents during the drug regulation life cycle

	Who writes it?	Who else is involved?	What is it for?
PI (product information)	Company sponsoring the drug	Content subject to TGA approval	To provide information to prescribers sufficient to ensure safe and effective use of the drug under nearly all circumstances ¹²⁻¹⁴
CMI (consumer medicine information)	Company sponsoring the drug	TGA evaluates compliance with regulations	To inform consumers about the drug and how to use it safely and effectively. CMI must be consistent with PI ¹⁵
Australian Prescriber New Drug comment	<i>Australian Prescriber</i> editorial staff	Sponsor invited to provide unpublished data for assessment	To provide an independent assessment of the place of a new drug in practice at the time of registration
PBS public summary document (PSD)	Pharmaceutical Benefits Branch, Department of Health and Ageing	Sponsor and PBAC negotiate any release of commercial-in-confidence information	To provide the public with information about the PBAC recommendation ¹⁶
NPS RADAR	NPS	Sponsor and PBAC invited to provide the full PBAC submission and response for assessment by NPS	To provide prescribers with information including the place in therapy of a new drug relative to existing treatments, and an explanation of the PBS listing ¹⁷

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.



National Prescribing Service Limited

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Our goal To improve health outcomes for Australians through prescribing that is: ▲ safe ▲ effective ▲ cost-effective
Our programs To enable prescribers to make the best prescribing decisions for their patients, NPS provides:
 ▲ information ▲ education ▲ support ▲ resources

National Prescribing Service Limited (NPS) is a member-based organisation providing accurate, balanced, evidence-based information and services to health professionals and the community on Quality Use of Medicines (QUM). To achieve this we work in partnership with GPs, pharmacists, specialists, other health professionals, government, pharmaceutical industry, consumer organisations and the community. NPS is an independent non-profit organisation funded by the Australian Government Department of Health and Ageing.