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.

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New drugs for old

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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] Other strategies may have a similar effect.

'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 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, is another example. 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 of perindopril arginine. This is factually incorrect and the current product information does not explain the dosing conversion. We cannot be absolutely certain that the clinical trial would have had the same result if a different formulation had been used.

The regulatory events that have transpired appear to be in contrast to the intention of the Australian government to encourage greater use of generic medicines and to develop the generic drug industry in Australia. As the regulatory precedent has now been established, other companies with 'blockbuster' medicines reaching the end of their patent life may apply for the listing of an alternative formulation of their drug. The patents will soon expire on drugs such as amlodipine, atorvastatin and olanzapine.

When strategies are used to prolong the lifespan of 'blockbuster' drugs, prescribers should consider the rationale and trial evidence for minor variations before prescribing the 'new' drugs. It is difficult to give practical advice about how individual prescribers can respond. One proposal is that prescribers discuss the issue with their patients and consider changing therapy to a different drug in the same class. This is a possible action in the context of an ACE inhibitor because the drugs in the class have similar therapeutic effects.

Regulatory authorities need to respond to these strategies to encourage competition. The general community also needs to be better informed of this practice. Our focus must remain on access to affordable drugs for all Australians rather than prolonging patents for profit.

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Further reading

New drugs from old. Drug Ther Bull 2006;44:73-7.

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Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

Serotonin syndrome

Editor, – In the case report on serotonin syndrome precipitated by an over-the-counter cold remedy (Aust Prescr 2006;29:71), several mechanisms that may have caused this were proposed. I would like to add another contributing mechanism which relates to the patient taking methadone 70 mg daily. Although not a cytochrome P450 2D6 (CYP2D6) substrate, methadone is a potent CYP2D6 inhibitor.[1] It is possible that methadone is able to convert a CYP2D6 extensive metaboliser to a poor metaboliser. This process is known as phenocopying. There are very few data on methadone altering the pharmacokinetics of dextromethorphan in plasma. However, another CYP2D6 inhibitor, quinidine, can raise plasma dextromethorphan concentrations about 40-fold.[2] Hence, the combination of several drugs individually increasing the brain serotonin concentration and the likelihood of methadone increasing the dextromethorphan concentration may also have contributed in part to the patient developing serotonin syndrome.

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