Drugs to avoid: an analysis of Australia's pharmaceuticals market

● A study by Australian academics, based on Prescrire's annual review of drugs to avoid.

Hospitalisations due to the adverse effects of drugs nearly doubled in the Australian state of New South Wales between 2001 and 2014. In 2019, it was estimated that adverse effects were responsible for 250 000 hospital admissions per year in Australia as a whole, and the country made medication safety a national priority. In this context, two academics examined Australia's pharmaceuticals market, analysing the authorisation status, reimbursement status and level of use of the drugs on Prescrire's annual list of drugs to avoid (1).

Of the 93 drugs on Prescrire's 2019 list of drugs to avoid, 57 were authorised in Australia at the time of the analysis, 9 of which were available over the counter (1,2).

As of 2019, 35 of these drugs were eligible for reimbursement through Australia's national drug insurance system, the Pharmaceutical Benefits Scheme. More than half of these drugs were used infrequently, but 16 were in frequent use despite the serious harms they cause. For example, 22% of patients treated for diabetes received a gliptin in 2016; more than 50 000 patients received a drug for Alzheimer's disease in 2014; and in 2017-2018, *denosumab* became the 8th most costly drug in terms of total government spending. *Olmesartan* and *celecoxib* were also frequently used despite their unfavourable harm-benefit balance. And in 2015, *duloxetine*, *citalopram*, *escitalopram* and *venlafaxine* accounted for almost half of antidepressant use in Australia (1).

Tolcapone is one of the 36 drugs on Prescrire's list of drugs to avoid that is not currently authorised in Australia. This drug, proposed for Parkinson's disease, was withdrawn from the European and Australian market 2 months after its authorisation, and subsequently re-authorised in the European Union but not in Australia. In 2011, Australia's Therapeutic Goods Administration advised against the off-label use of *quinine* for nocturnal cramps. However, for most of these 36 drugs that are not authorised in Australia, it was not possible to determine whether authorisation was sought and refused by the Australian authorities, or whether authorisation was not sought (1).

The authors of this study urged regulatory and reimbursement authorities to review the status of drugs whose harm-benefit balance is less favourable than that of alternative therapeutic options (1).

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Proposed multi-stakeholder platform to improve clinical trials in the European Union

● Prescrire has responded to the consultation on the proposed key priorities for the platform, but chose not to apply for membership, in order to safeguard its independence.

In January 2022, the European Commission, the Heads of Medicines Agencies (HMA) and the European Medicines Agency (EMA) launched the "Accelerating Clinical Trials in the European Union" (ACT EU) initiative.

One of the main objectives of this initiative is to establish a platform bringing together all relevant stakeholders, with a view to developing a better understanding of the perspectives of all parties involved in one way or another with clinical trials.

In March 2023, Prescrire responded to the public consultation seeking views on the creation of this platform (1). Among the dozen or so envisaged areas of focus, Prescrire felt that the multi-stakeholder group should initially concentrate on:

– implementing the Clinical Trials Regulation;

– analysing clinical trial data to support the development of healthcare policy and evidence-based decision-making;

– a training programme for clinical trial investigators, to include modules on drug development and the regulatory framework.

Prescrire also advocated developing methodological guidance in order to support:

– clinical research providing reliable, robust data and results regarding the efficacy and adverse effects of drugs and their utility for patients;

– identification of research bias.

Drawing on the lessons learned from covid-19, Prescrire observed that during the pandemic, international regulators, including the EMA, had stressed the importance of large randomised comparative clinical trials as best

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able to provide the robust, reliable evidence needed for regulatory decision-making.

Prescrire also emphasised the importance of the transparency necessary for mutual trust, and the need for details on the positions and perspectives of the different stakeholders involved in the platform to be made publicly available.

In order to safeguard its independence and avoid any conflicts of interest, Prescrire chose not to apply to join the platform.

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Post-marketing studies following conditional authorisation: often lacking

● The European Medicines Agency is failing to ensure that pharmaceutical companies comply with their obligations after being granted a conditional marketing authorisation.

In the European Union, a fast-tracked marketing authorisation can be granted on the basis of very limited evaluation data, theoretically for drugs that address an unmet medical need and are presumed to have a positive harm-benefit balance (1). This type of marketing authorisation is termed "conditional", since the pharmaceutical company is required to conduct further studies after it is granted (1).

The majority of drugs authorised under a conditional marketing authorisation are cancer drugs, on the basis of very patchy data on survival and quality of life (2). It is therefore important to ensure that the gaps in the data are filled and that the additional data are made available after marketing authorisation is granted.

A recent study examined whether this was indeed the case by analysing data from the initial public assessment reports for new cancer drugs submitted to the European Medicines Agency (EMA) between 2004 and 2014, and from their 5-year renewal assessment reports. Among the 56 new cancer drugs authorised during this period, 80% (45 drugs) had been granted conditional marketing authorisation (2).

A total of 200 additional requirements had been issued by the EMA for these 45 drugs, covering aspects of their efficacy, safety and dosing. At the end of the study observation period in 2019, 60% of these requirements had been completed and 10% were ongoing. In 30% of cases, the requested studies had not yet been initiated 5 years or more after market introduction (median 8 years), despite the fact that conditional marketing authorisations are re-assessed on an annual basis. For 15 of the 45 drugs, further data had been provided, resulting in conversion to permanent marketing authorisation. Among the 30 drugs for which additional data had not been provided, 24 had nonetheless been granted full marketing authorisation (see also "Negative post-marketing studies: often ignored" p. 304) (2).

Similar findings were obtained in a study of drugs granted conditional approval by the US Food and Drug Administration (FDA) between 2013 and 2016 (3). The authors of both studies have called on the European and US agencies to take a firmer line with pharmaceutical companies, and the authors of the US study have further advocated imposing financial penalties on companies that do not fulfil their obligations on time.

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