Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

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Professor Samuel F Berkovic
Past President, ESA
Director, Epilepsy Research Centre
University of Melbourne (Austin Health)

Dr Simon Harvey
President, ESA
Director, Children's Epilepsy Centre
Royal Children's Hospital

Dear Professor Berkovic and Dr Harvey,

I refer to your correspondence of 1 May 2009 (*via* e-mail) in which you raise concerns over the quality of evidence prompting warnings over a suicidality risk with antiepileptic agents. Your concerns and supporting documents were discussed at the 315th ADRAC Meeting on 29 May 2009 and I am writing to advise you of our discussions of the issues you raised.

We agree that the science behind the analysis conducted by the FDA has faults, including possible bias of the data for lamotrigine and topiramate and confounding due to a variety of indications. We do not have a firm view on the possible impact of data exclusion because the basis on which the trials were excluded was not clear.

We accept it is not entirely valid to draw conclusions regarding a suicidality risk with the class of antiepileptic agents on the basis of the overall analysis. Nevertheless, we suggest it is important to consider the data for the antiepileptic agents on an individual basis as there is a generally consistent pattern, which has emerged from randomised clinical trials that generally provide reliable data and in which risk is often under-estimated.

On the basis of data for the individual agents (OR > 1, upper CI range 4.4-67.9), we consider the data provide sufficient evidence for a clear suicidality signal with topiramate and lamotrigine and a possible signal for gabapentin, levetiracetam, oxcarbazepine, pregabalin and zonisomide. While the OR for carbamazepine and sodium valproate is < 1, the possibility of a risk with these agents also cannot be excluded since the upper CI is 4.42 and 1.84, respectively. Overall, ADRAC considers there is a small suicidality risk with anti-epileptic agents and further study is required to fully establish and define the risks.

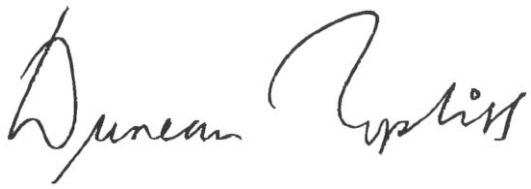
We acknowledge that the data are not uniform with regard to statistical significance. However, we consider it appropriate to take a conservative approach to matters of safety and suggest that the evidence to establish risk need not be as robust as that required to establish efficacy. ADRAC has also strongly advocated the dissemination of all safety information relating to medicines so that prescribers are comprehensively informed when deciding whether or not a particular drug is suitable and is likely to have a favourable risk-benefit profile for a particular individual. For these reasons, we are not in favour of recommending that the TGA review the requirements for suicidality warning with antiepileptic agents at this time.

ADRAC accepts the ESA's concerns that the risk associated with uncontrolled epilepsy due to reduced compliance may outweigh the risks of suicidality with antiepileptics. However, the information presented in product information documents for these agents appears to be factual and not alarmist. We expect that neurologists are unlikely to over-interpret the data or to emphasise them unnecessarily to their patients, particularly when the drugs are used to control epilepsy.

In summary, ADRAC acknowledges and understand the concerns of the ESA; however, we consider the data are sufficient to justify the action taken in relation to presenting information to prescribers about the possible risk of suicidality with antiepileptic agents. It is not expected that the information would be inappropriately emphasised to patients or that it will alter clinical practice in general. However, it is of importance to both the prescriber and the patient to help inform them of risk when reaching an agreed approach to the treatment of that individual.

Regarding the ESA's concern over the TGA's evaluation of the data that prompted the amendments to product information documents for antiepileptic agents, we cannot comment on this as the TGA did not seek, and was not required to seek, advice or comment from ADRAC before deciding this matter.

Yours sincerely,



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