FOI 037-1112 DOCUMENT 4.

Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Ms Teri Snowdon
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College of Psychiatrists
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Dear Ms Snowdon

Thank you for your letter of 26 August 2010 to Dr John Donohoe regarding correspondence between Dr Les Drew and the Therapeutic Goods Administration (TGA) about the current white cell count monitoring requirements for patients taking clozapine.

As mentioned in Dr Donohoe's letter to Dr Drew of 23 December 2009, the TGA has undertaken a review of the monitoring requirements for patients who have been prescribed clozapine in countries with developed regulatory systems.

A comprehensive examination of the monitoring requirements for patients who have been prescribed clozapine was undertaken by the US Food and Drug Administration (FDA) Psychopharmacological Drugs Advisory Committee in 2003, and presented to its meeting of 16 June 2003. A copy of the paper that was presented at the meeting may be found at: http://www.fda.gov/ohrms/dockets/ac/03/briefing/3959B1_01_A-Novartis-Backgrounder.pdf

That committee evaluated the impact of the then current clozapine monitoring system on the rate of agranulocytosis in the USA and internationally. It also considered whether reductions in monitoring frequency were warranted based on data from the Clozaril national registries. The review included data from the USA, UK and Australian Clozaril registries. Section 2.0 of the report describes the differences between these three monitoring systems. Although data from the Canadian registry were not part of the analyses undertaken by the FDA, the monitoring frequency in Canada is the same as the USA.

You will note from the report that Australia had, and continues to have, the least stringent monitoring system of all countries considered in the review. The monitoring frequency requirements in Australia have remained unchanged since the inception of its Clozaril Patient Monitoring Service (CPMS) in 1992.

Section 3 of the review provides data on the frequency of leukopenia and agranulocytosis in new and continuing patients in each of the 3 countries. In Australia, with monthly monitoring after weekly monitoring for the first 18 weeks of treatment, the rate of moderate leukopenia was 11.8 per 1000 patient years between weeks 19 – 52 and 6.1 per 1000 patient years from week 52.

These are very significant figures and indicate a need for ongoing monitoring if severe leukopenia and agranulocytosis is to be prevented in the majority of patients who would develop it if not monitored.

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The US data includes an estimate of the number of additional patients who would be expected to develop severe leukopenia and agranulocytosis without monitoring in section 3.2.7.

In undertaking a review of clozapine white cell count monitoring requirements, TGA considerations included:

- the findings of the FDA 2003 review
- that Australia has the least stringent monitoring system of all countries considered in the FDA review
- that Australia's monitoring frequency requirements have remained unchanged since the inception of its Clozaril Patient Monitoring Service (CPMS) in 1992, that is, rigor of these requirements has not been increased since then.

Dr Drew's comments were also taken into account in the review, and the results notified to him in a letter from the TGA of 24 February 2010.

The TGA concluded that there is no justification for reducing or ceasing the current white cell count monitoring requirements for patients taking clozapine in Australia.

I trust that the above information is of assistance.

Yours sincerely

Pio Cesarin
A/g Head, Office of Medicines Authorisation
September 2010