FOI 037-1112 DOCUMENT 1.

Question from TGA:

Please let me know if the current Clozaril Patient Monitoring System Protocol has the same requirements for patient monitoring as the EU, Canada and the USA. If it does not please list how the Australian system differs from the systems in those countries and advise when any divergence of monitoring requirements occurred. I'd also like to know whether there's any information on differences in outcomes with respect to neutropenia and agranulocytosis with use of differing monitoring systems.

Novartis response:

The data most relevant to the above question from TGA is contained in the attached Briefing Book, submitted to the FDA in 2003 for the Psychopharmacological Drugs Advisory Committee meeting on Clozaril blood monitoring frequency. The Committee's mandate was to evaluate the impact of the current Clozaril monitoring system on the rate of agranulocytosis and consider whether reductions in monitoring frequency were warranted based on the new data from the Clozaril national registries.

The briefing book presents data from the US, UK and Australian Clozaril registries, and includes a section on the differences between these three monitoring systems (Section 2.0). It is interesting to note that despite a reduction in monitoring frequency in the UK in 1995 and in the US in 1998, the monitoring frequency requirements in Australia at the time of the analyses were the least stringent, having remained unchanged since the inception of it's Clozaril Patient Monitoring Service (CPMS) in 1992.

The document also includes a description of the patient populations, definition of cohorts, methods of analysis and the differences between the 3 registries in terms of action taken when certain values for WBC and ANC are reported.

The analyses of these data from over 200,000 patients, representing over 1 million patient years, showed that the incidence rates for moderate leukopenia, severe leukopenia and agranulocytosis due to exposure to Clozaril had consistently declined in all 3 countries over the duration of treatment and by calendar year.

Based on the results of the analyses, the FDA decided to allow the monitoring frequency in the US to be reduced from every 2 weeks to monthly after at least 12 months of treatment. This change was implemented in 2005. Despite this reduction in monitoring frequency, the Australian system still has the least stringent requirements i.e. weekly for the first 18 weeks and monthly thereafter.

Although data from the Canadian registry were not part of the analyses for FDA, it should be noted that the monitoring frequency in Canada is the same as in the US.

To: Kerri.Mackay@tga.gov.au
cc: george.lillis@novartis.com
From: debby.surya@novartis.com
Date: 22/02/2010 05:32:32 PM
Subject: Re: clozapine monitoring [SEC=UNCLASSIFIED]

Dear Dr Mackay,

Please find attached our response to your enquiry regarding the clozapine monitoring.
I trust that this response is satisfactory.

Should you need further information, please let me know.

Kind regards
Debby

Debby Surya
Regulatory Consultant (Mon, Tues, Wed)
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Email : debby.surya@novartis.com

NOVARTIS

Kerri.Mackay@tga.gov.au

13/01/2010 11:00 AM

To debby.surya@novartis.com
cc george.lillis@novartis.com, Kerri.Mackay@tga.gov.au
Subject Re: clozapine monitoring [SEC=UNCLASSIFIED]

Thanks for letting me know your progress on this issue. Please get back to me when you have the information I require.

best regards

Kerri Mackay
Director Clinical Evaluation Section 1
Office of Prescription Medicines
Therapeutic Goods Administration

ph (02) 6232 8113

debby.surya@novartis.com

12/01/201005:46 PM

To Kerri.Mackay@tga.gov.au
cc george.lillis@novartis.com
Subject Re: clozapine monitoring [SEC=UNCLASSIFIED]

Dear Dr Mackay,

In reference to your email below, I would like to let you know that we are still waiting for the informations to come from our colleaques in head-office(HO) who are currently on vacation until early next week. Please let us know when you need our response by. We hope to be able to provide you with the response by late next week. However, we can not confirm this until we are in contact with our colleaques in HO who were already on vacation when we receive your email.
My apologies for this delay.

Kind regards
Debby

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NOVARTIS

Kerri.Mackay@tga.gov.au

18/12/2009 03:42 PM

To debby.surya@novartis.com
cc george.lillis@novartis.com
Subject clozapine monitoring [SEC=UNCLASSIFIED]

Dear Ms Surya,
The TGA has been contacted by a psychiatrist who considers that the current monitoring requirements for clozapine are unnecessarily onerous and has requested that the Minister for Health and Ageing commission a review of the controls on supply, prescription and use of clozapine. In order to give an informed response to this correspondent I need to know whether clozapine monitoring requirements differ between countries with developed medicine regulatory systems and, if so, what those differences are.

Please let me know if the current Clozaril Patient Monitoring System Protocol has the same requirements for patient monitoring as the EU, Canada and the USA. If it does not please list how the Australian system differs from the systems in those countries and advise when any divergence of monitoring requirements occurred. I'd also like to know whether there's any information on differences in outcomes with respect to neutropenia and agranulocytosis with use of differing monitoring systems.

many thanks for your assistance in this matter.

Kerri Mackay
Director Clinical Evaluation Section 1
Office of Prescription Medicines
Therapeutic Goods Administration

ph (02) 6232 8113

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 - Response_clozapine monitoring.pdf  - Briefing book _Final May 19, 2003_.pdf.zip