



MEDSAFE

NEW ZEALAND MEDICINES
AND MEDICAL DEVICES
SAFETY AUTHORITY

A BUSINESS UNIT OF
THE MINISTRY OF HEALTH

www.medsafe.govt.nz

4 July 2011

Safe and Quality Use of Medicines Group
Health Quality & Safety Commission
Ministry of Health
Private Bag 92 522
Auckland

Dear

Re: Dabigatran safety concerns

Thank you for your letter of 1 July requesting that Medsafe place dabigatran on the IMMP.

Currently Medsafe contracts the IMMP to conduct analyses on a medicine by medicine basis, rather than contracting the overall programme. The IMMP is not exclusive to Medsafe and any organisation or company can contract the Programme to perform a study.

The IMMP is a form of Prescription Event Monitoring (PEM) study.¹ These studies are supplementary to spontaneous reporting systems and are used to generate information on real-world usage of medicines. These studies can potentially detect new safety signals. However PEM studies also have weaknesses:

- Selection bias, as not all questions sent to doctors are returned
- Potentially takes longer to detect signals than spontaneous reporting systems
- Dependence on reporting by doctors and therefore dependent on quality of clinical notes
- Underreporting
- Restricted to general practice
- No measure of patient compliance
- Lack of a comparator group
- Detection of rare adverse reactions is not always possible
- Subject to stimulation bias

At the time when dabigatran was approved in New Zealand, Medsafe did not consider that there was a need to require the manufacturer to perform a specific post-marketing

¹ Shakir SAW 2006 'Prescription Event Monitoring' in Textbook of Pharmacoepidemiology Strom BL and Kimmel SE (Eds), John Wiley & Sons West Sussex, England.

study. No new safety information has been presented to Medsafe to change that view point.

As for all applications for approval to distribute medicines in New Zealand, Medsafe thoroughly reviewed the data provided by the manufacturer in support of their application. It was Medsafe's opinion that acceptable quality, efficacy and safety was demonstrated for this medicine. Therefore the Minister's delegate was recommended to approve dabigatran. This opinion has been echoed by other medicines regulators including the FDA, Health Canada and Europe. Medsafe also considers that PTAC and Pharmac found the safety of dabigatran to be acceptable, otherwise Pharmac would not have funded this medicine.

In response to the Safe and Quality Use of Medicines (SQM) Group's specific concerns, please note that all new medicines have a limited safety database. However, this is considered acceptable by medicines regulators who need to balance the need for timely access to new medicines with knowledge about safety. Please note that all new medicines are not routinely monitored by IMMP in New Zealand.

The manufacturer has studied the efficacy and safety of dabigatran in a number of studies. Phase II and phase III studies conducted for dabigatran include:

- For Surgical cover, BISTRO 1, BISTRO 2, Japanese trial 1160.50, RE-MOBILIZE, RE-MODEL, RENOVATE, RENOVATE II
- For atrial fibrillation, Petro- 1160.20, Petro-Ex- 1160.42, Japanese study 1160.49, RE-LY, RELY-ABLE.

During the clinical development for the atrial fibrillation indication more than 5,000 patients were exposed to dabigatran for more than two years. In terms of medicine development this is a considerable number of patients.

Since the launch of this medicine, overall patient exposure is more than 48,000 patient years, for all indications.

Medsafe would like to reassure SQM that the safety of all medicines is continually monitored in New Zealand. As part of this process, Medsafe contracts the New Zealand Pharmacovigilance Centre (NZPhvC) to collect and analyse spontaneous reports suspected to be associated with medicines. The Centre for Adverse Reactions Monitoring (CARM) alert Medsafe to emerging potential safety actions and Medsafe then takes appropriate action. This process is described in detail on the Medsafe website (<http://www.medsafe.govt.nz/Consumers/Safety-of-Medicines/Safety-and-Quality-of-Medicines.asp>).

The collection and analysis of spontaneous reports of suspected adverse reactions to medicines is considered to provide the best method of identifying new safety issues to medicines in a timely fashion². In addition to spontaneous reports, Medsafe also reviews safety information provided by companies, other regulators and published in the

² Davis S, King B, Raine JM 2007 'Spontaneous reporting – UK' In Pharmacovigilance: Second Edition; Mann RM and Andrews EB (Eds) John Wiley & Sons, West Sussex, England.

scientific literature. Medsafe discusses potential safety issues with other international medicines regulators and seeks expert advice from the Medicines Adverse Reactions Committee (MARC) when required.

Medsafe notes that the manufacturer for dabigatran has a Risk Management Plan in place. A number of potential safety issues have been identified for this medicine and risk minimisation activities implemented. In addition the company are also sponsoring a number of observational studies; one of these GLORIA-AF is an internationally conducted observational study specifically designed to review the real-world use of dabigatran. Since this study will include significantly more subjects than any study conducted solely in New Zealand it will be more likely to provide better information on rare adverse reactions and risk factors. In addition the results of this study are likely to be available sooner than the results from an IMMP study.

In conclusion Medsafe considers that there is adequate information on the safety of dabigatran to justify its approval and therefore its use in the general population. However, as for all new medicines more information is desirable. Medsafe notes that in this respect, the manufacturer is conducting a number of additional studies designed to collect this information. Medsafe therefore considers that additional IMMP monitoring is not necessary at present. However, if the SQM group or Commission have particular concerns regarding the safe use of this medicine they may wish to contract the IMMP to perform a study to investigate this.

I hope this information is of use to you and addresses your concerns that adequate safety monitoring systems are in place for dabigatran.

Yours sincerely

